

PASS information

Title	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01 _E vaccine in young children in sub-Saharan Africa.
Version identifier of the final study report	115056 (EPI-MALARIA-003 VS AME)
Date of last version of the final study report	Interim Report Final: 14 August 2024
EU PAS Register Number	EUPAS28541
Active substance	ATC code: J07XA01 RTS,S (portion of <i>Plasmodium falciparum</i> circumsporozoite protein fused with hepatitis B surface antigen [RTS], and combined with hepatitis B surface antigen [S]). AS01 (liposome-based Adjuvant System containing the immunoenhancers MPL [3-O-desacyl-4'-monophosphoryl lipid A] and QS-21).
Medicinal product	Mosquirix™
Product reference	EMA/H/W/002300
Procedure number	EMA/H/W/002300/MEA/003
Marketing Authorization Holder(s)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	Co-primary objectives: - To estimate the incidence of adverse events of special interest (AESI) in children vaccinated with RTS,S/AS01_E. - To estimate the incidence of etiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E. Objectives related to malaria are considered as secondary objectives.
Countries of study	Ghana, Kenya, Malawi
Author	Coordinating author: PPD, Freelance Scientific Writer (on behalf of GSK Biologicals)

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***GlaxoSmithKline Biologicals (GSK) PASS Study Report INS-BIO-PASS-1010
version 02***

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TABLE OF CONTENTS

	PAGE
1. ABSTRACT	12
2. LIST OF ABBREVIATIONS	31
3. ETHICS	34
3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	34
3.2. Ethical conduct of the study	34
3.3. Participant information and consent	34
4. INVESTIGATORS	34
5. OTHER RESPONSIBLE PARTIES	35
6. MILESTONES	35
7. RATIONALE AND BACKGROUND	36
7.1. Background	36
7.2. Rationale	36
8. RESEARCH QUESTION AND OBJECTIVES	38
8.1. Co-primary objectives	38
8.2. Secondary objectives	38
8.2.1. Safety	38
8.2.2. Effectiveness and impact	40
9. AMENDMENTS AND UPDATES	40
10. RESEARCH METHODS	42
10.1. Study design	42
10.2. Setting	43
10.3. Participants	43
10.4. Variables	44
10.4.1. Co-primary endpoints	44
10.4.2. Secondary endpoints	44
10.4.2.1. Safety endpoints	44
10.4.2.2. Effectiveness and impact endpoints	45
10.5. Data sources and measurement	45
10.6. Bias	46
10.7. Study size	47
10.8. Data transformation	47
10.9. Statistical methods	47
10.9.1. Main summary measures	47
10.9.2. Main statistical methods	47
10.9.2.1. Study cohorts	47
10.9.2.1.1. Enrolled Set	47
10.9.2.1.2. Analysis Set	48
10.9.2.2. Conduct of analyses	48

10.9.2.3.	Study participant disposition	49
10.9.2.4.	Demographics and characteristics at study entry	49
10.9.2.5.	Signs and symptoms, and medical history	49
10.9.2.6.	Exposure description	49
10.9.2.7.	COVID-19 assessment	49
10.9.2.8.	Protocol deviations	50
10.9.2.9.	Primary and secondary safety endpoint analyses	50
10.9.2.10.	Secondary effectiveness and impact endpoint analyses	50
10.9.2.11.	Exploratory analyses	52
10.9.2.12.	Other analyses	53
10.9.3.	Missing values	54
10.9.4.	Sensitivity analyses	54
10.9.5.	Amendments to the statistical analysis plan	54
10.10.	Quality control	55
11.	RESULTS	55
11.1.	Participants	55
11.1.1.	Disposition of participants	56
11.1.2.	Protocol deviations	61
11.2.	Descriptive data	65
11.2.1.	Home visits and attendance to health care facilities	65
11.2.2.	Demographic characteristics	65
11.2.3.	RTS,S/AS01 _E vaccine and concomitant vaccinations	66
11.2.4.	Study duration	67
11.2.5.	Health behaviors, signs and symptoms and medical history	68
11.3.	Outcome data	68
11.4.	Main results	68
11.4.1.	Summary description of main endpoints	69
11.4.2.	Analysis of co-primary objectives	76
11.4.2.1.	AESI	76
11.4.2.2.	Etiology-confirmed meningitis	80
11.4.3.	Analysis of secondary safety objectives	82
11.4.3.1.	Meningitis	82
11.4.3.2.	Cerebral malaria	86
11.4.3.3.	Deaths	89
11.4.3.4.	Hospitalization	95
11.4.3.5.	Anemia	95
11.4.4.	Analysis of secondary effectiveness and impact objectives	96
11.4.4.1.	Malaria	97
11.4.4.2.	Anemia	103
11.4.4.3.	Hospitalization	106
11.4.4.4.	Death	109
11.4.5.	Exploratory analyses	112
11.4.5.1.	Vaccine effectiveness against malaria among anemic children	112
11.4.5.2.	Averted cases based on Total Effect	112

11.4.5.3.	Vaccine Impact (Total Effect) accounting for Malaria Transmission Intensity estimated in the EPI-MAL-005 study	113
11.4.5.4.	Vaccine effectiveness and impact against malaria and severe malaria – evaluation of baseline covariate balance	115
11.5.	Other analyses	121
11.5.1.	Children with hemoglobinopathy and HIV-positive children	121
11.6.	Adverse events/adverse reactions	123
12.	DISCUSSION	130
12.1.	Key results	130
12.2.	Limitations	133
12.3.	Interpretation	136
12.4.	Generalizability	137
13.	OTHER INFORMATION	137
14.	CONCLUSION	137
15.	REFERENCES	138
16.	POST-TEXT TABLES	140
	APPENDICES	141

LIST OF TABLES

	PAGE
Table 1.1	Summary of safety: cumulative number of confirmed cases for the main endpoints – Active Surveillance – Analysis Set..... 18
Table 1.2	Summary of safety: cumulative number of confirmed cases for the main endpoints - Enhanced Hospitalization Surveillance - Analysis Set 19
Table 1.3	Summary safety: Incidence Rate and Incidence Rate Ratio of confirmed cases during at-risk period after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 for the main endpoints – Cluster design comparison - Active Surveillance – Analysis Set 20
Table 1.4	Summary of vaccine effectiveness (Total Effect) of RTS,S/AS01E vaccine on incidence of main endpoints 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance - Impact Analysis Set..... 23
Table 10.1	Changes to Protocol Defined Analysis Plan 48
Table 11.1	Study site enrollment..... 56
Table 11.2	Summary of study completion with reasons for withdrawal – Active Surveillance - Enrolled set 57
Table 11.3	Summary of study completion with reasons for withdrawal by RTS,S/AS01E vaccine status - Active Surveillance - Enrolled set 57
Table 11.4	Summary of study completion with reasons for withdrawal – Enhanced Hospitalization Surveillance - Enrolled set..... 58
Table 11.5	Participant enrollment by vaccination status – Exposed and Unexposed Clusters – Analysis Set..... 60
Table 11.6	Summary of important protocol deviations leading to elimination by study group and study site – Active Surveillance - Enrolled Set 62
Table 11.7	Summary of important protocol deviations leading to elimination by study group and study site – Enhanced Hospitalization Surveillance - Enrolled Set 64
Table 11.8	Number and percentage of participants who received RTS,S/AS01E vaccine by study group and study site – Active Surveillance - Analysis set 66

Table 11.9	Summary of safety: cumulative number of confirmed cases for the main endpoints – Active Surveillance – Analysis Set.....	69
Table 11.10	Summary of safety: cumulative number of confirmed cases for the main endpoints – Enhanced Hospitalization Surveillance - Analysis Set	70
Table 11.11	Summary safety: Incidence Rate and Incidence Rate Ratio of confirmed cases after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 for the main endpoints – Cluster design comparison - Active Surveillance – Analysis Set	72
Table 11.12	Summary of vaccine effectiveness (Total Effect) of RTS,S/AS01E vaccine on incidence of main endpoints 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance - Impact Analysis Set.....	75
Table 11.13	Incidence Rate and Incidence Rate Ratio of confirmed AESI cases (Final diagnosis) classified by body system and protocol definition after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance - Analysis Set	79
Table 11.14	Incidence rate and Incidence Rate Ratio of etiology-confirmed meningitis cases according to protocol definition (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule according to vaccination status– Cluster design comparison – Active Surveillance.....	81
Table 11.15	Incidence rate (IR) and Incidence Rate Ratio (IRR) of meningitis cases according to protocol definition (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance	84
Table 11.16	Incidence rate and Incidence Rate Ratio of cerebral malaria cases (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance.....	88
Table 11.17	Cumulative number (%) of deaths (Final diagnosis) by RTS,S/AS01E vaccination status – Exposed and Unexposed Clusters – Analysis Set	90
Table 11.18	Incidence rate and incidence rate ratio of death causes classified by protocol definition after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance - Analysis Set	93

Table 11.19	Incidence rate and incidence rate ratio of death (all causes) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status by gender – Cluster design comparison – Active Surveillance - Analysis Set.....	94
Table 11.20	Summary of the comparisons for vaccine effectiveness and impact endpoints	96
Table 11.21	Cumulative number (%) of malaria cases (Final diagnosis) by RTS,S/AS01E vaccination status – Exposed and Unexposed Clusters – Active Surveillance - Analysis Set	98
Table 11.22	Effectiveness and impact analyses of RTS,S/AS01E vaccine on incidence of confirmed malaria and severe malaria cases (Final diagnosis) 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance – Impact Analysis Set	101
Table 11.23	Impact and effectiveness analyses of RTS,S/AS01E vaccine on prevalence of anemia and severe anemia 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance – Impact Analysis Set.....	104
Table 11.24	Impact and effectiveness analyses of RTS,S/AS01E vaccine on incidence of hospitalizations 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance	107
Table 11.25	Impact and effectiveness analyses of RTS,S/AS01E vaccine on incidence of deaths 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance	110
Table 11.26	Cases averted (RTS,S vaccinated versus unvaccinated) based on Total Effect of RTS,S/AS01E vaccine on incidence of any Malaria 1 year after Dose 4 from Dose 3 by 3-monthly periods - Cluster design comparison – Active Surveillance - Impact Analysis set.....	113
Table 11.27	Total Effect of RTS,S/AS01E vaccine on incidence of confirmed malaria cases (final diagnosis) accounting for year - and center - specific Malaria transmission intensity (MTI) 2 years after Dose 4 from Dose 1, with baseline covariate balance assessed using propensity score overlap weighting – Cluster design comparison – Active Surveillance - Impact Analysis set	114
Table 11.28	Effectiveness and impact analyses of RTS,S/AS01E vaccine on incidence of confirmed malaria and severe malaria cases (Final diagnosis) 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4, with baseline covariate balance assessed using	

	propensity score overlap weighting - Cluster design comparison - Active Surveillance – Impact Analysis Set	119
Table 11.29	HIV and Hemoglobinopathy status by study group - Active Surveillance - Analysis set	121
Table 11.30	Summary of the number of participants and confirmed cases for the main endpoints by study group and study site – with HIV positive status – Active Surveillance - Analysis set.....	121
Table 11.31	Summary of the number of participants and confirmed cases for the main endpoints by study group and study site – with hemoglobinopathy – Active Surveillance - Analysis set	122
Table 11.32	Cumulative number (%) of expedited serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term by study group - Active Surveillance - Analysis set.....	124
Table 11.33	Cumulative number (%) of expedited serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term - Enhanced Hospitalization Surveillance - Analysis set.....	129

LIST OF FIGURES

	PAGE
Figure 10.1 Diagram of effectiveness and impact presenting the different vaccine effects for the cluster design.....	51
Figure 11.1 Consort Diagram – Participants in Active Surveillance	59
Figure 11.2 Consort Diagram – Participants in Enhanced Hospitalization Surveillance	60
Figure 11.3 Baseline covariate balance by exposure status for Direct/Overall/Total/Indirect Effect of RTS,S/AS01E vaccine: A propensity score overlap weighting approach - 1 year after Dose 4 from Dose 3 - Cluster design comparison - Active Surveillance - Impact Analysis set	116
Figure 11.4 Baseline covariate balance by exposure status for Direct/Overall/Total/Indirect effect of RTS,S/AS01E vaccine: A propensity score overlap weighting approach - 2 years after Dose 4 from Dose 4 - Cluster design comparison - Active Surveillance - Impact Analysis set.....	117

LIST OF ANNEXES

	PAGE
Annex 1	List of Stand-Alone Documents 141
Annex 2	Glossary of Terms..... 141
Annex 3	Trademarks..... 144
Annex 4	Case Definitions for Protocol Defined Adverse Events of Special Interest (AESI) 144
Annex 5	Report Sign-off..... 159

1. ABSTRACT

Title

A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01_E vaccine in young children in sub-Saharan Africa.

Keywords

RTS,S/AS01_E, malaria, sub-Saharan Africa, safety, effectiveness/impact.

Study Report revision history

Interim Study Report: 14 August 2024.

The Interim Analysis was performed on available data collected on all participants from Active Surveillance, with a data cut-off of 1 year after Dose 3/virtual Dose 3, in children who had received the 3 doses before 12 months of age.

Rationale and background

GlaxoSmithKline Biologicals SA (GSK) developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01_E, for routine immunization of children living in malaria-endemic countries of sub-Saharan Africa. The vaccine antigen, RTS,S, consists of a portion of the *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S). The antigen is adjuvanted with the AS01_E Adjuvant System, which consists of 2 immune enhancers 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and Quillaja saponaria Molina, fraction 21 (QS-21), in a liposomes suspension.

In 2015, RTS,S/AS01_E received a positive scientific opinion from the European Medicines Agency for use outside the European Union. In the frame of the Malaria Vaccine Implementation Program (MVIP), commissioned by the World Health Organization, a comprehensive post-approval plan (comprising 3 observational studies) was developed by GSK to further evaluate the safety, effectiveness and impact of RTS,S/AS01_E in the context of its real-life implementation, whereby the RTS,S/AS01_E vaccine would be introduced in selected areas in 3 sub-Saharan Africa countries by their respective routine national immunization programs.

- The EPI-MALARIA-002 VS AME (115055) study (referred to as EPI-MAL-002 in the remainder of the document) measured the baseline incidence of protocol defined adverse event of special interest (AESI), other adverse event (AE) leading to hospitalization, meningitis and malaria morbidity and mortality.
- The EPI-MALARIA-003 VS AME (115056) study (referred to as EPI-MAL-003 in the remainder of the document) was designed as a post-implementation safety study to detect potential rare and uncommon AEs following vaccination with RTS,S/AS01_E. The secondary objectives aimed to evaluate the effectiveness (Direct Effect) and impact (Indirect, Total and Overall Effects) of RTS,S/AS01_E.

- A third study (EPI-MALARIA-005 BOD AME [116682], referred to as EPI-MAL-005 in the remainder of the document), was conducted in parallel to EPI-MAL-002 and EPI-MAL-003 to measure malaria transmission intensity (MTI) and other malaria control interventions.

EPI-MAL-003 Research question and objectives

Co-primary objectives
• To estimate the incidence of adverse events of special interest (AESI) in children vaccinated with RTS,S/AS01_E. • To estimate the incidence of etiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E.
Secondary safety objectives
• To estimate the incidence of etiology-confirmed and/or probable meningitis (final classification). • To estimate the incidence of probable meningitis (final classification). • To estimate the incidence of etiology-confirmed, probable and/or clinically suspected meningitis (final classification). • To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy). • To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including <i>P. falciparum</i>]), overall and by gender. • To describe the causes of death, overall and by gender.
Secondary effectiveness and impact objectives
• To estimate the vaccine effectiveness (Direct Effect) and the impact (Indirect, Total and Overall Effects) of vaccination with RTS,S/AS01_E on. – the incidence of any malaria (including <i>P. falciparum</i> malaria), severe malaria (including <i>P. falciparum</i> malaria) and cerebral malaria diagnosed by RDT and/or microscopy – the prevalence of anemia among hospitalized children – the incidence of hospitalizations attributed to malaria (including <i>P. falciparum</i>) – the mortality rate (all-cause mortality and deaths attributed to malaria [including <i>P. falciparum</i>]) overall and by gender.

AE = adverse event; AESI = adverse events of special interest; RDT = rapid diagnostic test

Note: Table includes objectives relating to the Final Analysis, presented in this Final Study Report. Objectives relating to analyses of Other AE leading to hospitalization, cause of hospitalization and incidence of febrile convulsions, and before-after design analyses using data from the EPI-MAL-002 study, were only conducted for the Interim Analysis and not for the Final Analysis. Results for these analyses are presented in the EPI-MAL-003 Interim Report (14 August 2024)

Study design

- A disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; Interim Analysis only) and concurrent comparisons (Interim Analysis and Final Analysis) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated participants living in exposed or unexposed clusters* located in sub-Saharan Africa countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters.

*Exposed clusters: study sites where the RTS,S/AS01_E vaccine was to be implemented at the beginning of the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI

Unexposed clusters: study sites where the RTS,S/AS01_E vaccine was not to be implemented at the beginning of the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI.

- The design included 2 cohorts: Active Surveillance (home visits and continuous monitoring of outpatient visits and hospitalizations at all health care facilities) and Enhanced Hospitalization Surveillance (continuous monitoring of hospitalizations) in both exposed and unexposed clusters.
The enrollment to Active Surveillance was completed on 06 April 2021.
Following site Ethics Committee approval of Protocol Amendment 3, enrollment to Enhanced Hospitalization Surveillance and data collection was stopped (last participant enrolled 13 June 2025), with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for participants diagnosed with an AESI, meningitis or cerebral malaria.
- The diseases under surveillance for safety endpoints included AESI, other AE leading to hospitalization, meningitis, and severe malaria including cerebral malaria, and were monitored among the RTS,S/AS01_E vaccinated and unvaccinated children enrolled in Active Surveillance and in Enhanced Hospitalization Surveillance. The mortality rate, overall and by gender, was estimated.
The analysis of malaria cases and death included cases recorded during both outpatient visits or during home visits in the case of death, and hospitalizations. All other endpoints included cases recorded during hospitalizations only.
- The effectiveness (Direct Effect) of the RTS,S/AS01_E vaccine was investigated by monitoring all malaria (including severe and cerebral malaria) related events in vaccinated and unvaccinated children of the exposed clusters, enrolled in Active Surveillance. The impact (Indirect, Total and Overall Effect) of the vaccine was investigated in the Active Surveillance cohort by comparing the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the unexposed clusters to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters (Indirect Effect), in vaccinated children (Total Effect), or in all children of the exposed clusters (Overall Effect). Vaccine effectiveness was estimated as 1-Incidence Rate Ratio (IRR), and 1-Odds Ratio (OR) for anemia.
- The total study duration per site was approximately 62 months, including an estimated recruitment period of approximately 18 months in Active Surveillance and active follow-up through home visits up to 44 months. Study end per site occurred when the last child enrolled in Active Surveillance accrued a total follow-up period of 24 months after the fourth dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) given at a maximum age of 30 months.

Setting

- The study population was defined as study participants <5 years of age living in a geographically limited area with a demographic surveillance system in place, and a well-developed infrastructure to monitor population health and vaccination programs.
- In alignment with the MVIP, the study sites for the GSK observational Phase 4 studies were selected from the 3 countries where the RTS,S/AS01_E vaccine was to be implemented: Ghana, Kenya and Malawi.

Participants and study size (including dropouts)

- The EPI-MAL-003 study targeted enrolling at least 45 000 children in Active Surveillance:
 - 22 500 in exposed clusters (with a minimum of 20 250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22 500 study participants would receive 3 doses of RTS,S/AS01_E, 10% would receive 1 or 2 doses and 10% will not have any dose)
 - 22 500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.

Variables and Data Sources

Variables

Co-primary endpoints	
In children included in active or enhanced hospitalization surveillance:	• Occurrence of AESI. • Occurrence of etiology-confirmed meningitis.
Secondary safety endpoints	
In children included in active or enhanced hospitalization surveillance:	• Occurrence of probable meningitis (final classification). • Occurrence of clinically suspected meningitis (final classification). • Occurrence of meningitis cases identified at site level (first line laboratory). • Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
Effectiveness and impact endpoints	
In children included in active surveillance:	• Occurrence of episodes of malaria diagnosed by RDT and/or microscopy – Any malaria (including <i>P. falciparum</i> malaria) – Severe malaria (including <i>P. falciparum</i> malaria) – Cerebral malaria. • Occurrence of anemia at hospital entry among hospitalized children. • Occurrence of hospitalization – Hospitalizations for any malaria (including <i>P. falciparum</i> malaria), severe malaria (including <i>P. falciparum</i> malaria) and cerebral malaria. • Occurrence of death – All causes and malaria-attributed deaths (including <i>P. falciparum</i> malaria-attributed death).

AE = adverse event; AESI = adverse events of special interest; RDT = rapid diagnostic test

Note: Table includes endpoints relating to the Final Analysis, presented in this Study Report. Endpoints relating to analyses of Other AE leading to hospitalization, cause of hospitalization and incidence of febrile convulsions, and before-after design analyses using data from the EPI-MAL-002 study, were only conducted for the Interim Analysis and not for the Final Analysis. Results for these analyses are presented in the EPI-MAL-003 Interim Report (14 August 2024).

Incidence Rate (IR) computations were conducted for study participants from Active Surveillance, but not study participants from Enhanced Hospitalization Surveillance. The Enhanced Hospitalization Surveillance cohort data was only used for descriptive statistics of the main safety endpoints (AESI, meningitis, malaria and mortality).

Data Sources

HDSS (or equivalent surveillance system)	- Listings of all children living in the study area based on the demographic census - Total number of children <5 years of age (according to year and gender) recorded at the beginning of the study, at least once a year during the study duration and at the end of the study - Other demographic data (cause and date of deaths, migrations), if available - Information related to vaccination, if available.
Active surveillance (enrollment)	- Socio-demographic data - Active participation in any trial with an investigational product.
Active surveillance (home visits)	- Vaccination types and dates - Health history - Malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards - Verbal autopsy report.
Active surveillance (outpatient visits and hospitalizations at all health care facilities)	Data on visits at primary health care facilities and hospitals since enrollment or last home visit.
Enhanced hospitalization surveillance (hospitalizations)	- Socio-demographic data - Active participation in any trial with an investigational product - Health history - Malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards - Type of health care facility - Final diagnosis for the hospitalization visit on discharge for all children - Data relevant to the diagnosis of AESI, meningitis and malaria (including cerebral malaria) - Vaccination types and dates - Autopsy report.
Study conclusion (home visit)	- Vital status - Verbal autopsy report - Vaccination types and dates - Health history since last visit.
MTI Study EPI-MAL-005	- Estimation of annual parasite prevalence - Changes in diagnostic practices - Malaria control and prevention measures at the community and individual level.

AESI = adverse events of special interest; HDSS = health and demographic surveillance system; MTI = malaria transmission intensity

Results

Participants

- A total of 77 953 participants were enrolled in the study (Enrolled Set), comprising 44 998 participants in Active Surveillance and 32 955 in Enhanced Hospitalization Surveillance. In Active Surveillance, 22 503 participants were in exposed clusters and 22 495 in unexposed clusters, and 5 participants had missing information regarding the study group. In Enhanced Hospitalization Surveillance, 17 371 participants were in exposed clusters and 15 584 in unexposed clusters.
- In total, 44 912 participants from Active Surveillance were included in the Analysis Set (22 448 exposed clusters, 22 464 unexposed clusters).
- In the Analysis Set, the mean (standard deviation) age at informed consent was 2.74 (1.63) months: 3.07 (1.88) months in exposed clusters and 2.41 (1.25) months in unexposed clusters. The ratio of females:males was 49.4:50.6 in the exposed clusters and 50.2:49.8 in the unexposed clusters.
- In total, of the 22 448 participants in the Active Surveillance cohort in the exposed clusters, 14 443 (64.3%) received 4 doses of RTS,S/AS01_E.

Summary description of main endpoints

The number of participants and confirmed cases for the main endpoints from hospitalization (and/or outpatient visits for Malaria endpoint) and/or occurring outside of a health care facility for deaths (cumulative number) reported during the study period are summarized by cluster/vaccination status for participants in Active Surveillance in [Table 1.1](#) and for participants in Enhanced Hospitalization Surveillance in [Table 1.2](#).

Table 1.1 Summary of safety: cumulative number of confirmed cases for the main endpoints – Active Surveillance – Analysis Set

	Exposed cluster		Unexposed cluster	
	Vaccinated (N=20641)	Unvaccinated (N=1807)	Vaccinated (N=254)	Unvaccinated (N=22210)
	n (%) [n*]	n (%) [n*]	n (%) [n*]	n (%) [n*]
Primary endpoint analyses				
AESI	32 (0.16) [34]	2 (0.11) [2]	0	31 (0.14) [32]
Intussusception	4 (0.02) [4]	0	0	5 (0.02) [5]
Renal insufficiency	0	1 (0.06) [1]	0	0
ADEM/Encephalitis	1 (0.00) [1]	0	0	0
Generalized convulsive seizure	25 (0.12) [27]	1 (0.006) [1]	0	22 (0.10) [22]
Anaphylaxis	1 (0.00) [1]	0		
Thrombocytopenia	1 (0.00) [1]	0	0	4 (0.02) [4]
Juvenile chronic arthritis	0	0	0	1 (0.00) [1]
Etiology-confirmed meningitis (including bacterial-confirmed)	1 (0.00) [1]	0	0	2 (0.01) [2]
Secondary safety endpoint analyses				
Meningitis: etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	11 (0.1) [11]	1 (0.1) [1]	0	15 (0.1) [15]
Malaria - any	9026 (43.7) [20825]	314 (17.4) [731]	81 (31.9) [136]	10277 (46.3) [27071]
Malaria - cerebral	10 (0.05) [10]	0	0	14 (0.1) [14]
Death - any	315 (1.5)	41 (2.3)	2 (0.8)	325 (1.5)
Females	162 (1.6)	21 (2.3)	0	161 (1.4)
Males	153 (1.5)	20 (2.2)	2 (1.6)	164 (1.5)
Hospitalization - malaria	1426 (6.9) [1754]	73 (4.0) [92]	18 (7.1) [21]	1758 (7.9) [2193]
Anemia	1703 (8.25)	75 (4.15)	16 (6.30)	2087 (9.40)
Severe anemia	330 (1.60)	18 (1.00)	2 (0.79)	381 (1.72)

ADEM = Acute Disseminated Encephalomyelitis; AESI = adverse events of special interest

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of participants

n = number of participants reporting at least once the symptom

n* = at least one symptom experienced (regardless of the Term)

Table 1.2 Summary of safety: cumulative number of confirmed cases for the main endpoints - Enhanced Hospitalization Surveillance - Analysis Set

	Exposed cluster		Unexposed cluster	
	Vaccinated (N=5791)	Unvaccinated (N=11487)	Vaccinated (N=161)	Unvaccinated (N=15306)
	n (%) [n*]	n (%) [n*]	n (%) [n*]	n (%) [n*]
Primary endpoint analyses				
AESI	8 (0.14) [9]	6 (0.05) [9]	1 (0.62) [2]	12 (0.08) [12]
..Intussusception	2 (0.03) [2]	1 (0.01) [1]	0	4 (0.03) [4]
..Renal insufficiency	0	1 (0.01) [1]	0	0
ADEM/Encephalitis	1 (0.02) [1]	0	0	1 (0.01) [1]
Generalized convulsive seizure	6 (0.10) [6]	5 (0.04) [7]	2 (1.24) [2]	5 (0.03) [5]
Thrombocytopenia	0	0	0	2 (0.01) [2]
Etiology-confirmed meningitis (including bacterial-confirmed)	0	1 (0.01) [1]	0	1 (0.01) [1]
Secondary safety endpoint analyses				
Meningitis: etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	2 (0.03) [2]	2 (0.02) [2]	0	7 (0.05) [7]
Malaria - any	480 (8.3) [614]	1243 (10.8) [1604]	11 (6.8) [13]	1501 (9.8) [1836]
Malaria - cerebral	1 (0.02) [1]	3 (0.03) [3]	0	2 (0.01) [2]
Death - any	76 (1.3)	179 (1.6)	1 (0.6)	151 (1.0)
Females	39 (1.5)	80 (1.5)	0	67 (1.0)
Males	37 (1.2)	99 (1.6)	1 (1.1)	84 (1.0)

ADEM = Acute Disseminated Encephalomyelitis; AESI = adverse events of special interest

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of participants

n = number of participants reporting at least once the symptom

n* = at least one symptom experienced (regardless of the Term)

A summary of the incidence of confirmed cases during the at-risk period for the main endpoints after RTS,S/AS01_E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01_E vaccine/virtual Dose 4 are summarized for participants in Active Surveillance in [Table 1.3](#).

Table 1.3 Summary safety: Incidence Rate and Incidence Rate Ratio of confirmed cases during at-risk period after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 for the main endpoints – Cluster design comparison - Active Surveillance – Analysis Set

		After RTS,S/AS01E vaccine/virtual full schedule*			After RTS,S/AS01E vaccine/virtual Dose 4		
Endpoint / <i>at-risk period</i>		IR per 100 000 PYs (95% CI) [n]	Crude IRR (95% CI), p-value	IRR adjusted on country (95% CI), p-value	IR per 100 000 PYs (95% CI) [n]	Crude IRR (95% CI), p-value	IRR adjusted on country (95% CI), p-value
Primary endpoint							
AESI							
Generalized convulsive seizure / 2 weeks	Vacc	264.2 (114.1-520.5) [8]	NE	NE	339.2 (41.1-1225.4) [2]	NE	NE
	Unvacc	0 (0-111.6) [0]			0 (0-526.2) [0]		
Intussusception / 2 weeks	Vacc	0 (0-121.8) [0]	NE	NE	0 (0-625.6) [0]	NE	NE
	Unvacc	30.2 (0.8-168.5) [1]			0 (0-526.2) [0]		
Thrombocytopenia / 6 weeks	Vacc	0 (0-46.2) [0]	NE	NE	0 (0-218.5) [0]	NE	NE
	Unvacc	11.8 (0.3-65.6) [1]			49.9 (1.3-278.0) [1]		
Etiology-confirmed meningitis (incl. bacterial-confirmed) / 12 months	Vacc	2.6 (0.1-14.2) [1]	1.06 (0.07-16.98), 0.966	0.99 (0.06-15.85), 0.995	0 (0-25.9) [0]	NE	NE
	Unvacc	2.4 (0.1-13.4) [1]			0 (0-22.0) [0]		
Secondary safety endpoints							
Meningitis-protocol defined / 12 months	Vacc	20.4 (8.8-40.2) [8]	0.71 (0.29-1.73), 0.449	0.66 (0.27-1.61), 0.359	14.0 (1.7-50.7) [2]	1.17 (0.17-8.34), 0.872	1.00 (0.14-7.10), 0.999
	Unvacc	28.8 (14.9-50.4) [12]			12.0 (1.4-43.2) [2]		
Malaria – cerebral / 12 months	Vacc	12.8 (4.1-29.8) [5]	0.76 (0.24-2.39), 0.637	0.71 (0.22-2.23), 0.555	14.0 (1.7-50.7) [2]	0.59 (0.11-3.21), 0.539	0.52 (0.10-2.86), 0.455
	Unvacc	16.8 (6.8-34.6) [7]			23.9 (6.5-61.2) [4]		
Death – all-cause / 12 months	Vacc	502.5 (434.8-577.8) [197]	0.93 (0.76-1.12), 0.428	0.93 (0.76-1.12), 0.432	259.7 (182.8-357.9) [37]	0.91 (0.59-1.39), 0.649	0.93 (0.60-1.42), 0.726
	Unvacc	542.9 (474.4-618.5) [226]			286.9 (211.5-380.4) [48]		
Females	Vacc	497.7 (403.2-607.8) [96]	0.94 (0.71-1.23), 0.643	0.94 (0.71-1.23), 0.638	229.0 (130.9-371.9) [16]	0.84 (0.44-1.59), 0.588	0.86 (0.46-1.64), 0.652
	Unvacc	531.0 (436.8-639.4) [111]			273.2 (173.2-409.9) [23]		
Males	Vacc	507.1 (413.0-616.2) [101]	0.91 (0.70-1.19), 0.509	0.92 (0.70-1.20), 0.527	289.1 (179.0-442.0) [21]	0.96 (0.54-1.72), 0.894	0.98 (0.55-1.76), 0.954
	Unvacc	554.9 (458.1-666.1) [115]			300.8 (194.6-444.0) [25]		

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

Vacc = participants vaccinated with RTS,S/AS01E vaccine; Unvacc = participants not vaccinated with RTS,S/AS01E vaccine; AESI = adverse events of special interest

n = number of participants with at least one event reported / number of deaths during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Death: Incidence rate (IR) per 100 000 person-years = number of deaths per 100 000 person-years estimated as $n / \text{Person-years}$

AESI/Meningitis/Malaria: Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as $n / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

For analyses of effectiveness of participants in Active Surveillance, due to the imbalance in population size in RTS,S/AS01_E vaccinated (20 641) vs unvaccinated (1807) participants in exposed clusters, vaccine effectiveness for Direct Effect estimations should be interpreted with caution. A summary of vaccine effectiveness for Total Effect, which compares unvaccinated participants in unexposed clusters (22 210) to vaccinated participants in exposed clusters (20 641), are summarized for the main effectiveness and impact analysis as more robust estimates which took into account a larger portion of the enrolled population ([Table 1.4](#)):

- One year after Dose 4 of RTS,S/AS01_E evaluated from Dose 3 (i.e., follow-up time from Dose 3 until 12 months after Dose 4), for children who have received the 3 doses before 12 months of age and Dose 4 of RTS,S/AS01_E before 30 months of age.

In addition, results are also summarized for effectiveness and impact of RTS,S/AS01_E 2 years after Dose 4, estimated only among participants who had completed all 4 doses/virtual doses according to the vaccination schedule:

- Two years after Dose 4 of RTS,S/AS01_E, for children who received it before 30 months of age, evaluated from the Dose 4.

Table 1.4 Summary of vaccine effectiveness (Total Effect) of RTS,S/AS01E vaccine on incidence of main endpoints 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance - Impact Analysis Set

Effectiveness endpoint	Vaccination status	1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3			2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4		
		IR per 100 000 PYs (95% CI)	Crude IRR (95% CI) p-value	IRR adjusted on country (95% CI) p-value	IR per 100 000 PYs (95% CI)	Crude IRR (95% CI) p-value	IRR adjusted on country (95% CI) p-value
Any malaria	Vacc	38099.0 (37385.2-38823.1)	0.86 (0.84-0.88), <0.001	0.84 (0.81-0.87), <0.001	33065.0 (32353.1-33788.7)	0.91 (0.89-0.94), <0.001	0.92 (0.89-0.95), <0.001
	Unvacc	44194.3 (43536.4-44859.7)			36208.9 (35561.4-36865.3)		
Severe malaria	Vacc	369.0 (301.8-446.7)	0.73 (0.58-0.92), 0.009	0.71 (0.56-0.90), 0.005	455.8 (375.7-548.0)	0.89 (0.70-1.13), 0.348	0.86 (0.67-1.09), 0.204
	Unvacc	506.0 (437.8-581.8)			511.0 (436.6-594.4)		
Hospitalization – Malaria	Vacc	2793.6 (2602.8-2994.8)	0.78 (0.72-0.86), <0.001	0.75 (0.69-0.82), <0.001	2513.1 (2319.6-2718.4)	0.80 (0.72-0.88), <0.001	0.78 (0.70-0.86), <0.001
	Unvacc	3564.9 (3379.8-3757.5)			3144.9 (2956.1-3342.6)		
Death – all causes*	Vacc	112.4 (76.9-158.7)	0.91 (0.58-1.43), 0.687	0.94 (0.60-1.47), 0.793	238.0 (181.2-307.0)	1.00 (0.72-1.41), 0.985	1.04 (0.74-1.45), 0.840
	Unvacc	123.3 (90.9-163.5)			237.2 (187.5-296.1)		
Death - malaria	Vacc	38.7 (19.3-69.2)	0.94 (0.44-2.03), 0.876	0.95 (0.44-2.06), 0.903	84.7 (52.4-129.5)	0.93 (0.53-1.62), 0.794	0.95 (0.54-1.66), 0.846
	Unvacc	41.1 (23.5-66.7)			91.2 (61.6-130.3)		
		Prevalence (95% CI)	Crude OR (95% CI) p-value	OR adjusted on country (95% CI) p-value	Prevalence (95% CI)	Crude OR (95% CI) p-value	OR adjusted on country (95% CI) p-value
Anemia	Vacc	0.069 (0.064-0.073)	0.77 (0.71-0.84), <0.001	0.74 (0.68-0.81), <0.001	0.037 (0.034-0.040)	0.69 (0.61-0.77), <0.001	0.66 (0.59-0.74), <0.001
	Unvacc	0.087 (0.083-0.092)			0.053 (0.049-0.056)		
Severe anemia	Vacc	0.011 (0.009-0.013)	0.81 (0.66-1.00), 0.054	0.79 (0.64-0.97), 0.027	0.006 (0.005-0.008)	0.70 (0.53-0.91), 0.008	0.68 (0.52-0.88), 0.004
	Unvacc	0.014 (0.012-0.016)			0.009 (0.008-0.011)		

*All-cause death includes deaths associated with accidents and poisonings

Vacc = participants vaccinated with RTS,S/AS01E vaccine; Unvacc = participants not vaccinated with RTS,S/AS01E vaccine

Person-Years = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years

Adjusted IR ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

P-value = p-value for two-sided test H0: adjusted odds ratio = 1 (logistic model)

Prevalence = percentage of participants with at least one event (n/N)

OR adjusted = estimation of odds ratio using Binary Logistic regression model with Country as a fixed effect and unvaccinated as reference status

95% CI for prevalence = 95% confidence interval (Exact Binomial Method); LL = Lower Limit, UL = Upper Limit; 95% CI for adjusted OR = 95% confidence interval (logistic model)

Analyses of co-primary objectivesAESI

- Few cases of AESI were reported during the at-risk period after the full/virtual vaccination (i.e., combining the RTS,S/AS01_E 4 doses/virtual doses): 8 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group (at-risk period 2 weeks: IR 264.2 [95% CI: 114.1-520.5]) per 100 000 person-years [PYs]), 1 case of intussusception in the RTS,S/AS01_E unvaccinated group (at-risk period 2 weeks; IR 30.2 [95% CI: 0.8-168.5] per 100 000 PYs) and 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group (at-risk period 6 weeks; IR 11.8 [95% CI: 0.3-65.6] per 100 000 PYs). The low number of cases of each AESI, and cases not occurring in both the vaccinated and unvaccinated groups, prevented calculation of the IRR.
- Few cases of AESI were reported during the at-risk period after Dose 4/virtual Dose 4: 2 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group (at-risk period 2 weeks: IR 339.2 [95% CI: 41.1-1225.4] per 100 000 PYs) and 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group (at-risk period 6 weeks; IR 49.9 [95% CI: 1.3-278.0] per 100 000 PYs). The low number of cases of each AESI, and cases not occurring in both the vaccinated and unvaccinated groups, prevented calculation of the IRR.

Etiology-confirmed meningitis

- During the at-risk period of 12 months after the full/virtual vaccination, 2 cases of etiology-confirmed meningitis were reported: 1 case in the RTS,S/AS01_E vaccinated group and 1 case in the RTS,S/AS01_E unvaccinated group (crude IRR 1.06 [95% CI: 0.07-16.98; p=0.966]; IRR adjusted for country 0.99 [95% CI: 0.06-15.85; p=0.995]).
- No cases of etiology-confirmed meningitis were reported during the at-risk period of 12 months after Dose 4/virtual Dose 4.

Analyses of secondary safety objectivesMeningitis

- No statistically significant difference in IR of protocol defined meningitis (etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis) during the at-risk period of 12 months after RTS,S/AS01_E vaccine/virtual full (4-dose) schedule was observed:
IR 20.4 (95% CI: 8.8-40.2) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 28.8 (95% CI: 14.9-50.4) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.71 (95% CI: 0.29-1.73; p=0.449); IRR adjusted on country 0.66 (95% CI: 0.27-1.61; p=0.359).

- No statistically significant difference in IR of protocol defined meningitis during an at-risk period of 12 months after RTS,S/AS01_E vaccine/virtual Dose 4 was observed:
IR 14.0 (95% CI: 1.7-50.7) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 12.0 (95% CI: 1.4-43.2) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 1.17 (95% CI: 0.17-8.34; p=0.872); IRR adjusted on country 1.00 (95% CI: 0.14-7.10; p=0.999).

Cerebral malaria

- During an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual full (4-dose) schedule, 5 cases of cerebral malaria were reported in the RTS,S/AS01_E vaccinated group and 7 cases in the RTS,S/AS01_E unvaccinated group:
IR 12.8 (95% CI: 4.1-29.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 16.8 (95% CI: 6.8-34.6) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.76 (95% CI: 0.24-2.39; p=0.637); IRR adjusted on country 0.71 (95% CI: 0.22-2.23; p=0.555).
- During an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual Dose 4, 2 cases of cerebral malaria were reported in the RTS,S/AS01_E vaccinated group and 4 cases in the RTS,S/AS01_E unvaccinated group:
IR 14.0 (95% CI: 1.7-50.7) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 23.9 (95% CI: 6.5-61.2) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.59 (95% CI: 0.11-3.21; p=0.539); IRR adjusted on country 0.52 (95% CI: 0.10-2.86; p=0.455).

Death

- There was no statistically significant difference in all-cause mortality IR between RTS,S/AS01_E vaccinated and unvaccinated participants (overall and by gender) and overall death IR due to “other AE” (safety event different from the pre-defined AESI, meningitis and malaria) during an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual full (4-dose) schedule:

All-cause death:

IR 502.5 (95% CI: 434.8-577.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 542.9 (95% CI: 474.4-618.5) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.93 (95% CI: 0.76-1.12; p=0.428)
IRR adjusted on country 0.93 (95% CI: 0.76-1.12; p=0.432).

Females:

Crude IRR 0.94 (95% CI: 0.71-1.23; p=0.643)
IRR adjusted on country 0.94 (95% CI: 0.71-1.23; p=0.638).

Males:

Crude IRR 0.91 (95% CI: 0.70-1.19; p=0.509)
IRR adjusted on country 0.92 (95% CI: 0.70-1.20; p=0.527).

Death – “Other AE”:

IR 408.1 (95% CI: 347.3-476.5) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 430.0 (95% CI: 369.3-497.8) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.95 (95% CI: 0.77-1.17; p=0.631)

IRR adjusted on country 0.96 (95% CI: 0.77-1.18; p=0.677).

- There was no statistically significant difference in all-cause death (overall and by gender) IR between vaccinated and unvaccinated participants and overall death IR due to “other AE” during an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual Dose 4:

All-cause death:

IR 259.7 (95% CI: 182.8-357.9) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 286.9 (95% CI: 211.5-380.4) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.91 (95% CI: 0.59-1.39; p=0.649)

IRR adjusted on country 0.93 (95% CI: 0.60-1.42; p=0.726).

Females:

Crude IRR 0.84 (95% CI: 0.44-1.59; p=0.588)

IRR adjusted on country 0.86 (95% CI: 0.46-1.64; p=0.652).

Males:

Crude IRR 0.96 (95% CI: 0.54-1.72; p=0.894)

IRR adjusted on country 0.98 (95% CI: 0.55-1.76; p=0.954).

Death – “Other AE”:

IR 154.4 (95% CI: 96.8-233.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 185.3 (95% CI: 125.9-263.0) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.83 (95% CI: 0.48-1.44; p=0.513)

IRR adjusted on country 0.87 (95% CI: 0.50-1.50; p=0.605).

Analyses of secondary impact and effectiveness objectivesMalaria

- The vaccine was effective against any and severe malaria during the 12 month follow-up period after Dose 4 from Dose 3:
Any malaria
 Crude estimates: 14% (95% CI: 12-16), p<0.001 (Overall Effect, Total Effect); 16% (95% CI: 8-24), p<0.001 (Indirect Effect)
 Adjusted on country: 16% (95% CI: 13-19), p<0.001 (Overall Effect, Total Effect); 24% (95% CI: 13-34), p<0.001 (Indirect Effect)

- Severe malaria
Crude estimates: 26% (95% CI: 6-41), $p=0.012$ (Overall Effect); 27% (95% CI: 8-42), $p=0.009$ (Total Effect)
Adjusted on country: 28% (95% CI: 9-43), $p=0.006$ (Overall Effect); 29% (95% CI: 10-44), $p=0.005$ (Total Effect).
- The vaccine was effective against any, but not severe, malaria during the 24 month at-risk period after Dose 4 from Dose 4:
Any malaria
Crude estimates: 9% (95% CI: 6-11), $p<0.001$ (Overall Effect, Total Effect); 11% (95% CI: 1-21), $p=0.038$ (Indirect Effect)
Adjusted on country: 9% (95% CI: 5-12), $p<0.001$ (Overall Effect); 8% (95% CI: 5-11), $p<0.001$ (Total Effect); 18% (95% CI: 5-29), $p=0.010$ (Indirect Effect).

Anemia

- The vaccine was effective against any and severe anemia during the 12 month follow-up period after Dose 4 from Dose 3:
Any anemia
Crude estimates: 22% (95% CI: 15-29), $p<0.001$ (Overall Effect); 23% (95% CI: 16-29), $p<0.001$ (Total Effect)
Adjusted on country: 26% (95% CI: 19-32), $p<0.001$ (Overall Effect, Total Effect).
Severe anemia
Adjusted on country: 19% (95% CI: 1-34), $p=0.044$ (Overall Effect); 21% (95% CI: 3-36), $p=0.027$ (Total Effect).
- The vaccine was effective against any and severe anemia during the 24 month follow-up period after Dose 4 from Dose 4:
Any anemia
Crude estimates: 31% (95% CI: 23-39), $p<0.001$ (Overall Effect, Total Effect)
Adjusted on country: 34% (95% CI: 26-41), $p<0.001$ (Overall Effect, Total Effect); 40% (95% CI: 5-63), $p=0.031$ (Indirect Effect).
Severe anemia
Crude estimates: 30% (95% CI: 9-46), $p=0.008$ (Overall Effect), 30% (95% CI: 9-47), $p=0.008$ (Total Effect)
Adjusted on country: 32% (95% CI: 12-48), $p=0.004$ (Overall Effect, Total Effect).

Hospitalization

- The vaccine was effective against hospitalizations due to malaria during the 12 month follow-up period after Dose 4 from Dose 3:
Hospitalizations due to malaria
Crude estimates: 42% (95% CI: 24-56), $p<0.001$ (Direct Effect); 19% (95% CI: 12-26), $p<0.001$ (Overall Effect); 22% (95% CI: 14-28), $p<0.001$ (Total Effect)
Adjusted on country: 36% (95% CI: 15-51), $p=0.002$ (Direct Effect); 23% (95% CI: 16-30), $p<0.001$ (Overall Effect); 25% (95% CI: 18-31), $p<0.001$ (Total Effect).

- The vaccine was effective against hospitalizations due to malaria during the 24 month follow-up period after Dose 4 from Dose 4:
Hospitalizations due to malaria
 Crude estimates: 20% (95% CI: 12-28), $p < 0.001$ (Overall Effect, Total Effect)
 Adjusted on country: 23% (95% CI: 15-30), $p < 0.001$ (Overall Effect); 22% (95% CI: 14-30), $p < 0.001$ (Total Effect); 41% (95% CI: 9-62), $p = 0.016$ (Indirect Effect).

Death

- The vaccine was effective against all-cause death only for Direct Effect during the 12 month follow-up period after Dose 4 from Dose 3:
 Crude estimates: 74% (95% CI: 34-90), $p = 0.005$ (Direct Effect)
 Adjusted on country: 78% (95% CI: 42-92), $p = 0.002$ (Direct Effect).
- The vaccine was not effective against all-cause death and death due to malaria during the 24 month follow-up period after Dose 4 from Dose 4.

Due to the low numbers of fatalities and imbalance in population size in RTS,S/AS01_E vaccinated vs unvaccinated participants in exposed clusters, vaccine effectiveness estimates for Direct Effect should be interpreted with caution.

Discussion

This Final Analysis included 44 998 children from Active Surveillance, uniformly distributed between exposed and unexposed clusters. In addition, 32 955 children were included from the Enhanced Hospitalization Surveillance cohort. The RTS,S/AS01_E vaccination coverage with at least 1 dose in the exposed clusters was 92.0% of participants in Active Surveillance, and 33.5% of participants in Enhanced Hospitalization Surveillance, the lower coverage in the latter cohort in part reflecting an older age group, with many not eligible for vaccination.

For the co-primary objectives, few cases of confirmed AESI and etiology-confirmed meningitis were reported in participants from Active Surveillance during the at-risk period. After the RTS,S/AS01_E vaccine/virtual full schedule (combining the RTS,S/AS01_E 4 doses/virtual doses), 8 cases of generalized convulsive seizure in the vaccinated group, 1 case of intussusception in the unvaccinated group and 1 case of thrombocytopenia in the unvaccinated group were reported. Of the 8 seizure cases in vaccinated participants, all cases occurred with events of pyrexia. Febrile convulsions are a known risk with RTS,S/AS01_E vaccination. Additionally, 5 cases reported concurrent infective events including pneumonia and gastroenteritis. The seizures did not recur in participants that received subsequent doses. One case also reported an event of status epilepticus, however, this was not witnessed by healthcare professionals and was reported to have spontaneously resolved, making it less likely to represent true status epilepticus. One case of etiology-confirmed meningitis was reported in each of the vaccinated and unvaccinated groups (crude IRR 1.06 [95% CI: 0.07-16.98], $p = 0.966$). During the at-risk period after RTS,S/AS01_E vaccine/virtual Dose 4, 2 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group, 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group and no etiology-confirmed meningitis cases were reported.

For suspected cases of meningitis, lumbar puncture was to be performed according to routine medical practice for examination of cerebrospinal fluid (CSF). However, in total 36/139 (25.9%) suspected meningitis cases had a CSF sample collected and 31/139 (22.3%) CSF samples were sent to a second line laboratory. Nonetheless, when considering protocol defined meningitis (etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis), no statistically significant difference in IR in RTS,S/AS01_E vaccinated vs unvaccinated groups was observed.

After the vaccine/virtual full (4-dose) schedule, there were 5 cases of cerebral malaria in RTS,S/AS01_E vaccinated and 7 cases in RTS,S/AS01_E unvaccinated children, yielding a crude IRR of 0.76 (95% CI: 0.24-2.39; $p=0.637$). The all-cause mortality IR was 502.5 (95% CI: 434.8-577.8) per 100 000 PY in vaccinated vs 542.9 (95% CI: 474.4-618.5) per 100 000 PY in unvaccinated children. Similar mortality rates were observed in vaccinated children in both genders (females: IR 497.7 [95% CI: 403.2-607.8]; males: IR 507.1 [95% CI: 413.0-616.2]).

Due to the imbalance in population size in RTS,S/AS01_E vaccinated vs unvaccinated participants in exposed clusters, vaccine effectiveness (Direct Effect) estimations should be interpreted with caution, therefore impact analyses of the Total Effect were summarized as more robust estimates which took into account a larger portion of the enrolled population. In the main analysis period 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3, the IR of any malaria was 38 099 (95% CI: 37 385-38 823) per 100 000 PY in vaccinated vs 44 194 (95% CI: 43 536-44 860) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 14% (95% CI: 12-16; $p<0.001$). The IR of severe malaria was 369.0 (95% CI: 301.8-446.7) per 100 000 PY in vaccinated vs 506.0 (95% CI: 437.8-581.8) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 27% (95% CI: 8-42; $p=0.009$). IR of malaria-attributed hospitalization was 2793.6 (95% CI: 2602.8-2994.8) per 100 000 PY in vaccinated vs 3564.9 (95% CI: 3379.8-3757.5) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 22% (95% CI: 14-28; $p<0.001$). IRs of all-cause mortality were 112.4 (95% CI: 76.9-158.7) per 100 000 PY in vaccinated vs 123.3 (95% CI: 90.9-163.5) per 100 000 PY in unvaccinated children, resulting in a statistically non-significant crude vaccine effectiveness of 9% (95% CI: -43-42; $p=0.687$). ORs of anemia were 0.069 (95% CI: 0.064-0.073) per 100 000 PY in vaccinated vs 0.087 (95% CI: 0.083-0.092) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 23% (95% CI: 16-29; $p<0.001$). Vaccine effectiveness values for crude estimates were similar to country-adjusted estimates.

Exploratory analyses further confirmed robustness of findings. After adjustment for measured confounding using propensity score overlap weighting, the vaccine effectiveness estimate was 33%, $p<0.001$ (and 32%, $p<0.001$ when additionally adjusted on country), representing estimated Total Effect among individuals with overlapping baseline characteristics.

Conclusion

Safety signals observed in Phase 3 were not confirmed by the EPI-MAL-003 Final Analysis, and no new signals were identified. Meningitis events were rare and evenly distributed over RTS,S/AS01_E vaccinated and unvaccinated groups. Cerebral malaria events were rare and occurred both in RTS,S/AS01_E vaccinated and unvaccinated groups. Deaths occurred at similar rates in males and females. There was no evidence of an association between vaccine exposure and any prespecified AESI. Over 1 year after the full (4-dose) vaccination schedule, a positive impact against hospitalizations due to malaria, any and severe malaria, and hospitalizations due to anemia was observed.

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Names and affiliations of principal investigators

Refer to Modular Appendices for the list of investigators.

2. LIST OF ABBREVIATIONS

ADEM	Acute disseminated encephalomyelitis
AE	Adverse event
AESI	Adverse event of special interest
AME	Africa and Middle East
AMP	Agence de Médecine Préventive
AS	Active surveillance
AS01	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome
ATC	Anatomical Therapeutic Chemical
ATP	According to protocol
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CS	Circumsporozoite
CSF	Cerebrospinal fluid
DTP	Diphtheria, tetanus, pertussis trivalent vaccine
DTP/HepB/Hib	Diphtheria-tetanus-whole-cell pertussis-hepatitis B-Haemophilus influenza type b pentavalent vaccine
eCRF	Electronic case report form
EEP	External expert panel
EHS	Enhanced hospitalization surveillance
EMA	European Medicines Agency
EPI	Expanded program on immunization
EU	European Union
EU PAS	European Union electronic register of post-authorization studies
EXP	Exposed
GCP	Good clinical practice
GH	Ghana
GPP	Good pharmacoepidemiology practices
GSK	GlaxoSmithKline Biologicals SA
GVP	Good pharmacovigilance practices
Hb	Hemoglobin

HDSS	Health and demographic surveillance system
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IR	Incidence rates
IRB	Institutional Review Board
IRR	Incidence rate ratio
KE	Kenya
KHRC	Kintampo Health Research Centre
LAR	Legally acceptable representative
LL	Lower limit
MA	Malawi
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MPL	3-O-desacyl-4'-monophosphoryl lipid A (produced by GSK)
MTI	Malaria transmission intensity
MVIP	Malaria Vaccine Implementation Program
NHRC	Navrongo Health Research Centre
OR	Odds ratio
PASS	Post-authorization safety study
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
PT	Preferred term
PY	Person-years
QS-21	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenesis Inc., a Delaware, USA corporation)
RAFT (HUG)	Réseau en Afrique Francophone pour la Télémédecine (Hôpitaux Universitaire Genève)
RDT	Rapid diagnostic test
RMP	Risk management plan
RTS	Hybrid protein comprising HBs (hepatitis B surface antibody) and CS protein portions
RTS,S	Particulate antigen, containing both RTS and HBs antigen (S)

	proteins
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SOC	System organ class
SPAP PC	Safety Post Approval Plan Partnership Committee
SQI	Serious quality issue
TCS	Tata Consultancy Services
UNEXP	Unexposed
UL	Upper limit
WITS DIH	Wits University diagnostic innovation hub
WHO	World Health Organization

3. ETHICS

3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center IEC or IRB.

3.2. Ethical conduct of the study

Overall, this study was conducted in accordance with the ICH guideline for GCP, GPP [ISPE, 2015], other applicable guidelines, all applicable participant privacy requirements and the guiding principles of the Declaration of Helsinki.

During the course of the study, whenever potential issues with regard to the conduct of the study were identified, either via site monitoring activities or brought to GSK Biologicals' attention by other oversight mechanisms, these issues were investigated and appropriate corrective/preventive actions where possible were taken. Please refer to Section 10.10 for details.

3.3. Participant information and consent

Written informed consent was obtained from each participant's parent/LAR prior to the performance of any study-specific procedures. Electronic case report forms were provided for each participant's data to be recorded.

Refer to Protocol Section 9.2.7.1.1 and Section 9.2.7.2.1 for the informed consent process.

4. INVESTIGATORS

Refer to Modular Appendices for the list of investigators.

5. OTHER RESPONSIBLE PARTIES

Supplier	Outsourced Activity
WITS DIH	Laboratory testing and services
IQVIA	Site monitoring and management
SYNEOS Health	Clinical data management services
Business & Decision Life Sciences/Enovalife	Laboratory study management, Medical Data Reviewer activities
TCS	Administrative support
ICON	Study management support and data management services
4Clinics	Biostatistics and statistical programming
Keyrus/Alsinova	Biostatistics and statistical programming
AMP	Pharmacovigilance training
RAFT (HUG)	Site training and diagnosis support
Parexel	Real time health alert information system
Visual Response	Event organizer (SPAP PC meetings, Investigators and monitors meetings)
ThermoFisher	Study supplies/ancillaries

AMP = Agence de Médecine Préventive; RAFT (HUG) = Réseau en Afrique Francophone pour la Télémédecine (Hôpitaux Universitaire Genève); SPAP PC = Safety Post Approval Plan Partnership Committee; TCS = Tata Consultancy Services; WITS DIH = Wits University diagnostic innovation hub

6. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Q1 2019	Q1 2019	-
End of data collection	Q1 2025	29 September 2025	-
Registration in the EU PAS register	-	23 March 2019 Updated 17 March 2023	-
Study progress reports	1 progress report every 6 months	20 December 2019 06 May 2020 24 November 2020 29 April 2021 16 November 2021 28 April 2022 30 November 2022 02 May 2023 23 November 2023 06 May 2024 02 December 2024 05 May 2025	-
Protocol	Q4 2017	11 October 2017	-
Protocol Amendment 1	-	24 April 2019	-
Protocol Amendment 2	-	15 October 2020	-
Protocol Amendment 3	-	24 October 2024	-
Interim report	Q2 2023	14 August 2024	-
Final report	Q1 2026	06 May 2026	-

EU PAS = European Union electronic register of post-authorization studies; Q1/Q2/Q4 – first/second/fourth quarter

7. RATIONALE AND BACKGROUND

7.1. Background

GSK Biologicals has developed a pre-erythrocytic *P. falciparum* malaria vaccine, RTS,S/AS01_E, for routine immunization of children living in malaria-endemic countries of sub-Saharan Africa. RTS,S/AS01_E is the first vaccine to be implemented for the prevention of malaria and it is the first AS01-adjuvanted vaccine to be implemented in the pediatric population.

The vaccine antigen, RTS,S, consists of a portion of the *P. falciparum* CS protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S). The antigen is adjuvanted with the AS01_E Adjuvant System, which consists of 2 immune enhancers MPL and QS-21, in a liposomes suspension.

In 2015, RTS,S/AS01_E received a positive scientific opinion from the EMA for use outside the EU [[European Medicines Agency](#), 2015]. In the frame of the MVIP, commissioned by the WHO, a comprehensive post-approval plan (comprising 3 observational studies) was developed by GSK to further evaluate the safety, effectiveness and impact of RTS,S/AS01_E in the context of its real-life implementation [[Praet](#), 2022], whereby the RTS,S/AS01_E vaccine would be introduced in selected areas in 3 sub-Saharan Africa countries by their respective routine national immunization programs [[WHO](#), 2016].

7.2. Rationale

The safety profile of RTS,S/AS01_E has been evaluated during pre-authorization clinical trials conducted mainly in sub-Saharan Africa [[Nadeem](#), 2022]. The current EPI-MAL-003 study aimed to further evaluate the safety of the vaccine during initial implementation by monitoring for rare AEs such as protocol defined AESI (potentially associated with RTS,S/AS01_E, historically associated with vaccines other than RTS,S/AS01_E, or which may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines), for other AE leading to hospitalization and for meningitis (potential risk).

In addition to the efficacy data provided by the MALARIA-055 pre-authorization clinical trial [[The RTS,S Clinical Trials Partnership](#), 2015], evidence on the impact and effectiveness of RTS,S/AS01_E when administered post-implementation most close to routine medical practice was needed. Although primarily designed as a post-implementation safety study to detect potential rare and uncommon AEs following vaccination with RTS,S/AS01_E, the secondary objectives of EPI-MAL-003 also aimed to evaluate the effectiveness (Direct Effect) and impact (Indirect, Total and Overall Effects) of RTS,S/AS01_E when administered in settings similar to routine medical practice in sub-Saharan Africa.

It is important to note that background data on AEs are limited for malaria-endemic countries in sub-Saharan Africa. This makes the assessment of risks, potentially associated with the new vaccine following its implementation, challenging. More specifically, the incidence and onset of autoimmune diseases and some of the other AESI are not known for African populations. Thus, an epidemiological study (EPI-MAL-002) to collect AESI data was conducted before vaccine implementation. This pre-implementation study EPI-MAL-002 measured the baseline incidence of AESI, other AE leading to hospitalization, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, was also estimated. The results for the temporal (before-after comparison with EPI-MAL-002) comparisons of the occurrence of adverse and malaria events between RTS,S/AS01_E vaccinated and unvaccinated participants living in exposed or unexposed clusters located in sub-Saharan Africa countries are available in the EPI-MAL-003 Interim Report (14 August 2024) [Haine, 2025; Ndeketa, 2026]. In addition, EPI-MAL-005 was conducted in parallel to EPI-MAL-002 and EPI-MAL-003, to measure MTI and record malaria control interventions at the community level in the study site areas on a yearly basis, results for which are included in exploratory endpoint analyses in this EPI-MAL-003 Final Study Report.

Sites were selected for EPI-MAL-002, -003 and -005 based on the existence of HDSS or equivalent surveillance systems within MVIP selected areas. The capacity of the study sites to detect AESI and meningitis was strengthened early in EPI-MAL-002, to ensure improved sensitivity and specificity of case detection and to enable standardized calculation of incidence rates.

The current EPI-MAL-003 study targeted enrolling approximately 45 000 children in Active Surveillance; 22 500 children in the exposed clusters; with a minimum of 20 250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2250 unvaccinated children for evaluation of effectiveness and impact (assuming that 80% of the 22 500 study participants in the exposed clusters will receive 3 doses of RTS,S/AS01_E, 10% will receive 1 or 2 doses and 10% will not have any dose); 22 500 in the unexposed clusters for evaluation of vaccine safety, effectiveness and impact. Considering the limited number of sites where the safety study could have been performed, and following feasibility assessment with respect to recruitment target and practical conduct of the study, GSK considered that a sample size of approximately 45 000 study participants was the highest possible.

GSK acknowledges the limitations of these studies in terms of sample size, the difficulties to diagnose and characterize rare diseases such as autoimmune diseases in young children, the potential biases introduced by the sequential generation of data between the EPI-MAL-002 and EPI-MAL-003 studies, as well as the unpredictable occurrence of meningitis cases and paucity of data on other rare diseases of special interest in those settings.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To estimate the incidence of AESI¹ in children vaccinated with RTS,S/AS01_E.
- To estimate the incidence of etiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E.

8.2. Secondary objectives

8.2.1. Safety

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E):

- To estimate the incidence of etiology-confirmed and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of etiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To estimate the incidence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- To estimate the incidence of other AE leading to hospitalization*.
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.
- To describe the causes of hospitalization (including AESI, other AE, meningitis and malaria)*.
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following each dose of RTS,S/AS01_E*.

¹ Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode (HHE), generalised convulsive seizure
Intussusception, hepatic failure or renal insufficiency
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E)^{**}:

- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To assess the potential association between vaccination and meningitis by comparing the incidence of etiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and meningitis by comparing the incidence of etiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and meningitis by comparing the incidence of etiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and AESI by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and other AE leading to hospitalization by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.

* Analyses of Other AE leading to hospitalization, cause of hospitalization and incidence of febrile convulsions were only conducted for the Interim Analysis and not for the Final Analysis.

** Before-after design analyses using data from the EPI-MAL-002 study were only conducted for the Interim Analysis and not for the Final Analysis.
See Protocol Amendment 3 for the rationale.

8.2.2. Effectiveness and impact

- To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria diagnosed by RDT and/or microscopy.
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on:
 - the prevalence of anemia among hospitalized children.
 - the incidence of hospitalizations attributed to malaria (including *P. falciparum*).
 - the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]) overall and by gender.

9. AMENDMENTS AND UPDATES

The protocol was amended 3 times. A summary of the rationale for the amendments is provided in the following table; for details, please refer to Annex 7 of Protocol Amendment 3.

Protocol Amendment Number	Date	Rationale/background for key changes
1	24 April 2019	• Due to the delayed RTS,S/AS01_E vaccine implementation in Malawi in the EPI-MAL-002 study, baseline data were compromised for the before/after comparisons in this country in EPI-MAL-003. The EPI-MAL-003 sample size of the before/after comparison was updated, reference to EPI-MAL-002 study conduct in Malawi was removed and clarifications were provided in other sections.
2	15 October 2020	• The co-primary study objectives were revised to focus on events classified as identified risk (febrile convulsion) or potential risk (meningitis, cerebral malaria) as per the <i>Mosquirix</i> RMP, and the study objective 'other AEs leading to hospitalization' was changed to a secondary objective. • Due to the possible ambiguity of the term "other AEs leading to hospitalization or death", "or death" was removed to clarify the intent to monitor all hospitalizations due to other AEs including fatal ones which only occurred in the hospital. • The EHS eligibility criterion was revised to include only participants who were at least 6 weeks and <5 years of age to avoid the collection of events related to the perinatal period (except foot positional deformation as birth defect). • The MVIP was considering implementing the malaria vaccine in unexposed clusters as from 2023, directly impacting the temporal (before/after) and concurrent (exposed vs unexposed clusters) comparisons. EHS recruitment was therefore terminated on 31 October 2022 in sites that were not involved in EPI-MAL-002; study conclusion was conducted in a timely manner for enrolled participants in those sites.
3	24 October 2024	Protocol Amendment 3 reflects the findings of the MVIP [WHO, 2023], by simplifying the final analyses of the study as follows: • The EPI-MAL-002 study included analysis of potential risk factors for AESI, etiology-confirmed meningitis, cerebral malaria and death. Due to the low number of events, the value of these analyses was considered to be limited for EPI-MAL-003 and they were removed from the Final Analysis.

Protocol Amendment Number	Date	Rationale/background for key changes
		- All-cause hospitalization was assessed and reported following Phase 3 evaluation [The RTS,S Clinical Trials Partnership, 2015]. Analyses of "Other causes leading to hospitalization" in EPI-MAL-003 was considered to not be required and was removed from the Final Analysis. - The data from 12 clusters was to be used in the cluster randomized design which compares to only 3 clusters in the before-after analysis using data from the EPI-MAL-002 study. The before-after design analyses was considered to be prone to biases compared to the temporaneous cluster randomized design, which has a much larger enrolled population available for analyses, therefore these analyses were removed from the Final Analysis. - Febrile convulsion was a recognized AESI of RTS,S/AS01_E during Phase 3 evaluation [Guerra Mendoza, 2019], is included in the RMP as an accepted risk, and is included in the <i>Mosquirix</i> label as an uncommon AE. As this is an accepted risk and there is no proposal to remove febrile convulsions from the label, there was no requirement for further analyses of febrile convulsion, which was removed from the Final Analysis. As exposure data to RTS,S/AS01_E in the EHS population was missing, or uncertain, for approximately 70% of enrolled children of eligible age for vaccination, comparison of vaccinated vs unvaccinated groups would likely introduce substantial bias, and preclude any meaningful analyses. As the Interim Analysis results were reassuring - safety signals were not confirmed and there was impact on all-cause mortality and malaria-related mortality with no gender imbalance - revisions to the protocol were made to address the concerns over the vaccination status data for the EHS cohort as follows: - The EHS cohort data was only to be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality). - The EHS population will not be included in estimates of incidence rates and effectiveness and impact analyses in the Final Analysis. - Following site Ethics Committee approval of Protocol Amendment 3, enrollment to EHS and data collection was to be stopped (last participant enrolled 13 June 2025), with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for participants diagnosed with an AESI, meningitis or cerebral malaria. The initial recommended age for the administration of the fourth dose was 22 months in Malawi and 24 months in Ghana and Kenya, though much older children received Dose 4. For unvaccinated participants, the planification of home visits were based on the recommended vaccination schedule. Therefore, for the calculation of the study end per site, a maximum age of 30 months for Dose 4 (virtual Dose 4) was used to ensure an equivalent surveillance period, and limit the age gap, between vaccinated and unvaccinated participants. The definition of the study end was revised as follows: study end per site will occur when the last child enrolled in AS has accrued a total follow-up period of 24 months after the fourth dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) given at a maximum age of 30 months.

AE = adverse event; AESI = adverse events of special interest; AS = active surveillance; EHS = enhanced hospitalization surveillance; MVIP = Malaria Vaccine Implementation Program; RMP = risk management plan

10. RESEARCH METHODS

10.1. Study design

- EPI-MAL-003 was a disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; Interim Analysis only) and concurrent comparisons (Interim Analysis and Final Analysis) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated participants living in exposed or unexposed clusters* located in sub-Saharan Africa countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters.

*Exposed clusters: study sites where the RTS,S/AS01_E vaccine was to be implemented at the beginning of the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI

Unexposed clusters: study sites where the RTS,S/AS01_E vaccine was not to be implemented at the beginning of the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI.
- The design included 2 cohorts: Active Surveillance (home visits and continuous monitoring of outpatient visits and hospitalizations at all health care facilities) and Enhanced Hospitalization Surveillance (continuous monitoring of hospitalizations) in both exposed and unexposed clusters.

The enrollment to Active Surveillance was completed on 06 April 2021. Following site Ethics Committee approval of Protocol Amendment 3, enrollment to Enhanced Hospitalization Surveillance and data collection was stopped (last participant enrolled 13 June 2025), with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for participants diagnosed with an AESI, meningitis or cerebral malaria.
- The diseases under surveillance for safety endpoints included AESI, other AE leading to hospitalization, meningitis, and severe malaria including cerebral malaria, and were monitored among the RTS,S/AS01_E vaccinated and unvaccinated children enrolled in Active Surveillance and in Enhanced Hospitalization Surveillance. The mortality rate, overall and by gender, was estimated.

The analysis of malaria cases and death included cases recorded during both outpatient visits or during home visits in the case of death, and hospitalizations. All other endpoints included cases recorded during hospitalizations only.
- The effectiveness (Direct Effect) of the RTS,S/AS01_E vaccine was investigated by monitoring all malaria (including severe and cerebral malaria) related events in vaccinated and unvaccinated children of the exposed clusters, enrolled in Active Surveillance. The impact (Indirect, Total and Overall Effect) of the vaccine was investigated in the Active Surveillance cohort by comparing the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the unexposed clusters to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters (Indirect Effect), in vaccinated children (Total Effect), or in all children of the exposed clusters (Overall Effect). Vaccine effectiveness was estimated as 1-IRR, and 1-OR for anemia.

- The total study duration per site was approximately 62 months, including an estimated recruitment period of approximately 18 months in Active Surveillance and active follow-up through home visits up to 44 months. Study end per site occurred when the last child enrolled in Active Surveillance accrued a total follow-up period of 24 months after the fourth dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) given at a maximum age of 30 months.

Refer to Protocol Section 9.1 for a detailed overview of the study design including the rationale for the study design (Section 9.1.1).

10.2. Setting

- The study population was defined as study participants <5 years of age living in a geographically limited area with a demographic surveillance system in place, and a well-developed infrastructure to monitor population health and vaccination programs.
- In alignment with the MVIP, the study sites for the GSK observational Phase 4 studies were selected from the 3 countries where the RTS,S/AS01_E vaccine was to be implemented: Ghana, Kenya and Malawi.

Refer to Protocol Section 9.2 for further details of the study setting.

10.3. Participants

The EPI-MAL-003 study targeted enrolling at least 45 000 children in Active Surveillance:

- 22 500 in exposed clusters (with a minimum of 20 250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22 500 study participants would receive 3 doses of RTS,S/AS01_E, 10% would receive 1 or 2 doses and 10% will not have any dose)
- 22 500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.

For further details of the study population, refer to Protocol Section 9.2.1 and for participant recruitment to Active Surveillance, refer to Protocol Section 9.2.2.

Study participants needed to have met all inclusion criteria and none of the exclusion criteria. Refer to Protocol Section 9.2.3 and Section 9.2.4 for eligibility criteria for enrollment. For details of the study period, refer to Protocol Section 9.2.5. Details of the case definitions for AESI, meningitis, any malaria or severe malaria (including cerebral malaria), any anemia or severe anemia, hospitalization and death are provided in Protocol Section 9.2.6. Details of AEs and SAEs are provided in Protocol Section 11.1.

Refer to Protocol Section 9.2.7.1 for details of the study procedures for Active Surveillance, Section 9.2.7.2 for details of the study procedures for Enhanced Hospitalization Surveillance, Section 9.2.7.3 for biological sample handling and analysis, Section 9.2.7.4 for case ascertainment, Section 9.2.7.5 for management of AESI, meningitis cases and malaria episodes, Section 9.2.7.6 for package for standard of care and Section 9.2.7.7 for capacity building.

For study procedures during special circumstances (e.g., COVID-19 pandemic), refer to Protocol Section 9.2.8.

10.4. Variables

10.4.1. Co-primary endpoints

In children included in Active or Enhanced Hospitalization Surveillance:

- Occurrence of AESI.
- Occurrence of etiology-confirmed meningitis.

10.4.2. Secondary endpoints

10.4.2.1. Safety endpoints

In children included in Active or Enhanced Hospitalization Surveillance*:

- Occurrence of probable meningitis (final classification).
- Occurrence of clinically suspected meningitis (final classification).
- Occurrence of meningitis cases identified at site level (first line laboratory).
- Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- Occurrence of hospitalization (including those attributed to an AESI, meningitis or malaria)*.
- Occurrence of febrile convulsions during the 3-day period (Days 0 to 3) and 7-day period (Days 0 to 6) following each dose of RTS,S/AS01E*.
- Occurrence of 2 events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0 to 6) following each vaccination and foot positional deformation*.
- Occurrence of other AE leading to hospitalization*.

*Occurrence of hospitalization, other AE leading to hospitalization, febrile convulsions and quality indicators were only conducted for the Interim Analysis and not for the Final Analysis.

10.4.2.2. Effectiveness and impact endpoints

In children included in Active Surveillance:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
 - Any malaria (including *P. falciparum* malaria)
 - Severe malaria (including *P. falciparum* malaria)
 - Cerebral malaria.
- Occurrence of anemia at hospital entry among hospitalized children.
- Occurrence of hospitalization
 - All causes and hospitalizations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.
- Occurrence of death
 - All causes and malaria-attributed deaths (including *P. falciparum* malaria-attributed death).

Results for analyses of endpoints relating to occurrence of hospitalization, other AE leading to hospitalization, febrile convulsions and quality indicators, conducted for the Interim Analysis and not for the Final Analysis (see Protocol Amendment 3 for the rationale), are presented in the EPI-MAL-003 Interim Report (14 August 2024).

10.5. Data sources and measurement

HDSS (or equivalent surveillance system)	• Listings of all children living in the study area based on the demographic census • Total number of children <5 years of age (according to year and gender) recorded at the beginning of the study, at least once a year during the study duration and at the end of the study • Other demographic data (cause and date of deaths, migrations), if available • Information related to vaccination, if available.
Active surveillance (enrollment)	• Socio-demographic data • Active participation in any trial with an investigational product.
Active surveillance (home visits)	• Vaccination types and dates • Health history • Malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards • Verbal autopsy report.
Active surveillance (outpatient visits and hospitalizations at all health care facilities)	• Data on visits at primary health care facilities and hospitals since enrollment or last home visit.
Enhanced hospitalization surveillance (hospitalizations)	• Socio-demographic data • Active participation in any trial with an investigational product • Health history • Malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards • Type of health care facility • Final diagnosis for the hospitalization visit on discharge for all children • Data relevant to the diagnosis of AESI, meningitis and malaria (including

	cerebral malaria) • Vaccination types and dates • Autopsy report.
Study conclusion (home visit)	• Vital status • Verbal autopsy report • Vaccination types and dates • Health history since last visit.
MTI Study EPI-MAL-005	• Estimation of annual parasite prevalence • Changes in diagnostic practices • Malaria control and prevention measures at the community and individual level.

AESI = adverse events of special interest; HDSS = health and demographic surveillance system; MTI = malaria transmission intensity

Also refer to Protocol Section 9.4 for data sources used for the study: Section 9.4.1 for HDSS (or equivalent surveillance system) databases, Section 9.4.2 for Active Surveillance and Enhanced Hospitalization Surveillance of study EPI-MAL-003 and Section 9.4.4 for the MTI study EPI-MAL-005.

10.6. Bias

Several potential sources of bias should be considered with regards to this study.

Firstly, selection bias cannot be fully excluded in the exposed clusters where a small population of unvaccinated children was observed. The reason(s) parents/LARs refused vaccination may be different from vaccinated children, in addition their underlying risk factors may be different from the general population. Both could potentially introduce bias in the estimation of Direct and Overall vaccine effects, but the contribution of such a small number of participants is likely to be minimal.

Secondly, observer bias cannot be fully excluded as researchers and medical staff were not blinded to exposure status in clusters. This, in combination with different local clinical practices, could have led to differences in case ascertainment, which could bias effect estimates depending on the direction. This was at least partially mitigated as the External Expert Panel, who analyzed all collected data on meningitis, cerebral malaria and AESI, were blinded as much as possible to children's vaccination status.

Thirdly, information bias may have been introduced due to more scrutiny and more detailed health outcomes reporting (AESI, AE) from exposed clusters compared to unexposed clusters. As a mitigation measure, participating centers, medical and non-medical field staff received identical training on signs and symptoms of each AESI under observation, and data collection and reporting. In addition, differential recall bias during verbal autopsy cannot be fully ruled out, with responders more or less likely to report specific causes of death depending on vaccine status. Whilst such bias could modify effect estimates in either direction, depending on responses, it is likely to have only occurred in a small number of instances and therefore have a minimal effect on findings.

Finally, temporal differences across the EPI-MAL-002, -003 and -005 studies, in terms of data collection, population under observation, behavior due to climate change, socio-demographic factors, use of bed-nets and other prevention methods, could have all contributed, albeit minimally, to observed differences in effect estimates.

10.7. Study size

See Section 10.3 of this report for participant enrolment, and Protocol Section 9.5 for details of determination of study size.

10.8. Data transformation

For details of data management, refer to Protocol Section 9.6.

10.9. Statistical methods

The statistical analyses were performed using SAS Viya V.04.

Analyses for this Final Study Report are specified in detail in the SAP dated 17 April 2025.

10.9.1. Main summary measures

Main descriptive statistics (i.e., demographic characteristics) were computed by study group, RTS,S/AS01_E vaccination status, study site and overall.

Categorical variables were summarized by the frequency and the percentage of each category. As applicable, 95% CIs were described. The following statistics were presented for continuous variables: number of non-missing observations, mean, SD, median and range (minimum and maximum).

IR computations were conducted for study participants from Active Surveillance but not study participants from Enhanced Hospitalization Surveillance. The Enhanced Hospitalization Surveillance cohort data was only used for descriptive statistics of the main safety endpoints (AESI, meningitis, malaria and mortality).

10.9.2. Main statistical methods

10.9.2.1. Study cohorts

10.9.2.1.1. Enrolled Set

The Enrolled Set included all children enrolled in the study (i.e., either from exposed or unexposed clusters) through Active Surveillance or Enhanced Hospitalization Surveillance, and included both children vaccinated with RTS,S/AS01_E and unvaccinated.

10.9.2.1.2. Analysis Set

The Analysis Set included all evaluable study participants from Active Surveillance cohort (i.e., those meeting all eligibility criteria, complying with the enrollment procedures defined in the protocol, with no elimination criteria during the study).

A subset of the Analysis Set was defined for the secondary effectiveness and impact endpoints analysis to select children receiving the RTS,S/AS01_E vaccine according to the recommended schedule; the Impact Analysis Set included all study participants from the Analysis Set who had received their third dose of RTS,S/AS01_E vaccine or virtual dose before 12 months of age and/or the fourth dose of RTS,S/AS01_E vaccine or virtual dose before 30 months of age. Children receiving at least 1 of their first 3 doses of RTS,S/AS01_E vaccine after 12 months of age were not considered for the analysis.

Refer to the SAP Section 3 for further details of the analysis sets including a detailed list of reasons for elimination from the Enrolled Set and Analysis Set.

All analyses for the cluster design were conducted on the Analysis Set for safety analyses and on the Impact Analysis Set for impact analyses.

10.9.2.2. Conduct of analyses

A summary of changes in analyses from the original statistical plan outlined in the protocol is provided in [Table 10.1](#).

Table 10.1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Virtual vaccination dose date defined as the date of visit mimicking the vaccine schedule (Visits 1,2,3,6) minus 1 week (see Protocol Section 9.7.5.2.1).	Virtual vaccination Dose 1 defined as the age, computed for unvaccinated participants with missing Visits 1,2,3 according to the country specific schedule (see SAP Section 6.2.4.2.1).	Unbalanced number of missing Visit 1 between exposed and unexposed clusters.
In the models for cluster design comparison, the study site was planned to be considered as a random effect (see Protocol Section 9.7.6.7.2).	The model will include the study country as a fixed effect, instead of study site as random effect (see SAP Section 4.1.2).	In the Interim Analysis, random effect model with the study site as a random effect were rarely converging and was replaced by regression models with country as fixed effect.
For additional comparisons by subgroups for death events (analysis triggered by an observed imbalance in mortality in girls), the description of characteristics <u>at the first scheduled</u> visit compared between boys and girls was planned (see Protocol Section 9.7.6.7).	In the SAP, the description of characteristics <u>at study entry</u> visit compared between boys and girls was planned (see SAP Section 4.3.1.2.2).	As the reference date was not the first visit for unvaccinated children this comparison was not valuable.
Vaccine history will be collected from different sources (i.e., individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system). If any of the sources	We will consider all RTS,S vaccine history for the analyses even if there is no documented source to confirm the vaccination.	This approach is more conservative regarding the safety of the vaccine.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
confirm RTS,S/AS01 _E vaccination, it will be assumed that vaccination has taken place.		
The univariate and multivariable Cox model for the comparison of time to event of effectiveness or impact endpoints has been mentioned under Protocol Section 9.7.7.3.3.	The Cox model has been removed.	As per Protocol Amendment 3, the comparison of time to event of effectiveness or impact endpoints has been removed.

HDSS = health and demographic surveillance system; SAP = statistical analysis plan

10.9.2.3. Study participant disposition

Refer to the SAP Section 6.1.1 for the presentation of participant disposition data for the Enrolled Set and Analysis Set.

10.9.2.4. Demographics and characteristics at study entry

Separately from the exposed and the unexposed clusters, for the vaccinated and unvaccinated children enrolled in the Active and Enhanced Hospitalization Surveillance, demographics (age at study entry, gender, site, country) were summarized for the Enrolled Set and the Analysis Set, using descriptive statistics. Refer to the SAP Section 6.1.2 for further details.

10.9.2.5. Signs and symptoms, and medical history

For Active Surveillance, pooled data for signs and symptoms, malaria preventive measures, and health care seeking behavior were tabulated by RTS,S/AS01_E vaccination status and study site.

For hospitalized children from Active Surveillance, malaria preventive measures, health care seeking behavior, risk factors and comorbidity factors were described by RTS,S/AS01_E vaccination status and study site.

Refer to the SAP Section 6.1.3 for further details.

10.9.2.6. Exposure description

For all study participants from the exposed clusters, vaccine history was summarized. The RTS,S/AS01_E vaccine coverage in the exposed clusters was estimated. The number of RTS,S/AS01_E doses received and exposure to other vaccines were described.

Refer to the SAP Section 6.1.4 for further details.

10.9.2.7. COVID-19 assessment

No additional analyses due to the COVID-19 pandemic were conducted for the Final Analysis.

10.9.2.8. Protocol deviations

Important protocol deviations leading to elimination from the Enrolled Set were summarized. In addition, separate summaries were produced for protocol deviations related to COVID-19 (both important and non-important protocol deviations). Refer to the SAP Section 6.1.5 for further details.

Visits missed due to the COVID-19 pandemic, together with visits conducted remotely, were summarized.

10.9.2.9. Primary and secondary safety endpoint analyses

The analysis of malaria cases and death included cases recorded during both outpatient visits, or during home visits in the case of death, and hospitalizations. All other endpoints included cases recorded during hospitalizations only.

Analyses of incidence following RTS,S/AS01_E vaccination or virtual vaccination were only performed on children enrolled in the Active Surveillance Analysis Set. These analyses were computed on each confirmed endpoint as the number of first events reported post each dose/virtual dose over the follow-up period by the total person-time. A 95% CI was computed using an exact method for a Poisson-distributed variable. Incidence per 100 000 PYs are presented overall. IRs after the vaccine/virtual full schedule (i.e., combining the 4 doses/virtual doses) and after Dose 4/virtual Dose 4 are presented. The total PYs were computed as the sum of individual follow-up periods expressed in years. See SAP Section 4.2.2.1 for details of the computation of follow-up periods.

IRRs following the full (4-dose) schedule, adjusted for country, were computed for the cluster design comparison and exposed clusters comparison; see SAP Section 4.2.2.2 for further details. All comparisons were conducted using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002]. Vaccine effectiveness values represent 1-IRR and 1-OR for anemia.

For further details of secondary endpoint analyses, refer to the SAP Section 4.3.1.2.1 for analyses of IR following immunization (actual or virtual vaccination full [4-dose] schedule) including the at-risk periods for the safety events, and Section 4.3.1.2.2 for comparison of vaccinated and unvaccinated populations.

10.9.2.10. Secondary effectiveness and impact endpoint analyses

The analyses of effectiveness and impact were performed only on children enrolled in the Active Surveillance in exposed and unexposed clusters, who fulfilled the inclusion criteria for the Impact Analysis Set.

The main analysis on effectiveness and impact endpoints was performed:

- One year after Dose 4 of RTS,S/AS01_E evaluated from Dose 3, and for children who had received the 3 doses before 12 months of age and Dose 4 of RTS,S/AS01_E before 30 months of age.

Additional analyses were performed on effectiveness and impact endpoints at:

- Two years after Dose 3 of RTS,S/AS01_E evaluated from Dose 3 (given before 12 months of age), and for children who did not receive Dose 4 of RTS,S/AS01_E
- Two years after Dose 4 of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from Dose 1 of vaccine
- Two years after Dose 4 of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from Dose 3 of vaccine (received before 12 months of age)
- Two years after Dose 4 of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from Dose 4 of vaccine.

All comparisons were undertaken using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

Refer to the SAP Section 4.3.2.2.1 for derivation of IR and prevalence and Section 4.3.2.2.2 for comparison of IR of effectiveness or impact endpoints (effectiveness [Direct Effect], impact using the cluster design).

A summary of the comparisons for effectiveness and impact endpoints is given in Figure 10.1.

Figure 10.1 Diagram of effectiveness and impact presenting the different vaccine effects for the cluster design



Total effect defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated study participants from the EPI-MAL-003 exposed clusters

Direct effect defined as the comparison between unvaccinated and vaccinated study participants from the EPI-MAL-003 exposed clusters

Overall effect defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated and unvaccinated study participants from the EPI-MAL-003 exposed clusters

Indirect effect defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and unvaccinated study participants from the EPI-MAL-003 exposed clusters.

10.9.2.11. Exploratory analyses**Prevalence of malaria among anemic children**

The prevalence of any malaria and severe malaria among hospitalized children with anemia was estimated as the number of hospitalized children with any malaria and severe malaria among those with anemia, respectively. The same analysis was performed among those with severe anemia. A 95% CI was computed using the exact binomial method.

The prevalence in RTS,S/AS01_E vaccinated children from exposed clusters and RTS,S/AS01_E unvaccinated children from unexposed clusters was compared using logistic regression model with the study country as fixed effect. See SAP Section 4.1.2 for further details.

This analysis was performed 1 year after Dose 4 of RTS,S/AS01_E, evaluated from Dose 3; see SAP Section 4.3.2 for further details.

Averted cases based on Total Effect

Analysis of averted cases was performed to enhance the interpretation of vaccine impact in terms of cumulative number of cases averted per 1000 vaccinated participants.

The number of cases averted was calculated as the difference in the estimated cases between the RTS,S/AS01_E vaccinated and unvaccinated groups. Estimated cases in each group were calculated as the incidence of cases over time, and expressed as cumulative cases averted per 1000 participants followed up during the relevant period. The number of averted cases of any malaria was calculated (difference between incidences of RTS,S/AS01_E vaccinated and unvaccinated groups, expressed per 1000 population vaccinated) for each 3-month period and summed over the entire study period after Dose 3. See SAP Section 4.4.2 for further details.

The same analysis was performed for uncomplicated malaria, severe malaria cases, death due to malaria, all-cause death and hospitalization due to malaria.

This analysis was performed based on the Total Effect estimated in the main analysis (D3 until D4 + 1Y) (see SAP Section 4.3.2).

Vaccine Impact (Total Effect) accounting for Malaria Transmission Intensity estimated in the EPI-MAL-005 study

For any malaria and severe malaria, the Total Effect of vaccination impact was estimated accounting for seasonal MTI (i.e., parasite prevalence estimated in the EPI-MAL-005 study).

The year- and center-specific MTIs computed for children aged 6 months to <5 years were included as additional covariates in the Poisson or Negative binomial regression model (see SAP Section 4.1.2) to account for annual fluctuations and/or changes due to other malaria control interventions per center. Each participant was assigned an average MTI based on their follow-up period, using the corresponding year- and center-specific MTI from the EPI-MAL-005 study. This analysis was performed on the cohort of children followed up to 2 years after Dose 4 of RTS,S/AS01_E and evaluated from Dose 1 (see SAP Section 4.3.2).

In addition, baseline covariate balance was evaluated using standardized mean difference to ensure robust comparability between vaccinated and unvaccinated children (see Section [10.9.5](#)).

10.9.2.12. Other analyses

The following data are summarized by subgroups, as applicable:

- Participant flow at each study visit.
- Participants having home visits and participants who attended at least 1 outpatient visit.
- Study enrollment by calendar month, and study completion with reasons for withdrawals.
- HIV and hemoglobinopathy status, and frequency of CSF samples collected and tested.
- Number of participants and confirmed cases for the main safety endpoints (AESI, meningitis, cerebral malaria and death) for specific sub-populations such as children with hemoglobinopathy and HIV-positive children.
- Cumulative number of the following cases that occurred after vaccine Dose 1 or virtual Dose 1:
 - Confirmed AESI cases according to final diagnosis by body system and protocol definition
 - Meningitis cases (Final diagnosis)
 - Malaria cases (Final diagnosis)
 - Deaths
 - Hospitalization causes (Final diagnosis)
 - Anemia cases among hospitalized children.

10.9.3. Missing values

No imputation of missing data was undertaken in the context of the EPI-MAL-003 study Final Analysis.

However, if the 3 first home visits planned according to the recommended primary vaccination schedule were missing among unvaccinated children, the first virtual vaccination date was set based on the theoretical vaccine schedule (see details in SAP Section 6.2.4.2.1).

10.9.4. Sensitivity analyses

Not applicable.

10.9.5. Amendments to the statistical analysis plan

There were no amendments to the SAP for the Final Analysis.

Changes from protocol defined analyses may be found in SAP Section 4.7.

Exploratory analyses were conducted to understand the potential effect of participant differences between comparison groups, as captured by baseline covariates, and how these differences could influence vaccine effect estimates.

Propensity scores were calculated using logistic regression. Covariates included age at informed consent, closest health care facility, approximate distance between the study participant house and the closest health care facility, neighborhood of residence (urban, semi-urban, or rural), gender and number of persons living in the household. The dependent variable varied by treatment effect (participants' vaccination status for Direct and Total Effects; cluster exposure status for Indirect and Overall Effects).

Following the generation of propensity scores, 2 weighting techniques – inverse probability of treatment weighting and propensity score overlap weighting – were evaluated for use in subsequent analyses. Following the generation of propensity scores, propensity score overlap weighting was selected over inverse probability of treatment weighting because it provided better covariate balance and greater estimation stability.

In the final step, the Direct, Total, Indirect and Overall Effect of the vaccine on the incidence of confirmed malaria, was estimated using weighted Poisson or negative binomial regression.

10.10. Quality control

Refer to Protocol Section 9.8 for details of quality control measures taken during the conduct of the study.

To ensure compliance with GCP or other applicable guidelines and all applicable regulatory requirements, this study was subject to an audit by ADAMAS Consulting Ltd, Africa, on behalf of GSK. The independent audit was conducted in Malawi on 18 August 2022.

During the conduct of this study, 4 SQIs were reported as having a potential impact on GCP/GVP, of which only 1 (ID PPD) was considered a serious breach at the time of reporting details for which are summarized below:

- Reason for the SQI: potential major or critical regulatory citation (non-compliance to the Electronic Health Record requirement as per GCP; Source Document Agreement had not been updated).

Due to the safety risk associated with COVID-19, electronic source documents were implemented at site level in Malawi when conducting home visits via phone contact. The source documents were stored on an iPad, then printed, and then discarded after printing. As a consequence, monitors were unable to conduct source data verification checks. In addition, there was no audit trail for the collected data and the original.

The SQI was initially considered to be a serious breach as: the event(s) likely had a significant/potential impact on overall data validity of the study, and on data robustness/reliability. Subsequently, on receipt of additional information, the event was reassessed as a Major SQI, but not a serious breach.

11. RESULTS

All data from Active Surveillance were included for the Final Analysis. Data from Enhanced Hospital Surveillance were only used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality).

11.1. Participants

The first participant was enrolled on 21 March 2019 and the last study visit was on 06 August 2025.

A total of 77 953 participants were enrolled in the study (Enrolled Set), comprising 44 998 participants in Active Surveillance and 32 955 in Enhanced Hospitalization Surveillance (Table 11.1). In Active Surveillance, 22 503 participants were in exposed clusters and 22 495 in unexposed clusters, and 5 participants had missing information regarding the study group (Section 16 Table 16.1.1.1). In Enhanced Hospitalization Surveillance, 17 371 participants were in exposed clusters and 15 584 in unexposed clusters (Section 16 Table 16.1.1.2).

Table 11.1 Study site enrollment

Name of site (country)	Group label in tables	Number of participants enrolled	
		Active Surveillance	Enhanced Hospitalization Surveillance
Kintampo EXP (Ghana)	235635_GH_KHRC_EXP	5998	9449
Kintampo UNEXP (Ghana)	235635_GH_KHRC_UNEXP	6002	11 577
Navrongo EXP (Ghana)	235636_GH_NHRC_EXP	4005	5394
Navrongo UNEXP (Ghana)	235636_GH_NHRC_UNEXP	3998	2275
Ghana Total		20003	28695
Kombewa (Kenya)	235638_KE_Kombewa_EXP	2999	1131
Nyando (Kenya)	235641_KE_Nyando_UNEXP	3000	268
Gem (Kenya)	235637_KE_Gem_EXP	3001	391
Bondo (Kenya)	235637_KE_Bondo_UNEXP	2994	577
Kenya Total		11994	2367
Chikwawa (Malawi)	235639_MA_Chikwawa_UNEXP	3256	268
St Montfort (Malawi)	235639_MA_StMontfort_EXP	3242	266
Mangochi (Malawi)	235640_MA_Mangochi_EXP	3258	740
Monkey Bay (Malawi)	235640_MA_MonkeyBay_UNEXP	3245	619
Malawi Total		13001	1893
TOTAL		44998	32955

GH = Ghana; KE = Kenya; MA = Malawi; KHRC = Kintampo Health Research Centre; NHRC = Navrongo Health Research Centre; EXP = Exposed; UNEXP = Unexposed

Source: Table 16.1.1.1 (03FEB2026 22:48 GMT), Table 16.1.1.2 (03FEB2026 22:48 GMT)

11.1.1. Disposition of participants

In Active Surveillance, in total 38 314 (85.1%) participants completed the study and 6684 (14.9%) withdrew, the main reason being ‘migrated/moved from the study area’ and ‘lost to follow-up’ ([Table 11.2](#)).

Table 11.2 Summary of study completion with reasons for withdrawal – Active Surveillance - Enrolled set

	AS DTP group N=42019		AS catch-up group N=2974		AS missing group N=5		Total N=44998	
	n	%	n	%	n	%	n	%
Completed the study	35540	84.6	2773	93.2	1	20.0	38314	85.1
Withdrawn from the study	6479	15.4	201	6.8	4	80.0	6684	14.9
Primary reason for withdrawal								
Death*	771	1.8	40	1.3	0	0	811	1.8
Protocol Violation	102	0.2	2	0.1	3	60.0	107	0.2
Consent Withdrawal	781	1.9	32	1.1	0	0	813	1.8
Migrated / Moved From The Study Area	3107	7.4	81	2.7	0	0	3188	7.1
Lost To Follow-Up	1710	4.1	46	1.5	0	0	1756	3.9
Sponsor Study Termination	0	0	0	0	0	0	0	0
Other	8	0.02	0	0	1	20.0	9	0.02
Unknown	0	0	0	0	0	0	0	0

*Deaths reported for the entire study period, including those that occurred before Dose 1/virtual Dose 1

AS DTP group = Active surveillance DTP group

AS catch-up group = Active surveillance catch-up group

AS missing group = Missing information concerning study group

Completed = number of participants who completed the last study visit/contact

Withdrawn = number of participants who did not complete their last visit/contact

N = number of participants

n/% = number / percentage of participants in a given category

Source: Table 16.1.1.17 (03FEB2026 22:52 GMT)

The percentage of participants withdrawing from the study, and reasons for withdrawal, were balanced between vaccinated and unvaccinated groups ([Table 11.3](#)).

Table 11.3 Summary of study completion with reasons for withdrawal by RTS,S/AS01E vaccine status - Active Surveillance - Enrolled set

	RTSS vaccinated N=20943		Unvaccinated N=24055		Total N=44998	
	n	%	n	%	n	%
Completed the study	18395	87.8	19919	82.8	38314	85.1
Withdrawn from the study	2548	12.2	4136	17.2	6684	14.9
Primary reason for withdrawal						
Death*	319	1.5	492	2.0	811	1.8
Protocol Violation	29	0.1	78	0.3	107	0.2
Consent Withdrawal	221	1.1	592	2.5	813	1.8
Migrated / Moved From The Study Area	1351	6.5	1837	7.6	3188	7.1
Lost To Follow-Up	623	3.0	1133	4.7	1756	3.9
Sponsor Study Termination	0	0	0	0	0	0
Other	5	0.02	4	0.02	9	0.02
Unknown	0	0	0	0	0	0

*Deaths reported for the entire study period, including those that occurred before Dose 1/virtual Dose 1

RTS,S vaccinated = participants vaccinated with at least 1 dose of RTS,S/AS01E vaccine

Unvaccinated = participants without RTS,S/AS01E vaccine reported in eCRF

Completed = number of participants who completed the last study visit/contact

Withdrawn = number of participants who did not complete their last visit/contact

N = number of participants

n/% = number / percentage of participants in a given category

Source: Table 16.8.33 (31MAR2026 20:16 GMT)

In Enhanced Hospitalization Surveillance, in total 31 668 (96.1%) participants completed the study and 1287 (3.9%) withdrew, the main reason being ‘death’ and ‘lost to follow-up’ (Table 11.4).

Table 11.4 Summary of study completion with reasons for withdrawal – Enhanced Hospitalization Surveillance - Enrolled set

	EHS group N=32955	
	n	%
Completed the study	31668	96.1
Withdrawn from the study	1287	3.9
Primary reason for withdrawal		
Death	611	1.9
Protocol Violation	4	0.01
Consent Withdrawal	3	0.01
Migrated / Moved From The Study Area	194	0.6
Lost To Follow-Up	475	1.4
Sponsor Study Termination	0	0
Other	0	0
Unknown	0	0

EHS group = Enhanced Hospitalization Surveillance group

Completed = number of participants who completed the last study visit/contact

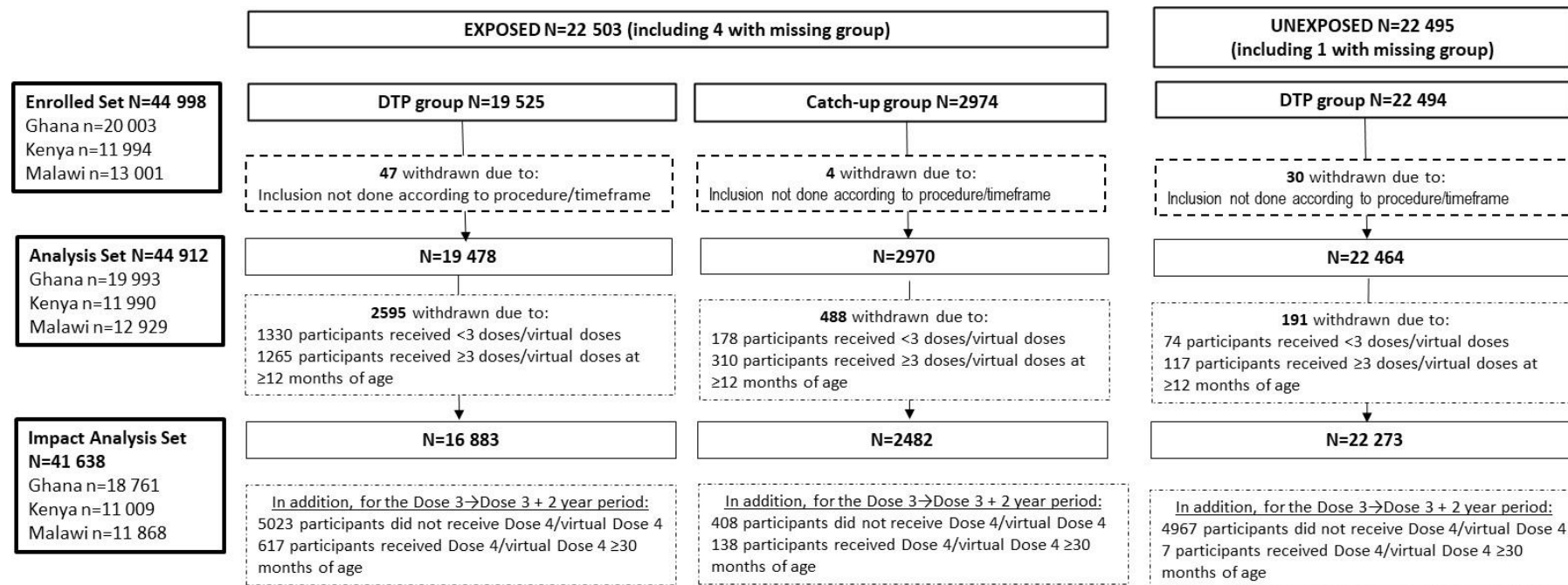
Withdrawn = number of participants who did not complete their last visit/contact

N = number of participants

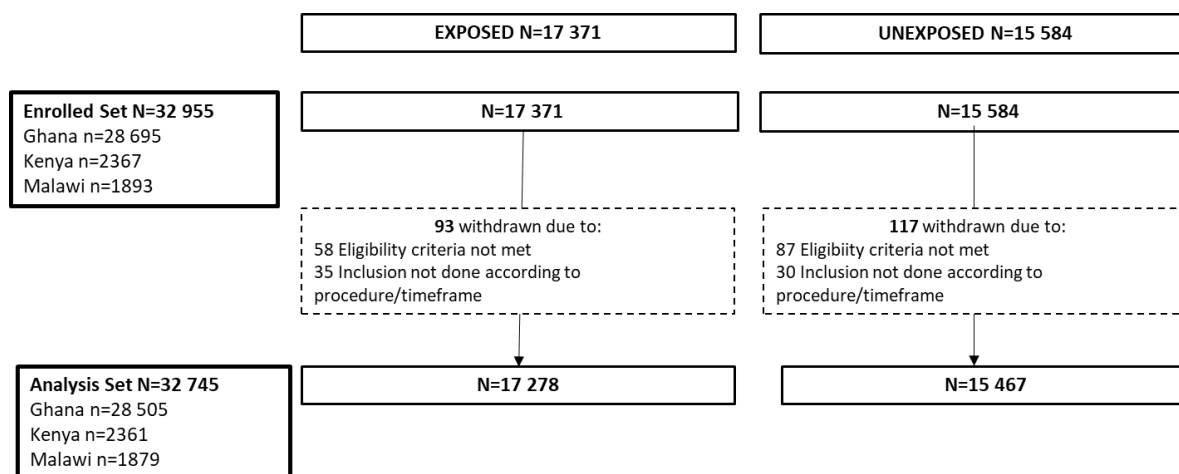
n/% = number / percentage of participants in a given category

Source: Table 16.1.1.18 (03FEB2026 22:52 GMT)

The number of participants by group and analysis set, with reasons for exclusion from analysis sets, are summarized for participants in Active Surveillance in Figure 11.1 and for participants in Enhanced Hospitalization Surveillance in Figure 11.2.

Figure 11.1 Consort Diagram – Participants in Active Surveillance

Source: Table 16.1.1.1 (03FEB2026 22:48 GMT)

Figure 11.2 Consort Diagram – Participants in Enhanced Hospitalization Surveillance

Source: Table 16.1.1.2 (03FEB2026 22:48 GMT)

Participant enrollment by cluster and vaccination status for the Analysis Set are summarized in [Table 11.5](#).

Table 11.5 Participant enrollment by vaccination status – Exposed and Unexposed Clusters – Analysis Set

Cluster	Active Surveillance		Enhanced Hospitalization Surveillance	
	RTS,S vaccinated	RTS,S unvaccinated	RTS,S vaccinated	RTS,S unvaccinated
Exposed	20641	1807	5791	11487
Unexposed	254	22210	161	15306

RTS,S vaccinated = participants vaccinated with at least 1 dose of RTS,S/AS01E vaccine

RTS,S unvaccinated = participants without RTS,S/AS01E vaccine reported in eCRF

Source: Table 16.1.1.3 (03FEB2026 22:47 GMT), Table 16.1.1.6 (03FEB2026 22:51 GMT)

Additional analyses for study enrollment by vaccination status and gender for participants in Active Surveillance are presented in Section 16 Table 16.1.1.3 to Table 16.1.1.5 and for participants in Enhanced Hospitalization Surveillance in Section 16 Table 16.1.1.6 to Table 16.1.1.8 for the Analysis Set.

In participants in Active Surveillance, participant flow at each study visit for the Analysis Set is presented in Section 16 Table 16.1.2.1 to Table 16.1.2.3 and study enrollment by calendar month in Section 16 Table 16.1.3.1 and Figure 16.1.3.3. In participants in Enhanced Hospitalization Surveillance, study enrollment by calendar month for the Analysis Set is presented in Section 16 Table 16.1.3.2.

11.1.2. Protocol deviations

Active Surveillance

Overall, 55 (0.2%) participants from exposed clusters and 31 (0.1%) participants from unexposed clusters were eliminated from the Analysis Set due to an important protocol deviation (deviations that could impact the completeness, accuracy, and/or reliability of critical study data or processes, or impact the study participants' rights, safety or wellbeing) ([Table 11.6](#)).

No important deviations due to COVID-19 led to elimination from the Analysis Set (Section [16](#) Table 16.1.10.2).

Table 11.6 Summary of important protocol deviations leading to elimination by study group and study site – Active Surveillance - Enrolled Set

Study site	Category Sub-category	AS DTP group				AS catch-up group				AS missing group				Total			
		N	occ	n	%	N	occ	n	%	N	occ	n	%	N	occ	n	%
Overall exposed clusters	At least one important protocol deviation	19525	47	47	0.2	2974	4	4	0.1	4	4	4	100	22503	55	55	0.2
	Eligibility criteria not met	19525	0	0	0	2974	0	0	0	4	4	4	100	22503	4	4	0.02
	Sub-category missing*	19525	0	0	0	2974	0	0	0	4	1	1	25.0	22503	1	1	0.004
	Protocol violation (inclusion/exclusion criteria)	19525	0	0	0	2974	0	0	0	4	3	3	75.0	22503	3	3	0.01
	Study procedures	19525	47	47	0.2	2974	4	4	0.1	4	0	0	0	22503	51	51	0.2
	Other deviation from study procedures	19525	47	47	0.2	2974	4	4	0.1	4	0	0	0	22503	51	51	0.2
Overall unexposed clusters	At least one important protocol deviation	22494	30	30	0.1	0	0	0	-	1	1	1	100	22495	31	31	0.1
	Eligibility criteria not met	22494	0	0	0	0	0	0	-	1	1	1	100	22495	1	1	0.004
	Protocol violation (inclusion/exclusion criteria)	22494	0	0	0	0	0	0	-	1	1	1	100	22495	1	1	0.004
	Study procedures	22494	30	30	0.1	0	0	0	-	1	0	0	0	22495	30	30	0.1
	Other deviation from study procedures	22494	30	30	0.1	0	0	0	-	1	0	0	0	22495	30	30	0.1
Overall	At least one important protocol deviation	42019	77	77	0.2	2974	4	4	0.1	5	5	5	100	44998	86	86	0.2
	Eligibility criteria not met	42019	0	0	0	2974	0	0	0	5	5	5	100	44998	5	5	0.01
	Sub-category missing*	42019	0	0	0	2974	0	0	0	5	1	1	20.0	44998	1	1	0.002
	Protocol violation (inclusion/exclusion criteria)	42019	0	0	0	2974	0	0	0	5	4	4	80.0	44998	4	4	0.01
	Study procedures	42019	77	77	0.2	2974	4	4	0.1	5	0	0	0	44998	81	81	0.2
	Other deviation from study procedures	42019	77	77	0.2	2974	4	4	0.1	5	0	0	0	44998	81	81	0.2

*Participant did not meet entry criteria: Study participant living in the HDSS or equivalent surveillance system area

AS DTP group = Active surveillance DTP group; AS catch-up group = Active surveillance catch-up group; AS missing group = Active surveillance missing group; Total = DTP, catch-up and missing groups of Active Surveillance; N = total number of participants; occ = number of protocol deviations in a given category, subcategory or in total; n = number of participants in a given category, subcategory or in total; % = (n/N) x 100

Source: Table 16.1.10.1 (03FEB2026 22:39 GMT)

Enhanced Hospitalization Surveillance

Overall, 93 (0.5%) participants from exposed clusters and 117 (0.8%) participants from unexposed clusters were eliminated from the Analysis Set due to an important protocol deviation (deviations that could impact the completeness, accuracy, and/or reliability of critical study data or processes, or impact the study participants' rights, safety or wellbeing) ([Table 11.7](#)).

No important deviations due to COVID-19 led to elimination from the Analysis Set (Section [16](#) Table 16.1.10.4).

Table 11.7 Summary of important protocol deviations leading to elimination by study group and study site – Enhanced Hospitalization Surveillance - Enrolled Set

Study site	Category Sub-category	EHS group			
		N	occ	n	%
Overall exposed clusters	At least one important protocol deviation	17371	93	93	0.5
	Eligibility criteria not met	17371	58	58	0.3
	Protocol violation (inclusion/exclusion criteria)	17371	58	58	0.3
	Study procedures	17371	35	35	0.2
	Other deviation from study procedures	17371	35	35	0.2
Overall unexposed clusters	At least one important protocol deviation	15584	117	117	0.8
	Eligibility criteria not met	15584	87	87	0.6
	Protocol violation (inclusion/exclusion criteria)	15584	87	87	0.6
	Study procedures	15584	30	30	0.2
	Other deviation from study procedures	15584	30	30	0.2
Overall	At least one important protocol deviation	32955	210	210	0.6
	Eligibility criteria not met	32955	145	145	0.4
	Protocol violation (inclusion/exclusion criteria)	32955	145	145	0.4
	Study procedures	32955	65	65	0.2
	Other deviation from study procedures	32955	65	65	0.2

EHS group = Enhanced Hospitalization Surveillance group; N = total number of participants; occ = number of protocol deviations in a given category, subcategory or in total
n = number of participants in a given category, subcategory or in total; % = (n/N) x 99

Source: Table 16.1.10.3 (03FEB2026 22:39 GMT)

11.2. Descriptive data

11.2.1. Home visits and attendance to health care facilities

Active Surveillance

Overall, of the 44 912 participants in the Analysis Set:

- 43 128 (96.0%) participants had at least 1 home visit reported: 21 379 (47.6%) in the exposed clusters and 21 749 (48.4%) in the unexposed clusters (Section 16 Table 16.1.2.4).
- 5227 (11.6%) participants were referred to a primary health care facility and 1262 (2.8%) participants were referred to hospital during at least 1 home visit (Section 16 Table 16.1.2.4).
- 34 373 (76.5%) participants attended at least 1 outpatient visit (Section 16 Table 16.1.2.7).

Additional analyses for the Analysis Set on home visits and health care facilities by vaccination status are presented in Section 16 Table 16.1.2.5, Table 16.1.2.6, Table 16.1.2.8 and Table 16.1.2.9. Data on hospitalizations are presented in Section 11.4.3.4.

11.2.2. Demographic characteristics

Active Surveillance

In the Analysis Set, the mean (SD) age at informed consent was 2.74 (1.63) months: 3.07 (1.88) months in exposed clusters and 2.41 (1.25) months in unexposed clusters (Section 16 Table 16.1.4.2). The ratio of females:males was 49.4:50.6 in the exposed clusters and 50.2:49.8 in the unexposed clusters. The demographic characteristics were broadly similar in both the Analysis Set and Enrolled Set (Section 16 Table 16.1.4.1).

Additional analyses of demographic and age characteristics for the Analysis Set are presented in Section 16 Table 16.1.4.5, Table 16.1.4.6, Table 16.1.4.10, Table 16.1.4.12 to Table 16.1.4.14. In the Impact Analysis Set, analyses of demographic characteristics are presented in Section 16 Table 16.1.4.7 to Table 16.1.4.9, Table 16.1.4.15 to Table 16.1.4.18.

Enhanced Hospitalization Surveillance

In the Analysis Set, the mean (SD) age at informed consent was 19.48 (15.64) months: 18.63 (14.90) months in exposed clusters and 20.42 (16.37) months in unexposed clusters (Section 16 Table 16.1.4.4). The ratio of females:males was 45.1:54.9 in the exposed clusters and 44.8:55.2 in the unexposed clusters. The demographic characteristics were broadly similar in both the Analysis Set and Enrolled Set (Section 16 Table 16.1.4.3).

Additional analyses of demographic and age characteristics for the Analysis Set are presented in Section 16 Table 16.1.4.11 and Table 16.1.4.19.

11.2.3. RTS,S/AS01_E vaccine and concomitant vaccinations

Vaccinations were to be documented using vaccination cards. Of note, only 48 doses of RTS,S/AS01_E in Active Surveillance (Listing 16.7.3) and 12 doses of RTS,S/AS01_E in Enhanced Hospitalization Surveillance were not documented (Listing 16.7.4) and 3 RTS,S/AS01_E dates in Enhanced Hospitalization Surveillance were missing (Listing 16.7.5).

Active Surveillance

In total, of the 44 912 participants in the Analysis Set (Table 11.8):

- 20 895 (46.5%) were vaccinated with at least 1 dose of RTS,S/AS01_E
24 017 (53.5%) were unvaccinated
 - Exposed clusters: in total 20 641 (92.0%) were vaccinated (17 671 DTP group, 2970 AS catch-up group), 1807 (8.0%) were unvaccinated (DTP group)
622 (2.8%) participants received 1 dose
870 (3.9%) participants received 2 doses
4706 (21.0%) participants received 3 doses
14 443 (64.3%) participants received 4 doses.
 - Unexposed clusters: in total 254 (1.1%) were vaccinated (DTP group), 22 210 (98.9%) were unvaccinated.

In the Analysis Set, per protocol, DTP/HepB/Hib vaccine was administered to all (100%) participants (Section 16 Table 16.1.5.5).

Analyses of participants receiving RTS,S/AS01_E by gender are presented in Section 16 Table 16.1.5.2 and Table 16.1.5.3. Analyses of time between RTS,S/AS01_E vaccine doses are presented in Section 16 Table 16.1.5.4.

Table 11.8 Number and percentage of participants who received RTS,S/AS01_E vaccine by study group and study site – Active Surveillance - Analysis set

Study site	Total number of doses received	AS DTP group N=41942			AS catch-up group N=2970			AS (DTP group + catch-up) N=44912		
		N	n	%	N	n	%	N	n	%
Overall exposed clusters	0	19478	1807	9.3	2970	0	0	22448	1807	8.0
	1	19478	538	2.8	2970	84	2.8	22448	622	2.8
	2	19478	776	4.0	2970	94	3.2	22448	870	3.9
	3	19478	4210	21.6	2970	496	16.7	22448	4706	21.0
	4	19478	12147	62.4	2970	2296	77.3	22448	14443	64.3
	Any of the 4 doses	19478	17671	90.7	2970	2970	100	22448	20641	92.0
Overall unexposed clusters	More than 4 doses	19478	0	0	2970	0	0	22448	0	0
	0	22464	22210	98.9	0	0	0	22464	22210	98.9
	1	22464	39	0.2	0	0	0	22464	39	0.2
	2	22464	35	0.2	0	0	0	22464	35	0.2
	3	22464	119	0.5	0	0	0	22464	119	0.5
	4	22464	61	0.3	0	0	0	22464	61	0.3
	Any of the 4 doses	22464	254	1.1	0	0	0	22464	254	1.1
	More than 4 doses	22464	0	0	0	0	0	22464	0	0

Study site	Total number of doses received	AS DTP group N=41942			AS catch-up group N=2970			AS (DTP group + catch-up) N=44912		
		N	n	%	N	n	%	N	n	%
Overall	0	41942	24017	57.3	2970	0	0	44912	24017	53.5
	1	41942	577	1.4	2970	84	2.8	44912	661	1.5
	2	41942	811	1.9	2970	94	3.2	44912	905	2.0
	3	41942	4329	10.3	2970	496	16.7	44912	4825	10.7
	4	41942	12208	29.1	2970	2296	77.3	44912	14504	32.3
	Any of the 4 doses	41942	17925	42.7	2970	2970	100	44912	20895	46.5
	More than 4 doses	41942	0	0	2970	0	0	44912	0	0

AS DTP group = Active surveillance DTP group

AS catch-up group = Active surveillance catch-up group

AS (DTP group + catch-up group) = Active surveillance

N = total number of participants

n/% = number/percentage of participants receiving the specified number of doses

Any of the 4 doses = participants receiving at least one dose among the scheduled 4 doses

Source: Table 16.1.5.1 (03FEB2026 21:09 GMT)

Enhanced Hospitalization Surveillance

In total, of the 32 745 participants in the Analysis Set (Section 16 Table 16.1.5.6):

- 5952 (18.2%) were vaccinated with at least 1 dose of RTS,S
26 793 (81.8%) were unvaccinated:
 - In the exposed clusters: 5791 (33.5%) were vaccinated (1958 [11.3%] received 4 doses of RTS,S/AS01_E), 11 487 (66.5%) were unvaccinated.
 - In the unexposed clusters: 161 (1.0%) were vaccinated, 15 306 (99.0%) were unvaccinated.

In the Analysis Set, DTP/HepB/Hib vaccine was administered to 19 473 (59.5%) participants (Section 16 Table 16.1.5.8).

Analyses of time between RTS,S/AS01_E vaccine doses are presented in Section 16 Table 16.1.5.7.

11.2.4. Study duration

Active Surveillance

In the Analysis Set, the overall mean (SD) duration of follow-up between informed consent and last contact was 4.15 (1.224) years (AS DTP group 4.14 [1.245] years; AS catch-up group 4.22 [0.876] years) (Section 16 Table 16.1.6.1).

- In the exposed clusters: the mean (SD) duration of follow-up was 4.17 (1.294) years (AS DTP group 4.16 [1.347] years; AS catch-up group 4.22 [0.876] years).
- In the unexposed clusters: the mean (SD) duration of follow-up was 4.13 (1.149) years (AS DTP group).

Descriptive analyses of follow-up periods after the RTS,S/AS01_E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01_E vaccine/virtual Dose 4 are presented in Section 16 Table 16.1.6.2.

11.2.5. Health behaviors, signs and symptoms and medical history

Active Surveillance

During the total of 438 624 home visits in the Analysis Set:

- At 224 656 (51.2%) visits, sleeping under a mosquito net was reported: 112 546 (51.6%) in the exposed clusters and 112 110 (50.8%) in the unexposed clusters (Section 16 Table 16.1.9.1).
- At 50 029 (11.4%) visits, usage of mosquito coils was reported: 20 121 (9.2%) in the exposed clusters and 29 908 (13.6%) in the unexposed clusters (Section 16 Table 16.1.9.1).
- At <10% of visits, usage of indoor residual spray, commercial spray (e.g., DOOM), herbs and other malaria preventive measures, and malaria preventive treatment was reported (Section 16 Table 16.1.9.1).
- At 16 923 (3.9%) visits, treatment for fever or malaria in the last 14 days was reported: 10 258 (4.7%) in the exposed clusters and 6665 (3.0%) in the unexposed clusters (Section 16 Table 16.1.9.3).

Additional analyses for preventive measures and for health care seeking behavior are presented in Section 16 Table 16.1.9.2 and Table 16.1.9.4, respectively.

Among hospitalized children, risk factors are presented in Section 16 Table 16.1.9.5 and pre-existing conditions in Section 16 Table 16.1.9.6. Signs and symptoms reported during home visits are presented in Section 16 Table 16.1.9.7.

11.3. Outcome data

The number of participants in the Enrolled Set and Analysis Set with reasons for exclusion are presented in Section 11.1.1.

11.4. Main results

IR computations were conducted for study participants from Active Surveillance, but not study participants from Enhanced Hospitalization Surveillance. The Enhanced Hospitalization Surveillance cohort data was only used for descriptive statistics of the main safety endpoints (AESI, meningitis, malaria [including cerebral malaria] and mortality).

The cumulative number of events were assessed after Dose 1/virtual Dose 1 for the study duration. IRs and IRRs were assessed during pre-defined at-risk periods for the event (see SAP Section 4.2.2.1 and Section 4.3.1.2.1).

11.4.1. Summary description of main endpoints

The analysis of malaria cases and death included cases recorded during both outpatient visits, or during home visits in the case of death, and hospitalizations. All other endpoints included events recorded during hospitalizations only.

The number of participants and confirmed cases for the main endpoints from hospitalization (and/or outpatient visits for Malaria endpoint) and/or occurring outside of a health care facility for deaths (cumulative number) reported during the study period are summarized by cluster/vaccination status for participants in Active Surveillance in [Table 11.9](#) and for participants in Enhanced Hospitalization Surveillance in [Table 11.10](#).

A summary of the number of participants and confirmed cases for the main endpoints by study site for participants in Active Surveillance is presented in Section 16 Table 16.1.1.9 (Enrolled Set) and Table 16.1.1.10 (Analysis Set), and for participants in Enhanced Hospitalization Surveillance in Section 16 Table 16.1.1.13 (Enrolled Set) and Table 16.1.1.14 (Analysis Set).

Table 11.9 Summary of safety: cumulative number of confirmed cases for the main endpoints – Active Surveillance – Analysis Set

	Exposed cluster		Unexposed cluster	
	Vaccinated (N=20641)	Unvaccinated (N=1807)	Vaccinated (N=254)	Unvaccinated (N=22210)
	n (%) [n*]	n (%) [n*]	n (%) [n*]	n (%) [n*]
Primary endpoint analyses				
AESI	32 (0.16) [34]	2 (0.11) [2]	0	31 (0.14) [32]
Intussusception	4 (0.02) [4]	0	0	5 (0.02) [5]
Renal insufficiency	0	1 (0.06) [1]	0	0
ADEM/Encephalitis	1 (0.00) [1]	0	0	0
Generalized convulsive seizure	25 (0.12) [27]	1 (0.006) [1]	0	22 (0.10) [22]
Anaphylaxis	1 (0.00) [1]	0		
Thrombocytopenia	1 (0.00) [1]	0	0	4 (0.02) [4]
Juvenile chronic arthritis	0	0	0	1 (0.00) [1]
Etiology-confirmed meningitis (including bacterial-confirmed)	1 (0.00) [1]	0	0	2 (0.01) [2]
Secondary safety endpoint analyses				
Meningitis: etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	11 (0.1) [11]	1 (0.1) [1]	0	15 (0.1) [15]
Malaria - any	9026 (43.7) [20825]	314 (17.4) [731]	81 (31.9) [136]	10277 (46.3) [27071]
Malaria - cerebral	10 (0.05) [10]	0	0	14 (0.1) [14]
Death - any	315 (1.5)	41 (2.3)	2 (0.8)	325 (1.5)
Females	162 (1.6)	21 (2.3)	0	161 (1.4)
Males	153 (1.5)	20 (2.2)	2 (1.6)	164 (1.5)
Hospitalization - Malaria	1426 (6.9) [1754]	73 (4.0) [92]	18 (7.1) [21]	1758 (7.9) [2193]
Anemia	1703 (8.25)	75 (4.15)	16 (6.30)	2087 (9.40)
Severe anemia	330 (1.60)	18 (1.00)	2 (0.79)	381 (1.72)

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of participants

n = number of participants reporting at least once the symptom

n* = at least one symptom experienced (regardless of the Term)

AESI = adverse events of special interest; ADEM = Acute Disseminated Encephalomyelitis

Source: Table 16.2.1.1 (03FEB2026 21:02 GMT), Table 16.2.1.2 (03FEB2026 21:02 GMT), Table 16.2.2.1 (03FEB2026 22:38 GMT), Table 16.2.2.2 (03FEB2026 22:38 GMT), Table 16.2.3.1 (03FEB2026 22:32 GMT), Table 16.2.3.2 (03FEB2026 22:32 GMT), Table 16.2.4.1 (03FEB2026 21:12 GMT) – Table 16.2.4.6 (03FEB2026 21:12 GMT), Table 16.2.5.1 (03FEB2026 22:28 GMT), Table 16.2.5.2 (03FEB2026 22:28 GMT), Table 16.2.6.1 (03FEB2026 21:07 GMT), Table 16.2.6.2 (03FEB2026 21:07 GMT)

Table 11.10 Summary of safety: cumulative number of confirmed cases for the main endpoints – Enhanced Hospitalization Surveillance - Analysis Set

	Exposed cluster		Unexposed cluster	
	Vaccinated (N=5791)	Unvaccinated (N=11487)	Vaccinated (N=161)	Unvaccinated (N=15306)
	n (%) [n*]	n (%) [n*]	n (%) [n*]	n (%) [n*]
Primary endpoint analyses				
AESI	8 (0.14) [9]	6 (0.05) [9]	1 (0.62) [2]	12 (0.08) [12]
..Intussusception	2 (0.03) [2]	1 (0.01) [1]	0	4 (0.03) [4]
..Renal insufficiency	0	1 (0.01) [1]	0	0
ADEM/Encephalitis	1 (0.02) [1]	0	0	1 (0.01) [1]
Generalized convulsive seizure	6 (0.10) [6]	5 (0.04) [7]	2 (1.24) [2]	5 (0.03) [5]
Thrombocytopenia	0	0	0	2 (0.01) [2]
Etiology-confirmed meningitis (including bacterial-confirmed)	0	1 (0.01) [1]	0	1 (0.01) [1]
Secondary safety endpoint analyses				
Meningitis: etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	2 (0.03) [2]	2 (0.02) [2]	0	7 (0.05) [7]
Malaria - any	480 (8.3) [614]	1243 (10.8) [1604]	11 (6.8) [13]	1501 (9.8) [1836]
Malaria - cerebral	1 (0.02) [1]	3 (0.03) [3]	0	2 (0.01) [2]
Death - any	76 (1.3)	179 (1.6)	1 (0.6)	151 (1.0)
Females	39 (1.5)	80 (1.5)	0	67 (1.0)
Males	37 (1.2)	99 (1.6)	1 (1.1)	84 (1.0)

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of participants

n = number of participants reporting at least once the symptom

n* = at least one symptom experienced (regardless of the Term)

AESI = adverse events of special interest; ADEM = Acute Disseminated Encephalomyelitis

Source: Table 16.2.1.3 (03FEB2026 21:02 GMT), Table 16.2.1.4 (03FEB2026 21:03 GMT), Table 16.2.2.3 (03FEB2026 22:38 GMT), Table 16.2.2.4 (03FEB2026 22:38 GMT), Table 16.2.3.3 (03FEB2026 22:32 GMT), Table 16.2.3.4 (03FEB2026 22:33 GMT), Table 16.2.4.7 (03FEB2026 21:11 GMT) – Table 16.2.4.12 (03FEB2026 21:12 GMT)

A summary of the incidence of confirmed cases during the at-risk period for the main endpoints after RTS,S/AS01_E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01_E vaccine/virtual Dose 4 are summarized for participants in Active Surveillance in [Table 11.11](#).

Table 11.11 Summary safety: Incidence Rate and Incidence Rate Ratio of confirmed cases after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 for the main endpoints – Cluster design comparison - Active Surveillance – Analysis Set

		After RTS,S/AS01E vaccine/virtual full schedule*			After RTS,S/AS01E vaccine/virtual Dose 4		
Endpoint / <i>at-risk period</i>		IR per 100 000 PYs (95% CI) [n]	Crude IRR (95% CI), p-value	IRR adjusted on country (95% CI), p-value	IR per 100 000 PYs (95% CI) [n]	Crude IRR (95% CI), p-value	IRR adjusted on country (95% CI), p-value
Primary endpoint							
AESI							
Generalized convulsive seizure / 2 weeks	Vacc	264.2 (114.1-520.5) [8]	NE	NE	339.2 (41.1-1225.4) [2]	NE	NE
	Unvacc	0 (0-111.6) [0]			0 (0-526.2) [0]		
Intussusception / 2 weeks	Vacc	0 (0-121.8) [0]	NE	NE	0 (0-625.6) [0]	NE	NE
	Unvacc	30.2 (0.8-168.5) [1]			0 (0-526.2) [0]		
Thrombocytopenia / 6 weeks	Vacc	0 (0-46.2) [0]	NE	NE	0 (0-218.5) [0]	NE	NE
	Unvacc	11.8 (0.3-65.6) [1]			49.9 (1.3-278.0) [1]		
Etiology-confirmed meningitis (incl. bacterial- confirmed) / 12 months	Vacc	2.6 (0.1-14.2) [1]	1.06 (0.07-16.98), 0.966	0.99 (0.06-15.85), 0.995	0 (0-25.9) [0]	NE	NE
	Unvacc	2.4 (0.1-13.4) [1]			0 (0-22.0) [0]		
Secondary safety endpoints							
Meningitis-protocol defined / 12 months	Vacc	20.4 (8.8-40.2) [8]	0.71 (0.29-1.73), 0.449	0.66 (0.27-1.61), 0.359	14.0 (1.7-50.7) [2]	1.17 (0.17-8.34), 0.872	1.00 (0.14-7.10), 0.999
	Unvacc	28.8 (14.9-50.4) [12]			12.0 (1.4-43.2) [2]		
Malaria – cerebral / 12 months	Vacc	12.8 (4.1-29.8) [5]	0.76 (0.24-2.39), 0.637	0.71 (0.22-2.23), 0.555	14.0 (1.7-50.7) [2]	0.59 (0.11-3.21), 0.539	0.52 (0.10-2.86), 0.455
	Unvacc	16.8 (6.8-34.6) [7]			23.9 (6.5-61.2) [4]		
Death – all-cause / 12 months	Vacc	502.5 (434.8-577.8) [197]	0.93 (0.76-1.12), 0.428	0.93 (0.76-1.12), 0.432	259.7 (182.8-357.9) [37]	0.91 (0.59-1.39), 0.649	0.93 (0.60-1.42), 0.726
	Unvacc	542.9 (474.4-618.5) [226]			286.9 (211.5-380.4) [48]		
Females	Vacc	497.7 (403.2-607.8) [96]	0.94 (0.71-1.23), 0.643	0.94 (0.71-1.23), 0.638	229.0 (130.9-371.9) [16]	0.84 (0.44-1.59), 0.588	0.86 (0.46-1.64), 0.652
	Unvacc	531.0 (436.8-639.4) [111]			273.2 (173.2-409.9) [23]		
Males	Vacc	507.1 (413.0-616.2) [101]	0.91 (0.70-1.19), 0.509	0.92 (0.70-1.20), 0.527	289.1 (179.0-442.0) [21]	0.96 (0.54-1.72), 0.894	0.98 (0.55-1.76), 0.954
	Unvacc	554.9 (458.1-666.1) [115]			300.8 (194.6-444.0) [25]		

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

Vacc = participants vaccinated with RTS,S/AS01E vaccine; Unvacc = participants not vaccinated with RTS,S/AS01E vaccine; AESI = adverse events of special interest

n = number of participants with at least one event reported / number of deaths during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Death: Incidence rate (IR) per 100 000 person-years = number of deaths per 100 000 person-years estimated as $n / \text{Person-years}$

AESI/Meningitis/Malaria: Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as $n / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

Source: Table 16.3.1.1 (03FEB2026 21:04 GMT), Table 16.3.1.3 (03FEB2026 21:05 GMT), Table 16.3.2.1 (03FEB2026 22:37 GMT), Table 16.3.2.3 (03FEB2026 22:38 GMT), Table 16.3.3.1 (03FEB2026 21:11 GMT), Table 16.3.3.3 (03FEB2026 21:11 GMT), Table 16.3.4.1 (03FEB2026 21:20 GMT), Table 16.3.4.3 (03FEB2026 21:21 GMT), Table 16.3.4.5 (03FEB2026 21:22 GMT), Table 16.3.4.7 (03FEB2026 21:20 GMT), Table 16.3.4.8 (03FEB2026 21:21 GMT), Table 16.3.4.9 (03FEB2026 21:23 GMT)

For analyses of effectiveness of participants in Active Surveillance, due to the imbalance in population size in RTS,S/AS01_E vaccinated (20 641) vs unvaccinated (1807) participants in exposed clusters, vaccine effectiveness for Direct Effect estimations should be interpreted with caution. A summary of vaccine effectiveness for Total Effect, which compares unvaccinated participants in unexposed clusters (22 210) to vaccinated participants in exposed clusters (20 641), are summarized for the main effectiveness and impact analysis as more robust estimates which took into account a larger portion of the enrolled population ([Table 11.12](#)):

- One year after Dose 4 of RTS,S/AS01_E evaluated from Dose 3 (i.e., for the duration of Dose 3 until 12 months after Dose 4), for children who have received the 3 doses before 12 months of age and Dose 4 of RTS,S/AS01_E before 30 months of age.

In addition, results are also summarized for effectiveness and impact of RTS,S/AS01_E 2 years after Dose 4, estimated only among participants who had completed all 4 doses/virtual doses according to the vaccination schedule:

- Two years after Dose 4 of RTS,S/AS01_E, for children who received it before 30 months of age, evaluated from the Dose 4.

Table 11.12 Summary of vaccine effectiveness (Total Effect) of RTS,S/AS01E vaccine on incidence of main endpoints 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance - Impact Analysis Set

Effectiveness endpoint	Vaccination status	1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3			2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4		
		IR per 100 000 PYs (95% CI)	Crude IRR (95% CI) p-value	IRR adjusted on country (95% CI) p-value	IR per 100 000 PYs (95% CI)	Crude IRR (95% CI) p-value	IRR adjusted on country (95% CI) p-value
Any malaria	Vacc	38099.0 (37385.2-38823.1)	0.86 (0.84-0.88), <0.001	0.84 (0.81-0.87), <0.001	33065.0 (32353.1-33788.7)	0.91 (0.89-0.94), <0.001	0.92 (0.89-0.95), <0.001
	Unvacc	44194.3 (43536.4-44859.7)			36208.9 (35561.4-36865.3)		
Severe malaria	Vacc	369.0 (301.8-446.7)	0.73 (0.58-0.92), 0.009	0.71 (0.56-0.90), 0.005	455.8 (375.7-548.0)	0.89 (0.70-1.13), 0.348	0.86 (0.67-1.09), 0.204
	Unvacc	506.0 (437.8-581.8)			511.0 (436.6-594.4)		
Hospitalization – malaria	Vacc	2793.6 (2602.8-2994.8)	0.78 (0.72-0.86), <0.001	0.75 (0.69-0.82), <0.001	2513.1 (2319.6-2718.4)	0.80 (0.72-0.88), <0.001	0.78 (0.70-0.86), <0.001
	Unvacc	3564.9 (3379.8-3757.5)			3144.9 (2956.1-3342.6)		
Death – all causes*	Vacc	112.4 (76.9-158.7)	0.91 (0.58-1.43), 0.687	0.94 (0.60-1.47), 0.793	238.0 (181.2-307.0)	1.00 (0.72-1.41), 0.985	1.04 (0.74-1.45), 0.840
	Unvacc	123.3 (90.9-163.5)			237.2 (187.5-296.1)		
Death - malaria	Vacc	38.7 (19.3-69.2)	0.94 (0.44-2.03), 0.876	0.95 (0.44-2.06), 0.903	84.7 (52.4-129.5)	0.93 (0.53-1.62), 0.794	0.95 (0.54-1.66), 0.846
	Unvacc	41.1 (23.5-66.7)			91.2 (61.6-130.3)		
		Prevalence (95% CI)	Crude OR (95% CI) p-value	OR adjusted on country (95% CI) p-value	Prevalence (95% CI)	Crude OR (95% CI) p-value	OR adjusted on country (95% CI) p-value
Anemia	Vacc	0.069 (0.064-0.073)	0.77 (0.71-0.84), <0.001	0.74 (0.68-0.81), <0.001	0.037 (0.034-0.040)	0.69 (0.61-0.77), <0.001	0.66 (0.59-0.74), <0.001
	Unvacc	0.087 (0.083-0.092)			0.053 (0.049-0.056)		
Severe anemia	Vacc	0.011 (0.009-0.013)	0.81 (0.66-1.00), 0.054	0.79 (0.64-0.97), 0.027	0.006 (0.005-0.008)	0.70 (0.53-0.91), 0.008	0.68 (0.52-0.88), 0.004
	Unvacc	0.014 (0.012-0.016)			0.009 (0.008-0.011)		

*All-cause death includes deaths associated with accidents and poisonings

Vacc = participants vaccinated with RTS,S/AS01E vaccine; Unvacc = participants not vaccinated with RTS,S/AS01E vaccine

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years); Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL); P-value = p-value for two-sided test H0: adjusted odds ratio = 1 (logistic model)

Prevalence = percentage of participants with at least one event (n/N)

OR adjusted = estimation of odds ratio using Binary Logistic regression model with Country as a fixed effect and unvaccinated as reference status

95% CI for prevalence = 95% confidence interval (Exact Binomial Method); LL = Lower Limit, UL = Upper Limit; 95% CI for adjusted OR = 95% confidence interval (logistic model)

Source: Table 16.4.1.3 (03FEB2026 22:35 GMT), Table 16.4.1.19 (03FEB2026 22:36 GMT), Table 16.4.2.3 (03FEB2026 21:08 GMT), Table 16.4.2.19 (03FEB2026 21:08 GMT), Table 16.4.3.3 (03FEB2026 22:30 GMT), Table 16.4.3.19 (03FEB2026 22:30 GMT), Table 16.4.4.7 (03FEB2026 22:11 GMT), Table 16.4.4.103 (03FEB2026 22:14 GMT)

11.4.2. Analysis of co-primary objectives**11.4.2.1. AESI****Cumulative number (%) of AESI***Active Surveillance*

In the Analysis Set, exposed clusters, 34 (0.15%) participants had at least 1 AESI (36 events) diagnosed at hospitalization (34 events in 32 participants RTS,S/AS01_E vaccinated and 2 events in 2 participants RTS,S/AS01_E unvaccinated) (Section 16 Table 16.2.1.1):

- RTS,S/AS01_E vaccinated:
 - Generalized convulsive seizure: 25 (0.12%) participants (27 events)
 - Intussusception: 4 (0.02%) participants (4 events)
 - ADEM/Encephalitis: 1 (0.00%) participant (1 event)
 - Anaphylaxis: 1 (0.00%) participant (1 event)
 - Thrombocytopenia: 1 (0.00%) participant (1 event).
- RTS,S/AS01_E unvaccinated:
 - Generalized convulsive seizure: 1 (0.06%) participant (1 event)
 - Renal insufficiency: 1 (0.06%) participant (1 event).
- No fatal AESI was reported.

In the Analysis Set, unexposed clusters, 31 (0.14%) participants had at least 1 AESI (32 events) diagnosed at hospitalization, all in RTS,S/AS01_E unvaccinated participants (Section 16 Table 16.2.1.2):

- RTS,S/AS01_E unvaccinated:
 - Generalized convulsive seizure: 22 (0.10%) participants (22 events)
 - Intussusception: 5 (0.02%) participants (5 events)
 - Thrombocytopenia: 4 (0.02%) participants (4 events)
 - Juvenile chronic arthritis: 1 (0.00%) participant (1 event).
- Fatal AESI were reported for 2 (0.01%) participants:
 - Intussusception: 1 participant
 - Generalized convulsive seizure: 1 participant.

Enhanced Hospitalization Surveillance

In the Analysis Set, exposed clusters, 14 (0.08%) participants had at least 1 AESI (18 events) diagnosed at hospitalization (9 events in 8 participants RTS,S/AS01_E vaccinated and 9 events in 6 participants RTS,S/AS01_E unvaccinated) (Section 16 Table 16.2.1.3):

- RTS,S/AS01_E vaccinated:
 - Generalized convulsive seizure: 6 (0.10%) participants (6 events)
 - Intussusception: 2 (0.03%) participants (2 events)
 - ADEM/Encephalitis: 1 (0.02%) participant (1 event).
- RTS,S/AS01_E unvaccinated:
 - Generalized convulsive seizure: 5 (0.04%) participants (7 events)
 - Intussusception: 1 (0.01%) participant (1 event)
 - Renal insufficiency: 1 (0.01%) participant (1 event).
- One fatal AESI (generalized convulsive seizure) was reported in a RTS,S/AS01_E vaccinated participant.

In the Analysis Set, unexposed clusters, 13 (0.08%) participants had at least 1 AESI (14 events) diagnosed at hospitalization (2 events in 1 participant RTS,S/AS01_E vaccinated and 12 events in 12 participants RTS,S/AS01_E unvaccinated) (Section 16 Table 16.2.1.4):

- RTS,S/AS01_E vaccinated:
 - Generalized convulsive seizure: 2 (1.24%) participants (2 events).
- RTS,S/AS01_E unvaccinated:
 - Generalized convulsive seizure: 5 (0.03%) participants (5 events)
 - Intussusception: 4 (0.03%) participants (4 events)
 - Thrombocytopenia: 2 (0.01%) participants (2 events)
 - ADEM/Encephalitis: 1 (0.01%) participant (1 event).
- One fatal AESI (thrombocytopenia) was reported in a RTS,S/AS01_E unvaccinated participant.

IR and IRR of AESI cases

After RTS,S/AS01_E vaccine/virtual full (4-dose) schedule

In the cluster design comparison, during the at-risk period for the AESI, 10 AESI were reported (Table 11.13):

- 8 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group were reported within the at-risk period of 2 weeks (all cases of seizure occurred with pyrexia; febrile convulsions are a known risk with RTS,S/AS01_E vaccination):
IR 264.2 (95% CI: 114.1-520.5) per 100 000 PYs.
- 1 case of intussusception in the RTS,S/AS01_E unvaccinated group was reported within the at-risk period of 2 weeks:
IR 30.2 (95% CI: 0.8-168.5) per 100 000 PYs.
- 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group was reported within the at-risk period of 6 weeks:
IR 11.8 (95% CI: 0.3-65.6) per 100 000 PYs.

After RTS,S/AS01_E vaccine/virtual Dose 4

In the cluster design comparison, during the at-risk period for the AESI, 3 AESI were reported ([Table 11.13](#)):

- 2 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group were reported within the at-risk period of 2 weeks (all cases of seizure occurred with pyrexia; febrile convulsions are a known risk with RTS,S/AS01_E vaccination):
IR 339.2 (95% CI: 41.1-1225.4) per 100 000 PYs.
- 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group was reported within the at-risk period of 6 weeks:
IR 49.9 (95% CI: 1.3-278.0) per 100 000 PYs.

The IR and IRR of AESI cases for within exposed clusters comparisons are presented in Section [16](#) Table 16.3.1.2 and Table 16.3.1.4.

Table 11.13 Incidence Rate and Incidence Rate Ratio of confirmed AESI cases (Final diagnosis) classified by body system and protocol definition after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance - Analysis Set

							IR per 100 000 PY 95% CI			Crude IRR 95% CI				IRR adjusted on Country 95% CI			
Protocol definition	At-risk period	Group	N	n*	n	Person- Years	Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																	
Generalised convulsive seizure	2 weeks	RTS,S vaccinated	20629	8	8	3028.3	264.2	114.1	520.5	NE				NE			
	2 weeks	Unvaccinated	21572	0	0	3306.1	0	0	111.6	-	-	-	-	-	-	-	-
Intussusception	2 weeks	RTS,S vaccinated	20629	0	0	3028.5	0	0	121.8	NE				NE			
	2 weeks	Unvaccinated	21572	1	1	3306.1	30.2	0.8	168.5	-	-	-	-	-	-	-	-
Thrombocytopenia	6 weeks	RTS,S vaccinated	20630	0	0	7989.6	0	0	46.2	NE				NE			
	6 weeks	Unvaccinated	21572	1	1	8495.2	11.8	0.3	65.6	-	-	-	-	-	-	-	-
After RTS,S/AS01E vaccine/virtual Dose 4																	
Generalised convulsive seizure	2 weeks	RTS,S vaccinated	14389	2	2	589.6	339.2	41.1	1225.4	NE				NE			
	2 weeks	Unvaccinated	17137	0	0	701.1	0	0	526.2	-	-	-	-	-	-	-	-
Thrombocytopenia	6 weeks	RTS,S vaccinated	14389	0	0	1688.4	0	0	218.5	NE				NE			
	6 weeks	Unvaccinated	17137	1	1	2004.4	49.9	1.3	278.0	-	-	-	-	-	-	-	-

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

Endpoint = hospitalized case confirmed as AESI and with final diagnosis assessed by External Expert Panel if available or by Principal Investigator (PI)

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose/dose 4 during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk; Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as n* / Person-years

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

Source: Table 16.3.1.1 (03FEB2026 21:04 GMT), Table 16.3.1.3 (03FEB2026 21:05 GMT)

11.4.2.2. Etiology-confirmed meningitis

Note: etiology-confirmed meningitis includes bacterial-confirmed meningitis.

Cumulative number (%) of etiology-confirmed meningitis*Active Surveillance*

In the Analysis Set, 3 cases of etiology-confirmed meningitis were reported in 3 participants:

- Exposed clusters: 1 (0.005%) participant, RTS,S/AS01_E vaccinated group (Section 16 Table 16.2.2.1)
- Unexposed clusters: 2 (0.01%) participants, RTS,S/AS01_E unvaccinated group (Section 16 Table 16.2.2.2).

Enhanced Hospitalization Surveillance

In the Analysis Set, 2 cases of etiology-confirmed meningitis were reported:

- Exposed clusters: 1 (0.01%) participant, RTS,S/AS01_E unvaccinated group (Section 16 Table 16.2.2.3)
- Unexposed clusters: 1 (0.01%) participant, RTS,S/AS01_E unvaccinated group (Section 16 Table 16.2.2.4).

IR and IRR of etiology-confirmed meningitis*After RTS,S/AS01_E vaccine/virtual full (4-dose) schedule*

In the cluster design comparison, during the 12 months at-risk period, 2 etiology-confirmed meningitis cases were reported (Table 11.14), 1 in the RTS,S/AS01_E vaccinated group and 1 in the RTS,S/AS01_E unvaccinated group:

- IR 2.6 (95% CI: 0.1-14.2) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 2.4 (95% CI: 0.1-13.4) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 1.06 (95% CI: 0.07-16.98; p=0.966)
IRR adjusted for country 0.99 (95% CI: 0.06-15.85; p=0.995).

No cases of etiology-confirmed meningitis were reported during the at-risk period of 12 months after Dose 4/virtual Dose 4.

The IR and IRR of etiology-confirmed meningitis, for within exposed clusters comparisons, are presented in Section 16 Table 16.3.2.2 and Table 16.3.2.4.

Table 11.14 Incidence rate and Incidence Rate Ratio of etiology-confirmed meningitis cases according to protocol definition (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule according to vaccination status– Cluster design comparison – Active Surveillance

							IR per 100 000 PY 95% CI			Crude IRR 95% CI			IRR adjusted on Country 95% CI				
Protocol definition	At-risk period	Group	N	n*	n	Person- Years	Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																	
Aetiology-confirmed meningitis (including Bacterial-confirmed)	12 months	RTS,S vaccinated	20632	1	1	39205.6	2.6	0.1	14.2	1.06	0.07	16.98	0.966	0.99	0.06	15.85	0.995
		Unvaccinated	21577	1	1	41629.6	2.4	0.1	13.4	-	-	-	-	-	-	-	-

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

Endpoint = final classification of meningitis case i.e. suspected meningitis case identified at hospitalization, confirmed at first line laboratory results and reviewed on second line laboratory results by external expert panel (EEP)

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose/dose 4 during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as $n^* / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

Source: Table 16.3.2.1 (03FEB2026 22:37 GMT)

11.4.3. Analysis of secondary safety objectives**11.4.3.1. Meningitis****Cumulative number (%) of meningitis cases**

A summary of the primary endpoint for etiology-confirmed (including bacterial-confirmed) meningitis cases is provided in Section 11.4.2.2.

Active Surveillance

In total 36/139 (25.9%) meningitis cases had a CSF sample collected and 31/139 (22.3%) CSF samples were sent to a second line laboratory (Section 16 Table 16.1.8.1). Due to the low proportion of CSF sampling conducted, data are summarized for any meningitis (including suspected meningitis ruled out afterwards) and protocol defined meningitis (etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis).

- **Any meningitis** was reported for (Section 16 Table 16.2.2.1 and Table 16.2.2.2):

Exposed clusters: 51 (0.2%) RTS,S/AS01_E vaccinated participants, 1 (0.1%)

RTS,S/AS01_E unvaccinated participant

Unexposed clusters: 3 (1.2%) RTS,S/AS01_E vaccinated participants, 77 (0.3%)

RTS,S/AS01_E unvaccinated participants.

Protocol defined meningitis was reported for:

Exposed clusters: 11 (0.1%) RTS,S vaccinated participants, 1 (0.1%) RTS,S/AS01_E unvaccinated participant

Unexposed clusters: 15 (0.1%) RTS,S/AS01_E unvaccinated participants.

Fatal meningitis was reported for:

Exposed clusters: 7 (0.03%) RTS,S/AS01_E vaccinated participants, 1 (0.1%)

RTS,S/AS01_E unvaccinated participant

Unexposed clusters: 14 (0.1%) RTS,S/AS01_E unvaccinated participants.

Enhanced Hospitalization Surveillance

- **Any meningitis** was reported for (Section 16 Table 16.2.2.3 and Table 16.2.2.4):

Exposed clusters: 12 (0.2%) RTS,S/AS01_E vaccinated participants, 11 (0.1%)

RTS,S/AS01_E unvaccinated participants

Unexposed clusters: 2 (1.2%) RTS,S vaccinated participants, 21 (0.1%)

RTS,S/AS01_E unvaccinated participants.

Protocol defined meningitis was reported for:

Exposed clusters: 2 (0.03%) RTS,S/AS01_E vaccinated participants, 2 (0.02%)

RTS,S/AS01_E unvaccinated participants

Unexposed clusters: 7 (0.05%) RTS,S/AS01_E unvaccinated participants.

Fatal meningitis was reported for:

Exposed clusters: 1 (0.01%) RTS,S/AS01_E unvaccinated participant

Unexposed clusters: 3 (0.02%) RTS,S/AS01_E unvaccinated participants.

IR and IRR of meningitis cases*After RTS,S/AS01_E vaccine/virtual full (4-dose) schedule*

In the cluster design comparison, no statistically significant difference in IR of protocol defined meningitis during an at-risk period of 12 months was observed ([Table 11.15](#)):

- IR 20.4 (95% CI: 8.8-40.2) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 28.8 (95% CI: 14.9-50.4) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.71 (95% CI: 0.29-1.73; p=0.449)
IRR adjusted on country 0.66 (95% CI: 0.27-1.61; p=0.359).

After RTS,S/AS01_E vaccine/virtual Dose 4

In the cluster design comparison, no statistically significant difference in IR of protocol defined meningitis during an at-risk period of 12 months was observed ([Table 11.15](#)):

- IR 14.0 (95% CI: 1.7-50.7) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 12.0 (95% CI: 1.4-43.2) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 1.17 (95% CI: 0.17-8.34; p=0.872)
IRR adjusted on country 1.00 (95% CI: 0.14-7.10; p=0.999).

The IR and IRR of meningitis cases for within exposed clusters comparisons are presented in Section [16](#) Table 16.3.2.2 and Table 16.3.2.4.

Table 11.15 Incidence rate (IR) and Incidence Rate Ratio (IRR) of meningitis cases according to protocol definition (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance

Protocol definition	At-risk period	Group	N	n*	n	Person-Years	IR per 100 000 PY 95% CI			Crude IRR 95% CI				IRR adjusted on Country 95% CI			
							Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																	
Aetiology-confirmed meningitis (including bacterial-confirmed)	12 months	Vacc	20632	1	1	39205.6	2.6	0.1	14.2	1.06	0.07	16.98	0.966	0.99	0.06	15.85	0.995
		Unvacc	21577	1	1	41629.6	2.4	0.1	13.4	-	-	-	-	-	-	-	-
Probable meningitis	12 months	Vacc	20632	2	2	39204.6	5.1	0.6	18.4	2.12	0.19	23.42	0.539	2.13	0.19	23.60	0.537
		Unvacc	21577	1	1	41629.6	2.4	0.1	13.4	-	-	-	-	-	-	-	-
Clinically suspected meningitis	12 months	Vacc	20632	5	5	39205.0	12.8	4.1	29.8	0.53	0.18	1.55	0.248	0.49	0.17	1.42	0.187
		Unvacc	21577	10	10	41627.9	24.0	11.5	44.2	-	-	-	-	-	-	-	-
Aetiology-confirmed, bacterial-confirmed or probable meningitis	12 months	Vacc	20632	3	3	39204.6	7.7	1.6	22.4	1.59	0.27	9.53	0.610	1.55	0.26	9.31	0.630
		Unvacc	21577	2	2	41629.5	4.8	0.6	17.4	-	-	-	-	-	-	-	-
Aetiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	12 months	Vacc	20632	8	8	39204.0	20.4	8.8	40.2	0.71	0.29	1.73	0.449	0.66	0.27	1.61	0.359
		Unvacc	21577	12	12	41627.8	28.8	14.9	50.4	-	-	-	-	-	-	-	-
After RTS,S/AS01E vaccine/virtual Dose 4																	
Aetiology-confirmed meningitis (including bacterial-confirmed)	12 months	Vacc	14380	0	0	14249.4	0	0	25.9	NE	-	-	-	NE	-	-	-
		Unvacc	17132	0	0	16731.8	0	0	22.0	-	0.07	18.77	0.910	1.05	0.07	16.83	0.973
Probable meningitis	12 months	Vacc	14380	1	1	14248.6	7.0	0.2	39.1	1.17	0.07	18.77	0.910	1.05	0.07	16.83	0.973
		Unvacc	17132	1	1	16731.8	6.0	0.2	33.3	-	-	-	-	-	-	-	-
Clinically suspected meningitis	12 months	Vacc	14380	1	1	14249.3	7.0	0.2	39.1	1.17	0.07	18.77	0.910	0.95	0.06	15.19	0.971
		Unvacc	17132	1	1	16731.8	6.0	0.2	33.3	-	-	-	-	-	-	-	-
Aetiology-confirmed, bacterial-confirmed or probable meningitis	12 months	Vacc	14380	1	1	14248.6	7.0	0.2	39.1	1.17	0.07	18.77	0.910	1.05	0.07	16.83	0.973
		Unvacc	17132	1	1	16731.8	6.0	0.2	33.3	-	-	-	-	-	-	-	-
Aetiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis	12 months	Vacc	14380	2	2	14248.6	14.0	1.7	50.7	1.17	0.17	8.34	0.872	1.00	0.14	7.10	0.999
		Unvacc	17132	2	2	16731.8	12.0	1.4	43.2	-	-	-	-	-	-	-	-

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

Vacc = participants vaccinated with RTS,S/AS01E vaccine; Unvacc = participants not vaccinated with RTS,S/AS01E vaccine

Endpoint = final classification of meningitis case i.e. suspected meningitis case identified at hospitalization, confirmed at first line laboratory results and reviewed on second line laboratory results by external expert panel (EEP)

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose/dose 4 during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as $n^* / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

Source: Table 16.3.2.1 (03FEB2026 22:37 GMT), Table 16.3.2.3 (03FEB2026 22:38 GMT)

11.4.3.2. Cerebral malaria**Cumulative number (%) of cerebral malaria cases***Active Surveillance*

The cumulative number of malaria cases by vaccination status for exposed and unexposed clusters for all categories of malaria are provided in Section 11.4.4.1 (Table 11.21). For the safety endpoint of cerebral malaria:

- Twenty four cases of cerebral malaria were reported (Section 16 Table 16.2.3.1, Table 16.2.3.2):
Exposed clusters: 10 (0.05%) cases in RTS,S/AS01_E vaccinated participants
Unexposed clusters: 14 (0.1%) cases in RTS,S/AS01_E unvaccinated participants.

Enhanced Hospitalization Surveillance

The cumulative number of malaria cases by vaccination status for exposed and unexposed clusters for all categories of malaria are provided in Section 11.4.4.1. For the safety endpoint of cerebral malaria:

- Six cases of cerebral malaria were reported (Section 16 Table 16.2.3.3, Table 16.2.3.4):
Exposed clusters: 1 (0.02%) case in RTS,S/AS01_E vaccinated participant, 3 (0.03%) cases in RTS,S/AS01_E unvaccinated participants
Unexposed clusters: 2 (0.01%) cases in RTS,S/AS01_E unvaccinated participants.

IR and IRR of cerebral malaria*After RTS,S/AS01_E vaccine/virtual full (4-dose) schedule*

In the cluster design comparison, during an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual full (4-dose) schedule, 5 cases of cerebral malaria were reported in the RTS,S/AS01_E vaccinated group and 7 cases in the RTS,S/AS01_E unvaccinated group (Table 11.16).

- IR 12.8 (95% CI: 4.1-29.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group
 IR 16.8 (95% CI: 6.8-34.6) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
 Crude IRR 0.76 (95% CI: 0.24-2.39; p=0.637)
 IRR adjusted on country 0.71 (95% CI: 0.22-2.23; p=0.555).

After RTS,S/AS01_E vaccine/virtual Dose 4

In the cluster design comparison, during an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual Dose 4, 2 cases of cerebral malaria were reported in the RTS,S/AS01_E vaccinated group and 4 cases in the RTS,S/AS01_E unvaccinated group (Table 11.16).

- IR 14.0 (95% CI: 1.7-50.7) per 100 000 PY in the RTS,S/AS01_E vaccinated group
IR 23.9 (95% CI: 6.5-61.2) per 100 000 PY in the RTS,S/AS01_E unvaccinated group
Crude IRR 0.59 (95% CI: 0.11-3.21; p=0.539)
IRR adjusted on country 0.52 (95% CI: 0.10-2.86; p=0.455).

The IR and IRR of cerebral malaria cases for within exposed clusters comparisons are presented in Section 16 Table 16.3.3.2 and Table 16.3.3.4.

Table 11.16 Incidence rate and Incidence Rate Ratio of cerebral malaria cases (Final diagnosis) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance

							IR per 100 000 PY 95% CI			Crude IRR 95% CI			IRR adjusted on Country 95% CI				
Protocol definition	At-risk period	Group	N	n*	n	Person- Years	Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																	
Cerebral Malaria Cases	12 months	RTS,S vaccinated	20632	5	5	39203.6	12.8	4.1	29.8	0.76	0.24	2.39	0.637	0.71	0.22	2.23	0.555
	12 months	Unvaccinated	21577	7	7	41627.4	16.8	6.8	34.6	-	-	-	-	-	-	-	-
After RTS,S/AS01E vaccine/virtual Dose 4																	
Cerebral Malaria Cases	12 months	RTS,S vaccinated	14380	2	2	14248.6	14.0	1.7	50.7	0.59	0.11	3.21	0.539	0.52	0.10	2.86	0.455
	12 months	Unvaccinated	17132	4	4	16729.7	23.9	6.5	61.2	-	-	-	-	-	-	-	-

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose/dose 4 during follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Endpoint = hospitalized case confirmed as cerebral malaria and with final diagnosis assessed by external expert panel (EEP)

Incidence rate (IR) per 100 000 person-years = number of first events post each dose/dose 4 per 100 000 person-years estimated as $n^* / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

Source: Table 16.3.3.1 (03FEB2026 21:11 GMT), Table 16.3.3.3 (03FEB2026 21:11 GMT)

11.4.3.3. Deaths**Cumulative number (%) of deaths***Active Surveillance*

A summary of the cumulative number of deaths (all causes and by category) in RTS,S/AS01_E vaccinated and unvaccinated participants in exposed and unexposed clusters is provided in

[Table 11.17](#). Additional results for cause of death by MedDRA PT, and analyses by gender, are provided in [Section 16](#) Table 16.2.4.1 to Table 16.2.4.6.

- All-cause death was reported for:
 - Exposed clusters: 315 (1.5%) RTS,S/AS01_E vaccinated participants (78 at hospital, 198 verbal autopsy), 41 (2.3%) RTS,S/AS01_E unvaccinated participants (10 at hospital, 27 verbal autopsy)
 - Unexposed clusters: 2 (0.8%) RTS,S/AS01_E vaccinated participants (1 at hospital, 1 verbal autopsy) and 325 (1.5%) RTS,S/AS01_E unvaccinated participants (68 at hospital, 217 verbal autopsy).
- All-cause death in females was reported for:
 - Exposed clusters: 162 (1.6%) RTS,S/AS01_E vaccinated participants, 21 (2.3%) RTS,S/AS01_E unvaccinated participants.
 - Unexposed clusters: 161 (1.4%) RTS,S/AS01_E unvaccinated participants.
- All-cause death in males was reported for:
 - Exposed clusters: 153 (1.5%) RTS,S/AS01_E vaccinated participants, 20 (2.2%) RTS,S/AS01_E unvaccinated participants.
 - Unexposed clusters: 2 (1.6%) RTS,S/AS01_E vaccinated participants, 164 (1.5%) RTS,S/AS01_E unvaccinated participants.

Enhanced Hospitalization Surveillance

A summary of the cumulative number of deaths (all causes and by category) in RTS,S/AS01_E vaccinated and unvaccinated participants in exposed and unexposed clusters is provided in

[Table 11.17](#). Additional results for cause of death by MedDRA PT, and analyses by gender, are provided in [Section 16](#) Table 16.2.4.7 to Table 16.2.4.12.

- All-cause death was reported for:
 - Exposed clusters: 76 (1.3%) RTS,S/AS01_E vaccinated participants (29 at hospital, 38 verbal autopsy), 179 (1.6%) RTS,S/AS01_E unvaccinated participants (69 at hospital, 102 verbal autopsy)
 - Unexposed clusters: 1 (0.6%) RTS,S/AS01_E vaccinated participants and 151 (1.0%) RTS,S/AS01_E unvaccinated participants (74 at hospital, 61 verbal autopsy).

- All-cause death in females was reported for:
Exposed clusters: 39 (1.5%) RTS,S/AS01_E vaccinated participants, 80 (1.5%) RTS,S/AS01_E unvaccinated participants
Unexposed clusters: 67 (1.0%) RTS,S/AS01_E unvaccinated participants.
- All-cause death in males was reported for:
Exposed clusters: 37 (1.2%) RTS,S/AS01_E vaccinated participants, 99 (1.6%) RTS,S/AS01_E unvaccinated participants
Unexposed clusters: 1 (1.1%) RTS,S/AS01_E vaccinated participant, 84 (1.0%) RTS,S/AS01_E unvaccinated participants.

Table 11.17 Cumulative number (%) of deaths (Final diagnosis) by RTS,S/AS01E vaccination status – Exposed and Unexposed Clusters – Analysis Set

Cluster	Active Surveillance		Enhanced Hospitalization Surveillance	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Exposed	(N=20 641) n (%)	(N=1807) n (%)	(N=5791) n (%)	(N=11 487) n (%)
Death – all causes*	315 (1.5)	41 (2.3)	76 (1.3)	179 (1.6)
Death - AE	246 (1.2)	39 (2.2)	71 (1.2)	161 (1.4)
Death – Malaria	67 (0.3)	2 (0.1)	4 (0.1)	16 (0.1)
Death – <i>P. falciparum</i>	28 (0.1)	0	1 (0.02)	3 (0.03)
Death - Meningitis	1 (0.005)	0	1 (0.02)	1 (0.01)
Death - AESI	1 (0.005)	0	0	1 (0.01)
Unexposed	(N=254) n (%)	(N=22 210) n (%)	(N=161) n (%)	(N=15 306) n (%)
Death – all causes*	2 (0.8)	325 (1.5)	1 (0.6)	151 (1.0)
Death - AE	2 (0.8)	247 (1.1)	1 (0.6)	121 (0.8)
Death – Malaria	0	66 (0.3)	0	26 (0.2)
Death – <i>P. falciparum</i>	0	27 (0.1)	0	10 (0.1)
Death - Meningitis	0	7 (0.03)	0	2 (0.01)
Death - AESI	0	5 (0.02)	0	2 (0.01)

*All-cause death includes deaths associated with accidents and poisonings

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

AE = Adverse event; AESI = Adverse event of special interest

N = total number of participants

n = number of participants in a given category

% = percentage of participants in a given category

Source: Table 16.2.4.1 (03FEB2026 21:12 GMT), Table 16.2.4.4 (03FEB2026 21:12 GMT), Table 16.2.4.7 (03FEB2026 21:11 GMT), Table 16.2.4.10 (03FEB2026 21:12 GMT)

IR and IRR of death

The IR and IRR for death reported during the at-risk period of 12 months (Table 11.18 and Table 11.19):

After RTS,S/AS01_E vaccine/virtual full (4-dose) schedule

In the cluster design comparison, there was no statistically significant difference between RTS,S/AS01_E vaccinated and unvaccinated participants in the IR of all-cause death (overall and by gender) and overall death due to “other AE” (safety events different from the pre-defined AESI, meningitis and malaria) during an at-risk period of 12 months after the full/virtual vaccination schedule ([Table 11.18](#) and [Table 11.19](#)):

- **All-cause death:**

IR 502.5 (95% CI: 434.8-577.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 542.9 (95% CI: 474.4-618.5) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.93 (95% CI: 0.76-1.12; p=0.428)

IRR adjusted on country 0.93 (95% CI: 0.76-1.12; p=0.432).

Females:

Crude IRR 0.94 (95% CI: 0.71-1.23; p=0.643)

IRR adjusted on country 0.94 (95% CI: 0.71-1.23; p=0.638).

Males:

Crude IRR 0.91 (95% CI: 0.70-1.19; p=0.509)

IRR adjusted on country 0.92 (95% CI: 0.70-1.20; p=0.527).

- **Death – “Other AE”:**

IR 408.1 (95% CI: 347.3-476.5) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 430.0 (95% CI: 369.3-497.8) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.95 (95% CI: 0.77-1.17; p=0.631)

IRR adjusted on country 0.96 (95% CI: 0.77-1.18; p=0.677).

After RTS,S/AS01_E vaccine/virtual Dose 4

In the cluster design comparison, there was no statistically significant difference between RTS,S/AS01_E vaccinated and unvaccinated participants in the IR of all-cause death (overall and by gender) and overall death due to “other AE” (safety events different from the pre-defined AESI, meningitis and malaria) during an at-risk period of 12 months after the RTS,S/AS01_E vaccine/virtual Dose 4 ([Table 11.18](#) and [Table 11.19](#)):

- **All-cause death:**

IR 259.7 (95% CI: 182.8-357.9) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 286.9 (95% CI: 211.5-380.4) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.91 (95% CI: 0.59-1.39; p=0.649)

IRR adjusted on country 0.93 (95% CI: 0.60-1.42; p=0.726).

Females:

Crude IRR 0.84 (95% CI: 0.44-1.59; p=0.588)

IRR adjusted on country 0.86 (95% CI: 0.46-1.64; p=0.652).

Males:

Crude IRR 0.96 (95% CI: 0.54-1.72; p=0.894)

IRR adjusted on country 0.98 (95% CI: 0.55-1.76; p=0.954).

- **Death – “Other AE”:**

IR 154.4 (95% CI: 96.8-233.8) per 100 000 PY in the RTS,S/AS01_E vaccinated group

IR 185.3 (95% CI: 125.9-263.0) per 100 000 PY in the RTS,S/AS01_E unvaccinated group

Crude IRR 0.83 (95% CI: 0.48-1.44; p=0.513)

IRR adjusted on country 0.87 (95% CI: 0.50-1.50; p=0.605).

The IR and IRR by cause of death for the within exposed clusters comparisons are presented in Section 16 Table 16.3.4.2, Table 16.3.4.4 to Table 16.3.4.6, Table 16.3.4.10 to Table 16.3.4.12. The IR and IRR of death causes excluding specific causes of death for the cluster design and within exposed clusters comparison, overall and by gender, are presented in Section 16 Table 16.3.4.13 to Table 16.3.4.24.

Table 11.18 Incidence rate and incidence rate ratio of death causes classified by protocol definition after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status– Cluster design comparison – Active Surveillance - Analysis Set

						IR per 100 000 PY 95% CI			Crude IRR 95% CI				IRR adjusted on Country 95% CI			
Protocol definition	At-risk period	Group	N	n	Person- Years	Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																
Death - all causes**	12 months	RTS,S vaccinated	20632	197	39205.6	502.5	434.8	577.8	0.93	0.76	1.12	0.428	0.93	0.76	1.12	0.432
		Unvaccinated	21577	226	41629.6	542.9	474.4	618.5	-	-	-	-	-	-	-	-
Death - AESI	12 months	RTS,S vaccinated	20632	1	39205.6	2.6	0.1	14.2	0.27	0.03	2.38	0.236	0.24	0.03	2.14	0.201
		Unvaccinated	21577	4	41629.6	9.6	2.6	24.6	-	-	-	-	-	-	-	-
Death - P. falciparum	12 months	RTS,S vaccinated	20632	16	39205.6	40.8	23.3	66.3	0.85	0.44	1.64	0.627	0.84	0.43	1.61	0.594
		Unvaccinated	21577	20	41629.6	48.0	29.3	74.2	-	-	-	-	-	-	-	-
Death - Malaria	12 months	RTS,S vaccinated	20632	35	39205.6	89.3	62.2	124.2	0.98	0.62	1.55	0.924	0.96	0.61	1.53	0.877
		Unvaccinated	21577	38	41629.6	91.3	64.6	125.3	-	-	-	-	-	-	-	-
Death - Meningitis	12 months	RTS,S vaccinated	20632	1	39205.6	2.6	0.1	14.2	0.21	0.02	1.82	0.157	0.20	0.02	1.69	0.139
		Unvaccinated	21577	5	41629.6	12.0	3.9	28.0	-	-	-	-	-	-	-	-
Death - AE	12 months	RTS,S vaccinated	20632	160	39205.6	408.1	347.3	476.5	0.95	0.77	1.17	0.631	0.96	0.77	1.18	0.677
		Unvaccinated	21577	179	41629.6	430.0	369.3	497.8	-	-	-	-	-	-	-	-
After RTS,S/AS01E vaccine/virtual Dose 4																
Death - all causes**	12 months	RTS,S vaccinated	14380	37	14249.4	259.7	182.8	357.9	0.91	0.59	1.39	0.649	0.93	0.60	1.42	0.726
		Unvaccinated	17132	48	16731.8	286.9	211.5	380.4	-	-	-	-	-	-	-	-
Death - AESI	12 months	RTS,S vaccinated	14380	0	14249.4	0	0	25.9	NE	-	-	-	NE	-	-	-
		Unvaccinated	17132	0	16731.8	0	0	22.0	-	-	-	-	-	-	-	-
Death - P. falciparum	12 months	RTS,S vaccinated	14380	5	14249.4	35.1	11.4	81.9	0.73	0.24	2.24	0.587	0.72	0.23	2.20	0.560
		Unvaccinated	17132	8	16731.8	47.8	20.6	94.2	-	-	-	-	-	-	-	-
Death - Malaria	12 months	RTS,S vaccinated	14380	15	14249.4	105.3	58.9	173.6	1.10	0.54	2.23	0.789	1.10	0.54	2.23	0.792
		Unvaccinated	17132	16	16731.8	95.6	54.7	155.3	-	-	-	-	-	-	-	-
Death - Meningitis	12 months	RTS,S vaccinated	14380	0	14249.4	0	0	25.9	NE	-	-	-	NE	-	-	-
		Unvaccinated	17132	1	16731.8	6.0	0.2	33.3	-	-	-	-	-	-	-	-
Death - AE	12 months	RTS,S vaccinated	14380	22	14249.4	154.4	96.8	233.8	0.83	0.48	1.44	0.513	0.87	0.50	1.50	0.605
		Unvaccinated	17132	31	16731.8	185.3	125.9	263.0	-	-	-	-	-	-	-	-

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

**All-cause death includes deaths associated with accidents and poisonings

AE = adverse event; AESI = adverse event of special interest

N = number of evaluable participants with follow-up during the at-risk period ; n = number of deaths during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Incidence rate (IR) per 100 000 person-years = number of deaths per 100 000 person-years estimated as $n / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

NE = Estimation could not be evaluated due to not enough events

Source: Table 16.3.4.1 (03FEB2026 21:20 GMT), Table 16.3.4.7 (03FEB2026 21:20 GMT)

Table 11.19 Incidence rate and incidence rate ratio of death (all causes) after RTS,S/AS01E vaccine/virtual full (4-dose) schedule and after RTS,S/AS01E vaccine/virtual Dose 4 according to vaccination status by gender – Cluster design comparison – Active Surveillance - Analysis Set

						IR per 100 000 PY 95% CI			Crude IRR 95% CI				IRR adjusted on Country 95% CI			
Protocol definition	At-risk period	Group	N	n	Person- Years	Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
After RTS,S/AS01E vaccine/virtual full schedule*																
FEMALES																
Death - all causes**	12 months	RTS,S vaccinated	10185	96	19287.8	497.7	403.2	607.8	0.94	0.71	1.23	0.643	0.94	0.71	1.23	0.638
		Unvaccinated	10853	111	20905.5	531.0	436.8	639.4	-	-	-	-	-	-	-	-
MALES																
Death - all causes**	12 months	RTS,S vaccinated	10447	101	19917.8	507.1	413.0	616.2	0.91	0.70	1.19	0.509	0.92	0.70	1.20	0.527
		Unvaccinated	10724	115	20724.1	554.9	458.1	666.1	-	-	-	-	-	-	-	-
After RTS,S/AS01E vaccine/virtual Dose 4																
FEMALES																
Death - all causes**	12 months	RTS,S vaccinated	7049	16	6986.1	229.0	130.9	371.9	0.84	0.44	1.59	0.588	0.86	0.46	1.64	0.652
		Unvaccinated	8625	23	8419.5	273.2	173.2	409.9	-	-	-	-	-	-	-	-
MALES																
Death - all causes**	12 months	RTS,S vaccinated	7331	21	7263.2	289.1	179.0	442.0	0.96	0.54	1.72	0.894	0.98	0.55	1.76	0.954
		Unvaccinated	8507	25	8312.3	300.8	194.6	444.0	-	-	-	-	-	-	-	-

*RTS,S/AS01E vaccine/virtual full schedule, i.e., combining the RTS,S/AS01E 4 doses/virtual doses and with follow-up of 1 year after Dose 4

**All-cause death includes deaths associated with accidents and poisonings

N = number of evaluable participants with follow-up during the at-risk period ; n = number of deaths during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of deaths per 100 000 person-years estimated as $n / \text{Person-years}$

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

Source: Table 16.3.4.3 (03FEB2026 21:21 GMT), Table 16.3.4.5 (03FEB2026 21:22 GMT), Table 16.3.4.8 (03FEB2026 21:21 GMT), Table 16.3.4.9 (03FEB2026 21:23 GMT)

11.4.3.4. Hospitalization**Cumulative number (%) of hospitalizations due to malaria***Active Surveillance*

In the Analysis Set, hospitalizations due to malaria were reported for exposed and unexposed clusters (Section 16 Table 16.2.5.1, Table 16.2.5.2):

- Exposed clusters:
1426 (6.9%) RTS,S/AS01_E vaccinated participants (1754 hospitalizations), due to *P. falciparum* in 1420 (6.9%) participants (1747 hospitalizations)
73 (4.0%) RTS,S/AS01_E unvaccinated participants (92 hospitalizations), due to *P. falciparum* in 73 (4.0%) participants (92 hospitalizations).
- Unexposed clusters:
18 (7.1%) RTS,S/AS01_E vaccinated participants (21 hospitalizations), due to *P. falciparum* in 18 (7.1%) RTS,S/AS01_E vaccinated participants (21 hospitalizations)
1758 (7.9%) RTS,S/AS01_E unvaccinated participants (2193 hospitalizations), due to *P. falciparum* in 1736 (7.8%) participants (2170 hospitalizations).

11.4.3.5. Anemia**Cumulative number (%) of anemia/severe anemia cases***Active Surveillance*

In the Analysis Set, hospitalizations due to anemia were reported for exposed and unexposed clusters (Section 16 Table 16.2.6.1, Table 16.2.6.2):

- Exposed clusters:
1703 (8.25%) RTS,S/AS01_E vaccinated participants (2249 hospitalizations), due to severe anemia in 330 (1.60%) participants (382 hospitalizations)
75 (4.15%) RTS,S/AS01_E unvaccinated participants (112 hospitalizations), due to severe anemia in 18 (1.00%) participants (19 hospitalizations).
- Unexposed clusters:
16 (6.30%) RTS,S/AS01_E vaccinated participants (22 hospitalizations), due to severe anemia in 2 (0.79%) participants (2 hospitalizations)
2087 (9.40%) RTS,S/AS01_E unvaccinated participants (2837 hospitalizations), due to severe anemia in 381 (1.72%) participants (440 hospitalizations).

11.4.4. Analysis of secondary effectiveness and impact objectives

Comparisons for vaccine effectiveness and impact endpoints are summarized in [Table 11.20](#).

Due to the imbalance in population size in RTS,S/AS01_E vaccinated (20 641) vs unvaccinated (1807) participants in exposed clusters for vaccine effectiveness (Direct Effect) estimations, and the imbalance in population size in RTS,S/AS01_E unvaccinated participants in unexposed clusters (22 210) vs unvaccinated in exposed clusters (1807) for vaccine impact (Indirect Effect) estimations, results should be interpreted with caution.

Table 11.20 Summary of the comparisons for vaccine effectiveness and impact endpoints

	EPI-MAL-003 CLUSTERS	
VACCINE IMPACT	UNEXPOSED	EXPOSED
Total Effect	Unvaccinated (N=22 210) vs	Vaccinated (N=20 641)
Overall Effect	Unvaccinated (N=22 210) vs	Vaccinated & Unvaccinated (N=22 448)
Indirect Effect	Unvaccinated (N=22 210) vs	Unvaccinated (N=1807)
EFFECTIVENESS	EXPOSED	
Direct Effect	Unvaccinated (N=1807) vs Vaccinated (N=20 641)	

Vaccinated = participants vaccinated with at least 1 dose of RTS,S/AS01_E vaccine

Unvaccinated = participants without RTS,S/AS01_E vaccine reported in eCRF

Source: Table 16.1.1.3 (03FEB2026 22:47 GMT)

As predefined in the SAP (SAP Section 4.3.2), results are presented for the main effectiveness and impact analysis:

- One year after Dose 4 of RTS,S/AS01_E evaluated from Dose 3 (i.e., for the duration of Dose 3 until 12 months after Dose 4), for children who have received the 3 doses before 12 months of age and Dose 4 of RTS,S/AS01_E before 30 months of age.

In addition, results are also summarized for effectiveness and impact of RTS,S/AS01_E 2 years after Dose 4, estimated only among participants who had completed all 4 doses/virtual doses according to the vaccination schedule:

- Two years after Dose 4 of RTS,S/AS01_E, for children who received it before 30 months of age, evaluated from the Dose 4.

Additional analyses are presented in post-text tables, as referenced in the following sections, on effectiveness and impact endpoints at:

- Two years after Dose 3 of RTS,S/AS01_E vaccine evaluated from Dose 3 (given before 12 months of age), and for children who did not receive Dose 4 of RTS,S/AS01_E
- Two years after Dose 4 of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from Dose 1 of vaccine

- Two years after Dose 4 of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from Dose 3 of vaccine (received before 12 months of age).

11.4.4.1. Malaria

Cumulative number (%) of malaria cases

Active Surveillance

A summary of the cumulative number of any malaria cases diagnosed per protocol, any uncomplicated malaria, and any severe malaria by RTS,S/AS01_E vaccination status in exposed and unexposed clusters is provided in [Table 11.21](#). Results for cerebral malaria are summarized in Section [11.4.3.2](#).

- The proportion of any malaria diagnosed per protocol was:
Exposed clusters: 43.7% (9026\20 641) in RTS,S/AS01_E vaccinated participants, 17.4% (314\1807) in RTS,S/AS01_E unvaccinated participants
Unexposed clusters: 31.9% (81\254) in RTS,S/AS01_E vaccinated participants and 46.3% (10 277\22 210) in RTS,S/AS01_E unvaccinated participants.
 The proportion of severe malaria was:
Exposed clusters: 1.3% (268\20 641) in RTS,S/AS01_E vaccinated participants and 0.8% (14\1807) in RTS,S/AS01_E unvaccinated participants
Unexposed clusters: 2.8% (7\254) in RTS,S/AS01_E vaccinated participants and 1.6% (357\22 210) in RTS,S/AS01_E unvaccinated participants.
- One case of *P. ovale* was reported in a RTS,S/AS01_E vaccinated participant. No cases of *P. vivax* or *P. malaria* were reported.

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final**Table 11.21 Cumulative number (%) of malaria cases (Final diagnosis) by RTS,S/AS01E vaccination status – Exposed and Unexposed Clusters – Active Surveillance - Analysis Set**

	RTS,S vaccinated			Unvaccinated			Overall		
	Outpatient visit or			Outpatient visit or			Outpatient visit or		
	Participants N=20641	Hospitalizations N=88065	Events N=20825	Participants N=1807	Hospitalizations N=2192	Events N=731	Participants N=22448	Hospitalizations N=90257	Events N=21556
Exposed clusters									
Any Malaria per protocol	9026 (43.7%)	21597 (24.5%)	20825 (100%)	314 (17.4%)	762 (34.8%)	731 (100%)	9340 (41.6%)	22359 (24.8%)	21556 (100%)
Any uncomplicated Malaria	8901 (43.1%)	21249 (24.1%)	20523 (98.5%)	304 (16.8%)	745 (34.0%)	717 (98.1%)	9205 (41.0%)	21994 (24.4%)	21240 (98.5%)
- Uncomplicated P. falciparum	8616 (41.7%)	20576 (23.4%)	19854 (95.3%)	282 (15.6%)	696 (31.8%)	668 (91.4%)	8898 (39.6%)	21272 (23.6%)	20522 (95.2%)
- Uncomplicated P. ovale	1 (0.005%)	1 (0.001%)	1 (0.005%)	0	0	0	1 (0.004%)	1 (0.001%)	1 (0.005%)
- Uncomplicated P. vivax	0	0	0	0	0	0	0	0	0
- Uncomplicated P. malaria	5 (0.02%)	5 (0.01%)	5 (0.02%)	0	0	0	5 (0.02%)	5 (0.01%)	5 (0.02%)
- Uncomplicated subtype unknown	514 (2.5%)	664 (0.8%)	660 (3.2%)	32 (1.8%)	49 (2.2%)	49 (6.7%)	546 (2.4%)	713 (0.8%)	709 (3.3%)
- Uncomplicated multiple subtype	3 (0.01%)	3 (0.003%)	3 (0.01%)	0	0	0	3 (0.01%)	3 (0.003%)	3 (0.01%)
Any severe Malaria	268 (1.3%)	348 (0.4%)	302 (1.5%)	14 (0.8%)	17 (0.8%)	14 (1.9%)	282 (1.3%)	365 (0.4%)	316 (1.5%)
- Severe P. falciparum	262 (1.3%)	336 (0.4%)	290 (1.4%)	14 (0.8%)	17 (0.8%)	14 (1.9%)	276 (1.2%)	353 (0.4%)	304 (1.4%)
- Severe P. ovale	1 (0.005%)	1 (0.001%)	1 (0.005%)	0	0	0	1 (0.004%)	1 (0.001%)	1 (0.005%)
- Severe P. vivax	0	0	0	0	0	0	0	0	0
- Severe P. malaria	0	0	0	0	0	0	0	0	0
- Severe subtype unknown	6 (0.03%)	10 (0.01%)	10 (0.05%)	0	0	0	6 (0.03%)	10 (0.01%)	10 (0.05%)
- Severe multiple subtype	1 (0.005%)	1 (0.001%)	1 (0.005%)	0	0	0	1 (0.004%)	1 (0.001%)	1 (0.005%)
Cerebral Malaria cases	10 (0.05%)	10 (0.01%)	10 (0.05%)	0	0	0	10 (0.04%)	10 (0.01%)	10 (0.05%)
Unexposed clusters	N=254	N=700	N=136	N=22210	N=100855	N=27071	N=22464	N=101555	N=27207
Any Malaria per protocol	81 (31.9%)	137 (19.6%)	136 (100%)	10277 (46.3%)	28170 (27.9%)	27071 (100%)	10358 (46.1%)	28307 (27.9%)	27207 (100%)
Any uncomplicated Malaria	76 (29.9%)	130 (18.6%)	129 (94.9%)	10171 (45.8%)	27698 (27.5%)	26694 (98.6%)	10247 (45.6%)	27828 (27.4%)	26823 (98.6%)
- Uncomplicated P. falciparum	59 (23.2%)	95 (13.6%)	94 (69.1%)	8822 (39.7%)	24896 (24.7%)	23928 (88.4%)	8881 (39.5%)	24991 (24.6%)	24022 (88.3%)
- Uncomplicated P. ovale	0	0	0	2 (0.01%)	2 (0.002%)	2 (0.01%)	2 (0.01%)	2 (0.002%)	2 (0.01%)
- Uncomplicated P. vivax	0	0	0	0	0	0	0	0	0
- Uncomplicated P. malaria	0	0	0	0	0	0	0	0	0
- Uncomplicated subtype unknown	21 (8.3%)	35 (5.0%)	35 (25.7%)	1714 (7.7%)	2800 (2.8%)	2764 (10.2%)	1735 (7.7%)	2835 (2.8%)	2799 (10.3%)
- Uncomplicated multiple subtype	0	0	0	0	0	0	0	0	0
Any severe Malaria	7 (2.8%)	7 (1.0%)	7 (5.1%)	357 (1.6%)	472 (0.5%)	377 (1.4%)	364 (1.6%)	479 (0.5%)	384 (1.4%)
- Severe P. falciparum	7 (2.8%)	7 (1.0%)	7 (5.1%)	346 (1.6%)	450 (0.4%)	359 (1.3%)	353 (1.6%)	457 (0.5%)	366 (1.3%)

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

	RTS,S vaccinated			Unvaccinated			Overall		
	Outpatient visit or Hospitalizations			Outpatient visit or Hospitalizations			Outpatient visit or Hospitalizations		
	Participants	Hospitalizations	Events	Participants	Hospitalizations	Events	Participants	Hospitalizations	Events
- Severe P. ovale	0	0	0	0	0	0	0	0	0
- Severe P. vivax	0	0	0	0	0	0	0	0	0
- Severe P. malaria	0	0	0	0	0	0	0	0	0
- Severe subtype unknown	0	0	0	17 (0.1%)	22 (0.02%)	18 (0.1%)	17 (0.1%)	22 (0.02%)	18 (0.1%)
- Severe multiple subtype	0	0	0	0	0	0	0	0	0
Cerebral Malaria cases	0	0	0	14 (0.1%)	20 (0.02%)	14 (0.1%)	14 (0.1%)	20 (0.02%)	14 (0.1%)

RTS,S vaccinated = participants vaccinated with RTS,S/AS01E vaccine

Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

Participants = number and percentage of participants reporting at least once the symptom after first dose

Outpatient visit or Hospitalizations = number and percentage of hospitalization or outpatient visits after first dose

Events = number and percentage of events after first dose

Note: cases could be counted more than once (e.g.: Cerebral malaria cases are also counted as severe malaria cases)

Source: Table 16.2.3.1 (03FEB2026 22:32 GMT), Table 16.2.3.2 (03FEB2026 22:32 GMT)

IR and IRR of malaria

A summary of IR and vaccine impact and effectiveness (1-IRR) against malaria and severe malaria over the 1 year period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and the 2 year period after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 for any malaria and severe malaria is presented in [Table 11.22](#).

1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3

- The vaccine was effective against any and severe malaria during the 12 month follow-up period after Dose 4 from Dose 3:

Any malaria

Crude estimates: 14%, $p < 0.001$ (Overall Effect, Total Effect); 16%, $p < 0.001$ (Indirect Effect)

Adjusted on country: 16%, $p < 0.001$ (Overall Effect, Total Effect); 24%, $p < 0.001$ (Indirect Effect)

Severe malaria

Crude estimates: 26%, $p = 0.012$ (Overall Effect); 27%, $p = 0.009$ (Total Effect)

Adjusted on country: 28%, $p = 0.006$ (Overall Effect); 29%, $p = 0.005$ (Total Effect).

2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4

- The vaccine was effective against any, but not severe, malaria during the 24 month follow-up period after Dose 4 from Dose 4:

Any malaria

Crude estimates: 9%, $p < 0.001$ (Overall Effect, Total Effect); 11%, $p = 0.038$ (Indirect Effect)

Adjusted on country: 9%, $p < 0.001$ (Overall Effect); 8%, $p < 0.001$ (Total Effect); 18%, $p = 0.010$ (Indirect Effect).

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Table 11.22 Effectiveness and impact analyses of RTS,S/AS01E vaccine on incidence of confirmed malaria and severe malaria cases (Final diagnosis) 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance – Impact Analysis Set

Protocol definition	At-risk period	Exposure/ Vaccination Status				Incidence rate per 100 000 person-years				Crude IR ratio				IR Ratio adjusted on Country			
			N	n	n*	Person- Years	Value	95% CI		Value	95% CI			Value	95% CI		
								LL	UL		LL	UL	P-value		LL	UL	P-value
1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3																	
DIRECT EFFECT																	
Any Malaria Per Protocol	12 months	Vaccinated	12634	5407	10842	28457.4	38099.0	37385.2	38823.1	1.03	0.94	1.14	0.535	1.14	1.00	1.30	0.046
		Unvaccinated	504	201	422	1142.3	36943.9	33502.7	40642.6	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Vaccinated	12634	98	105	28457.4	369.0	301.8	446.7	0.70	0.31	1.60	0.400	0.68	0.30	1.56	0.365
		Unvaccinated	504	6	6	1142.3	525.3	192.8	1143.3	-	-	-	-	-	-	-	-
OVERALL EFFECT																	
Any Malaria Per Protocol	12 months	Exposed	13138	5608	11264	29599.7	38054.5	37354.9	38763.8	0.86	0.84	0.88	<.001	0.84	0.81	0.87	<.001
		Unexposed	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Exposed	13138	104	111	29599.7	375.0	308.5	451.6	0.74	0.59	0.94	0.012	0.72	0.57	0.91	0.006
		Unexposed	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Any Malaria Per Protocol	12 months	Vaccinated	12634	5407	10842	28457.4	38099.0	37385.2	38823.1	0.86	0.84	0.88	<.001	0.84	0.81	0.87	<.001
		Unvaccinated	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Vaccinated	12634	98	105	28457.4	369.0	301.8	446.7	0.73	0.58	0.92	0.009	0.71	0.56	0.90	0.005
		Unvaccinated	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Any Malaria Per Protocol	12 months	Exposed	504	201	422	1142.3	36943.9	33502.7	40642.6	0.84	0.76	0.92	<.001	0.76	0.66	0.87	<.001
		Unexposed	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Exposed	504	6	6	1142.3	525.3	192.8	1143.3	1.04	0.46	2.34	0.928	0.90	0.40	2.02	0.794
		Unexposed	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-
2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4																	
DIRECT EFFECT																	
Any Malaria Per Protocol	24 months	Vaccinated	12621	4525	8197	24790.5	33065.0	32353.1	33788.7	1.03	0.92	1.16	0.612	1.13	0.98	1.31	0.099
		Unvaccinated	504	155	303	944.0	32098.5	28585.7	35923.8	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Vaccinated	12621	99	113	24790.5	455.8	375.7	548.0	2.15	0.53	8.71	0.283	1.95	0.48	7.92	0.349
		Unvaccinated	504	2	2	944.0	211.9	25.7	765.4	-	-	-	-	-	-	-	-

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Protocol definition	At-risk period	Exposure/ Vaccination Status	N	n	n*	Person- Years	Incidence rate per 100 000 person-years			Crude IR ratio				IR Ratio adjusted on Country			
							Value	95% CI		Value	95% CI			Value	95% CI		
								LL	UL		LL	UL	P-value		LL	UL	P-value
OVERALL EFFECT																	
Any Malaria Per Protocol	24 months	Exposed	13125	4680	8500	25734.5	33029.6	32331.1	33739.4	0.91	0.89	0.94	<.001	0.91	0.88	0.95	<.001
		Unexposed	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Exposed	13125	101	115	25734.5	446.9	368.9	536.4	0.87	0.69	1.11	0.268	0.84	0.66	1.06	0.146
		Unexposed	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Any Malaria Per Protocol	24 months	Vaccinated	12621	4525	8197	24790.5	33065.0	32353.1	33788.7	0.91	0.89	0.94	<.001	0.92	0.89	0.95	<.001
		Unvaccinated	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Vaccinated	12621	99	113	24790.5	455.8	375.7	548.0	0.89	0.70	1.13	0.348	0.86	0.67	1.09	0.204
		Unvaccinated	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Any Malaria Per Protocol	24 months	Exposed	504	155	303	944.0	32098.5	28585.7	35923.8	0.89	0.79	0.99	0.038	0.82	0.71	0.95	0.010
		Unexposed	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Exposed	504	2	2	944.0	211.9	25.7	765.4	0.41	0.10	1.67	0.216	0.34	0.08	1.38	0.131
		Unexposed	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-

Confirmed cases = confirmed cases from hospitalization according to final diagnosis

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of evaluable participants with follow-up during at-risk period; n* = total number of events reported during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years estimated as n* / Person-years

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

Source: Table 16.4.1.1 (03FEB2026 22:36 GMT), Table 16.4.1.2 (03FEB2026 22:34 GMT), Table 16.4.1.3 (03FEB2026 22:35 GMT), Table 16.4.1.4 (03FEB2026 22:33 GMT), Table 16.4.1.17 (03FEB2026 22:37 GMT), Table 16.4.1.18 (03FEB2026 22:35 GMT), Table 16.4.1.19 (03FEB2026 22:36 GMT), Table 16.4.1.20 (03FEB2026 22:33 GMT)

Vaccine effectiveness of RTS,S/AS01_E vaccine on incidence of confirmed malaria cases 2 years after Dose 3 from Dose 3 are presented in Section 16 Table 16.4.1.5 to Table 16.4.1.8, 2 years after Dose 4 from Dose 1 in Section 16 Table 16.4.1.9 to Table 16.4.1.12 and 2 years after Dose 4 from Dose 3 in Section 16 Table 16.4.1.13 to Table 16.4.1.16.

Total Effect of RTS,S/AS01_E vaccine on the prevalence of malaria in children with anemia/severe anemia 1 year after Dose 4 from Dose 3 are presented in Section 16 Table 16.4.5.1 and Table 16.4.5.2.

11.4.4.2. Anemia

A summary of prevalence and vaccine impact and effectiveness (1-OR) against any anemia and severe anemia among hospitalized children over the 1 year period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and the 2 year period after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 is presented in [Table 11.23](#).

1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3

- The vaccine was effective against any and severe anemia during the 12 month follow-up period after Dose 4 from Dose 3:
Any anemia
 Crude estimates: 22%, p<0.001 (Overall Effect); 23%, p<0.001 (Total Effect)
 Adjusted on country: 26%, p<0.001 (Overall Effect, Total Effect).
Severe anemia
 Adjusted on country: 19%, p=0.044 (Overall Effect); 21%, p=0.027 (Total Effect).

2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4

- The vaccine was effective against any and severe anemia during the 24 month follow-up period after Dose 4 from Dose 4:
Any anemia
 Crude estimates: 31%, p<0.001 (Overall Effect, Total Effect)
 Adjusted on country: 34%, p<0.001 (Overall Effect, Total Effect); 40%, p=0.031 (Indirect Effect).
Severe anemia
 Crude estimates: 30%, p=0.008 (Overall Effect, Total Effect)
 Adjusted on country: 32%, p=0.004 (Overall Effect, Total Effect).

Table 11.23 Impact and effectiveness analyses of RTS,S/AS01E vaccine on prevalence of anemia and severe anemia 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance – Impact Analysis Set

Protocol definition	Exposure/ Vaccination Status	N	n	n*	Prevalence			Crude OR			P-value	OR adjusted on Country			
					Value	95% CI	LL	UL	Value	95% CI		LL	UL	Value	95% CI
1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3															
DIRECT EFFECT															
Anemia	RTS,S vaccinated	12634	866	1064	0.069	0.064	0.073	0.79	0.57	1.09	0.147	0.87	0.63	1.20	0.387
	Unvaccinated	504	43	64	0.085	0.062	0.113	-	-	-	-	-	-	-	-
Severe anemia	RTS,S vaccinated	12634	142	154	0.011	0.009	0.013	0.56	0.29	1.07	0.081	0.60	0.31	1.15	0.122
	Unvaccinated	504	10	10	0.020	0.010	0.036	-	-	-	-	-	-	-	-
OVERALL EFFECT															
Anemia	Exposed	13138	909	1128	0.069	0.065	0.074	0.78	0.71	0.85	<.001	0.74	0.68	0.81	<.001
	Unexposed	17128	1494	1870	0.087	0.083	0.092	-	-	-	-	-	-	-	-
Severe anemia	Exposed	13138	152	164	0.012	0.010	0.014	0.84	0.68	1.03	0.091	0.81	0.66	0.99	0.044
	Unexposed	17128	236	259	0.014	0.012	0.016	-	-	-	-	-	-	-	-
TOTAL EFFECT															
Anemia	RTS,S vaccinated	12634	866	1064	0.069	0.064	0.073	0.77	0.71	0.84	<.001	0.74	0.68	0.81	<.001
	Unvaccinated	17128	1494	1870	0.087	0.083	0.092	-	-	-	-	-	-	-	-
Severe anemia	RTS,S vaccinated	12634	142	154	0.011	0.009	0.013	0.81	0.66	1.00	0.054	0.79	0.64	0.97	0.027
	Unvaccinated	17128	236	259	0.014	0.012	0.016	-	-	-	-	-	-	-	-
INDIRECT EFFECT															
Anemia	Exposed	504	43	64	0.085	0.062	0.113	0.98	0.71	1.34	0.881	0.82	0.59	1.14	0.235
	Unexposed	17128	1494	1870	0.087	0.083	0.092	-	-	-	-	-	-	-	-
Severe anemia	Exposed	504	10	10	0.020	0.010	0.036	1.45	0.76	2.75	0.255	1.24	0.65	2.35	0.517
	Unexposed	17128	236	259	0.014	0.012	0.016	-	-	-	-	-	-	-	-
2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4															
DIRECT EFFECT															
Anemia	RTS,S vaccinated	12621	464	545	0.037	0.034	0.040	0.97	0.61	1.56	0.913	1.10	0.68	1.75	0.705
	Unvaccinated	504	19	24	0.038	0.023	0.058	-	-	-	-	-	-	-	-
Severe anemia	RTS,S vaccinated	12621	82	88	0.006	0.005	0.008	0.82	0.30	2.24	0.695	0.88	0.32	2.40	0.795
	Unvaccinated	504	4	4	0.008	0.002	0.020	-	-	-	-	-	-	-	-

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Protocol definition	Exposure/ Vaccination Status	N	n	n*	Prevalence			Crude OR			P-value	OR adjusted on Country			
					Value	95% CI	LL	UL	Value	95% CI		LL	UL	Value	95% CI
OVERALL EFFECT															
Anemia	Exposed	13125	483	569	0.037	0.034	0.040	0.69	0.61	0.77	<.001	0.66	0.59	0.74	<.001
	Unexposed	17071	898	1036	0.053	0.049	0.056	-	-	-	-	-	-	-	-
Severe anemia	Exposed	13125	86	92	0.007	0.005	0.008	0.70	0.54	0.91	0.008	0.68	0.52	0.88	0.004
	Unexposed	17071	159	168	0.009	0.008	0.011	-	-	-	-	-	-	-	-
TOTAL EFFECT															
Anemia	RTS,S vaccinated	12621	464	545	0.037	0.034	0.040	0.69	0.61	0.77	<.001	0.66	0.59	0.74	<.001
	Unvaccinated	17071	898	1036	0.053	0.049	0.056	-	-	-	-	-	-	-	-
Severe anemia	RTS,S vaccinated	12621	82	88	0.006	0.005	0.008	0.70	0.53	0.91	0.008	0.68	0.52	0.88	0.004
	Unvaccinated	17071	159	168	0.009	0.008	0.011	-	-	-	-	-	-	-	-
INDIRECT EFFECT															
Anemia	Exposed	504	19	24	0.038	0.023	0.058	0.71	0.44	1.12	0.140	0.60	0.37	0.95	0.031
	Unexposed	17071	898	1036	0.053	0.049	0.056	-	-	-	-	-	-	-	-
Severe anemia	Exposed	504	4	4	0.008	0.002	0.020	0.85	0.31	2.30	0.751	0.73	0.27	1.99	0.544
	Unexposed	17071	159	168	0.009	0.008	0.011	-	-	-	-	-	-	-	-

RTS,S vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

Prevalence = percentage of participants with at least one event (n/N)

OR adjusted = estimation of odds ratio using Binary Logistic regression model with Country as a fixed effect and unvaccinated/unexposed as reference status

N = number of evaluable participants with follow-up during the at-risk period;

n = number of participants with at least one event reported during the follow-up period

n* = total number of events reported during the follow-up period

95% CI for prevalence = 95% confidence interval (Exact Binomial Method); LL = Lower Limit, UL = Upper Limit

95% CI for adjusted OR = 95% confidence interval (logistic model)

P-value = p-value for two-sided test H0: adjusted odds ratio = 1 (logistic model)

Source: Table 16.4.2.1 (03FEB2026 21:09 GMT), Table 16.4.2.2 (03FEB2026 21:08 GMT), Table 16.4.2.3 (03FEB2026 21:08 GMT), Table 16.4.2.4 (03FEB2026 21:07 GMT), Table 16.4.2.17 (03FEB2026 21:09 GMT), Table 16.4.2.18 (03FEB2026 21:08 GMT), Table 16.4.2.19 (03FEB2026 21:08 GMT), Table 16.4.2.20 (03FEB2026 21:08 GMT)

Vaccine effectiveness of RTS,S/AS01_E vaccine on the prevalence of anemia 2 years after Dose 3 from Dose 3 are presented in Section 16 Table 16.4.2.5 to Table 16.4.2.8, 2 years after Dose 4 from Dose 1 in Section 16 Table 16.4.2.9 to Table 16.4.2.12 and 2 years after Dose 4 from Dose 3 in Section 16 Table 16.4.2.13 to Table 16.4.2.16.

11.4.4.3. Hospitalization

A summary of IR and vaccine impact and effectiveness (1-IRR) against hospitalizations due to malaria over the 1 year period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and the 2 year period after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 is presented in [Table 11.24](#).

1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3

- The vaccine was effective against hospitalizations due to malaria and hospitalizations due to *P. falciparum* during the 12 month follow-up period after Dose 4 from Dose 3:
Hospitalizations due to malaria
 Crude estimates: 42%, p<0.001 (Direct Effect); 19%, p<0.001 (Overall Effect); 22%, p<0.001 (Total Effect)
 Adjusted on country: 36%, p=0.002 (Direct Effect); 23%, p<0.001 (Overall Effect); 25%, p<0.001 (Total Effect)
Hospitalizations due *P. falciparum*
 Crude estimates: 42%, p<0.001 (Direct Effect); 19%, p<0.001 (Overall Effect), 21%, p<0.001 (Total Effect)
 Adjusted on country: 36%, p=0.002 (Direct Effect); 23%, p<0.001 (Overall Effect), 25%, p<0.001 (Total Effect).

2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4

- The vaccine was effective against hospitalizations due to malaria during the 24 month follow-up period after Dose 4 from Dose 4:
Hospitalizations due to malaria
 Crude estimates: 20%, p<0.001 (Overall Effect, Total Effect)
 Adjusted on country: 23%, p<0.001 (Overall Effect); 22%, p<0.001 (Total Effect); 41%, p=0.016 (Indirect Effect)
Hospitalizations due *P. falciparum*
 Crude estimates: 20%, p<0.001 (Overall Effect, Total Effect)
 Adjusted on country: 23%, p<0.001 (Overall Effect); 22%, p<0.001 (Total Effect), 41%, p=0.017 (Indirect Effect).

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Table 11.24 Impact and effectiveness analyses of RTS,S/AS01E vaccine on incidence of hospitalizations 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance

Protocol definition	At-risk period	Exposure/ Vaccination Status				Person- Years	Incidence rate per 100 000 person-years 95% CI			Crude IR ratio 95% CI				IR Ratio adjusted on Country 95% CI			
			N	n	n*		Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
			1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3														
DIRECT EFFECT																	
Hospitalization – Malaria	12 months	Vaccinated	12634	692	795	28457.4	2793.6	2602.8	2994.8	0.58	0.44	0.76	<.001	0.64	0.49	0.85	0.002
		Unvaccinated	504	44	55	1142.3	4815.0	3627.3	6267.3	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	12 months	Vaccinated	12634	690	793	28457.4	2786.6	2596.0	2987.5	0.58	0.44	0.76	<.001	0.64	0.49	0.84	0.002
		Unvaccinated	504	44	55	1142.3	4815.0	3627.3	6267.3	-	-	-	-	-	-	-	-
OVERALL EFFECT																	
Hospitalization – Malaria	12 months	Exposed	13138	736	850	29599.7	2871.7	2681.8	3071.4	0.81	0.74	0.88	<.001	0.77	0.70	0.84	<.001
		Unexposed	17128	1154	1388	38934.9	3564.9	3379.8	3757.5	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	12 months	Exposed	13138	734	848	29599.7	2864.9	2675.3	3064.4	0.81	0.74	0.88	<.001	0.77	0.71	0.84	<.001
		Unexposed	17128	1143	1377	38934.9	3536.7	3352.3	3728.5	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Hospitalization – Malaria	12 months	Vaccinated	12634	692	795	28457.4	2793.6	2602.8	2994.8	0.78	0.72	0.86	<.001	0.75	0.69	0.82	<.001
		Unvaccinated	17128	1154	1388	38934.9	3564.9	3379.8	3757.5	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	12 months	Vaccinated	12634	690	793	28457.4	2786.6	2596.0	2987.5	0.79	0.72	0.86	<.001	0.75	0.69	0.82	<.001
		Unvaccinated	17128	1143	1377	38934.9	3536.7	3352.3	3728.5	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Hospitalization – Malaria	12 months	Exposed	504	44	55	1142.3	4815.0	3627.3	6267.3	1.35	1.03	1.77	0.029	1.14	0.87	1.50	0.325
		Unexposed	17128	1154	1388	38934.9	3564.9	3379.8	3757.5	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	12 months	Exposed	504	44	55	1142.3	4815.0	3627.3	6267.3	1.36	1.04	1.78	0.025	1.16	0.88	1.51	0.292
		Unexposed	17128	1143	1377	38934.9	3536.7	3352.3	3728.5	-	-	-	-	-	-	-	-

CONFIDENTIAL

115056 (EPI-MALARIA-003 VS AME)
Report Final

Protocol definition	At-risk period	Exposure/ Vaccination Status	N	n	n*	Person- Years	Incidence rate per 100 000 person-years 95% CI			Crude IR ratio 95% CI				IR Ratio adjusted on Country 95% CI			
							Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4																	
DIRECT EFFECT																	
Hospitalization – Malaria	24 months	Vaccinated	12621	529	623	24790.5	2513.1	2319.6	2718.4	1.13	0.73	1.74	0.583	1.27	0.82	1.96	0.283
		Unvaccinated	504	20	21	944.0	2224.6	1377.1	3400.6	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	24 months	Vaccinated	12621	527	620	24790.5	2501.0	2307.9	2705.8	1.12	0.73	1.74	0.598	1.26	0.82	1.95	0.293
		Unvaccinated	504	20	21	944.0	2224.6	1377.1	3400.6	-	-	-	-	-	-	-	-
OVERALL EFFECT																	
Hospitalization – Malaria	24 months	Exposed	13125	549	644	25734.5	2502.5	2312.9	2703.4	0.80	0.72	0.88	<.001	0.77	0.70	0.85	<.001
		Unexposed	17071	897	1034	32878.6	3144.9	2956.1	3342.6	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	24 months	Exposed	13125	547	641	25734.5	2490.8	2301.7	2691.3	0.80	0.72	0.88	<.001	0.77	0.70	0.85	<.001
		Unexposed	17071	892	1029	32878.6	3129.7	2941.4	3326.9	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Hospitalization – Malaria	24 months	Vaccinated	12621	529	623	24790.5	2513.1	2319.6	2718.4	0.80	0.72	0.88	<.001	0.78	0.70	0.86	<.001
		Unvaccinated	17071	897	1034	32878.6	3144.9	2956.1	3342.6	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	24 months	Vaccinated	12621	527	620	24790.5	2501.0	2307.9	2705.8	0.80	0.72	0.88	<.001	0.78	0.70	0.86	<.001
		Unvaccinated	17071	892	1029	32878.6	3129.7	2941.4	3326.9	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Hospitalization – Malaria	24 months	Exposed	504	20	21	944.0	2224.6	1377.1	3400.6	0.71	0.46	1.09	0.116	0.59	0.38	0.91	0.016
		Unexposed	17071	897	1034	32878.6	3144.9	2956.1	3342.6	-	-	-	-	-	-	-	-
Hospitalization – P. falciparum	24 months	Exposed	504	20	21	944.0	2224.6	1377.1	3400.6	0.71	0.46	1.09	0.122	0.59	0.38	0.91	0.017
		Unexposed	17071	892	1029	32878.6	3129.7	2941.4	3326.9	-	-	-	-	-	-	-	-

Confirmed cases = confirmed cases from hospitalization according to final diagnosis

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of evaluable participants with follow-up during at-risk period; n* = total number of events reported during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years); Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years estimated as n* / Person-years; Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status; 95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

Source: Table 16.4.3.1 (03FEB2026 22:31 GMT), Table 16.4.3.2 (03FEB2026 22:29 GMT), Table 16.4.3.3 (03FEB2026 22:30 GMT), Table 16.4.3.4 (03FEB2026 22:28 GMT), Table 16.4.3.17 (03FEB2026 22:31 GMT), Table 16.4.3.18 (03FEB2026 22:29 GMT), Table 16.4.3.19 (03FEB2026 22:30 GMT), Table 16.4.3.20 (03FEB2026 22:28 GMT)

Vaccine effectiveness of RTS,S/AS01_E vaccine on incidence of hospitalization 2 years after Dose 3 from Dose 3 are presented in Section 16 Table 16.4.3.5 to Table 16.4.3.8, 2 years after Dose 4 from Dose 1 in Section 16 Table 16.4.3.9 to Table 16.4.3.12 and 2 years after Dose 4 from Dose 3 in Section 16 Table 16.4.3.13 to Table 16.4.3.16.

11.4.4.4. Death

A summary of IR and vaccine impact and effectiveness (1-IRR) against all deaths and deaths due to malaria over the 1 year period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and the 2 year period after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 is presented in [Table 11.25](#).

1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3

- The vaccine was effective against all-cause death only for Direct Effect during the 12 month follow-up period after Dose 4 from Dose 3:
Crude estimates: 74%, p=0.005 (Direct Effect)
Adjusted on country: 78%, p=0.002 (Direct Effect).

Due to the low numbers of fatalities and imbalance in population size in RTS,S/AS01_E vaccinated vs unvaccinated participants in exposed clusters, vaccine effectiveness estimates for Direct Effect should be interpreted with caution.

Vaccine effectiveness of RTS,S/AS01_E vaccine on incidence of death 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 by gender are presented in Section 16 Table 16.4.4.2, Table 16.4.4.3, Table 16.4.4.5, Table 16.4.4.6, Table 16.4.4.8, Table 16.4.4.9, Table 16.4.4.11 and Table 16.4.4.12 and excluding specific cause of deaths in Section 16 Table 16.4.4.13 to Table 16.4.4.24.

2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4

The vaccine was not effective against all-cause death and death due to malaria during the 24 month follow-up period after Dose 4 from Dose 4.

Vaccine effectiveness of RTS,S/AS01_E vaccine on incidence of death 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 by gender are presented in Section 16 Table 16.4.4.98, Table 16.4.4.99, 16.4.4.101, Table 16.4.4.102, Table 16.4.4.104, Table 16.4.4.105, Table 16.4.4.107 and Table 16.4.4.108, and excluding specific cause of deaths in Section 16 Table 16.4.4.109 to Table 16.4.4.120.

Table 11.25 Impact and effectiveness analyses of RTS,S/AS01E vaccine on incidence of deaths 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 - Active Surveillance

Protocol definition	At-risk period	Exposure/ Vaccination status	N	n	Person- Years	Incidence rate per 100 000 person-years 95% CI			Crude IR ratio 95% CI				IR ratio adjusted on Country 95% CI			
						Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3																
DIRECT EFFECT																
Death - all causes*	12 months	RTS,S vaccinated	12634	32	28457.4	112.4	76.9	158.7	0.26	0.10	0.66	0.005	0.22	0.08	0.58	0.002
		Unvaccinated	504	5	1142.3	437.7	142.1	1021.5	-	-	-	-	-	-	-	-
Death - Malaria	12 months	RTS,S vaccinated	12634	11	28457.4	38.7	19.3	69.2	0.44	0.06	3.42	0.434	0.39	0.05	3.11	0.376
		Unvaccinated	504	1	1142.3	87.5	2.2	487.8	-	-	-	-	-	-	-	-
OVERALL EFFECT																
Death - all causes*	12 months	Exposed	13138	37	29599.7	125.0	88.0	172.3	1.01	0.66	1.56	0.950	1.05	0.68	1.61	0.825
		Unexposed	17128	48	38934.9	123.3	90.9	163.5	-	-	-	-	-	-	-	-
Death - Malaria	12 months	Exposed	13138	12	29599.7	40.5	20.9	70.8	0.99	0.47	2.09	0.972	1.00	0.47	2.11	0.996
		Unexposed	17128	16	38934.9	41.1	23.5	66.7	-	-	-	-	-	-	-	-
TOTAL EFFECT																
Death - all causes*	12 months	RTS,S vaccinated	12634	32	28457.4	112.4	76.9	158.7	0.91	0.58	1.43	0.687	0.94	0.60	1.47	0.793
		Unvaccinated	17128	48	38934.9	123.3	90.9	163.5	-	-	-	-	-	-	-	-
Death - Malaria	12 months	RTS,S vaccinated	12634	11	28457.4	38.7	19.3	69.2	0.94	0.44	2.03	0.876	0.95	0.44	2.06	0.903
		Unvaccinated	17128	16	38934.9	41.1	23.5	66.7	-	-	-	-	-	-	-	-
INDIRECT EFFECT																
Death - all causes*	12 months	Exposed	504	5	1142.3	437.7	142.1	1021.5	3.55	1.41	8.92	0.007	4.04	1.59	10.29	0.003
		Unexposed	17128	48	38934.9	123.3	90.9	163.5	-	-	-	-	-	-	-	-
Death - Malaria	12 months	Exposed	504	1	1142.3	87.5	2.2	487.8	2.13	0.28	16.06	0.463	2.07	0.27	15.82	0.482
		Unexposed	17128	16	38934.9	41.1	23.5	66.7	-	-	-	-	-	-	-	-

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115056 (EPI-MALARIA-003 VS AME)
Report Final

Protocol definition	At-risk period	Exposure/ Vaccination status	N	n	Person- Years	Incidence rate per 100 000 person-years 95% CI			Crude IR ratio 95% CI			IR ratio adjusted on Country 95% CI				
						Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4																
DIRECT EFFECT																
Death - all causes*	24 months	RTS,S vaccinated	12621	59	24790.5	238.0	181.2	307.0	0.45	0.18	1.12	0.086	0.40	0.16	1.00	0.051
		Unvaccinated	504	5	944.0	529.7	172.0	1236.1	-	-	-	-	-	-	-	-
Death - Malaria	24 months	RTS,S vaccinated	12621	21	24790.5	84.7	52.4	129.5	0.80	0.11	5.94	0.827	0.68	0.09	5.10	0.706
		Unvaccinated	504	1	944.0	105.9	2.7	590.2	-	-	-	-	-	-	-	-
OVERALL EFFECT																
Death - all causes*	24 months	Exposed	13125	64	25734.5	248.7	191.5	317.6	1.05	0.75	1.46	0.780	1.09	0.78	1.51	0.626
		Unexposed	17071	78	32878.6	237.2	187.5	296.1	-	-	-	-	-	-	-	-
Death - Malaria	24 months	Exposed	13125	22	25734.5	85.5	53.6	129.4	0.94	0.54	1.62	0.816	0.95	0.55	1.66	0.866
		Unexposed	17071	30	32878.6	91.2	61.6	130.3	-	-	-	-	-	-	-	-
TOTAL EFFECT																
Death - all causes*	24 months	RTS,S vaccinated	12621	59	24790.5	238.0	181.2	307.0	1.00	0.72	1.41	0.985	1.04	0.74	1.45	0.840
		Unvaccinated	17071	78	32878.6	237.2	187.5	296.1	-	-	-	-	-	-	-	-
Death - Malaria	24 months	RTS,S vaccinated	12621	21	24790.5	84.7	52.4	129.5	0.93	0.53	1.62	0.794	0.95	0.54	1.66	0.846
		Unvaccinated	17071	30	32878.6	91.2	61.6	130.3	-	-	-	-	-	-	-	-
INDIRECT EFFECT																
Death - all causes*	24 months	Exposed	504	5	944.0	529.7	172.0	1236.1	2.23	0.90	5.51	0.082	2.55	1.02	6.35	0.045
		Unexposed	17071	78	32878.6	237.2	187.5	296.1	-	-	-	-	-	-	-	-
Death - Malaria	24 months	Exposed	504	1	944.0	105.9	2.7	590.2	1.16	0.16	8.51	0.883	1.15	0.16	8.49	0.891
		Unexposed	17071	30	32878.6	91.2	61.6	130.3	-	-	-	-	-	-	-	-

*All-cause death includes deaths associated with accidents and poisonings

RTS,S vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of evaluable participants with follow-up during the at-risk period ; n = number of deaths during the follow-up period at-risk

Person-Years (PYs) = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of deaths per 100 000 person-years estimated as n / Person-years

Adjusted IR ratio (IRR) = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

Source: Table 16.4.4.1 (03FEB2026 22:20 GMT), Table 16.4.4.4 (03FEB2026 22:02 GMT), Table 16.4.4.7 (03FEB2026 22:11 GMT), Table 16.4.4.10 (03FEB2026 21:54 GMT),
Table 16.4.4.97 (03FEB2026 22:22 GMT), Table 16.4.4.100 (03FEB2026 22:05 GMT), Table 16.4.4.103 (03FEB2026 22:14 GMT), Table 16.4.4.106 (03FEB2026 21:56 GMT)

Vaccine effectiveness of RTS,S/AS01_E vaccine on incidence of death 2 years after Dose 3 from Dose 3 are presented in Section 16 Table 16.4.4.25 to Table 16.4.4.36 (excluding specific cause of deaths in Section 16 Table 16.4.4.37 to Table 16.4.4.48), 2 years after Dose 4 from Dose 1 in Section 16 Table 16.4.4.49 to Table 16.4.4.60 (excluding specific cause of deaths in Section 16 Table 16.4.4.61 to Table 16.4.4.72) and 2 years after Dose 4 from Dose 3 in Section 16 Table 16.4.4.73 to Table 16.4.4.84 (excluding specific causes of death in Section 16 Table 16.4.4.85 to Table 16.4.4.96).

11.4.5. Exploratory analyses

11.4.5.1. Vaccine effectiveness against malaria among anemic children

Vaccine effectiveness (Total Effect) on the prevalence of malaria in children with anemia and severe anemia was also assessed during the 12 month follow-up period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 (Section 16 Table 16.4.5.1 and Table 16.4.5.2).

- The vaccine was effective (1-OR) against any and severe malaria for children with any and severe anemia.

Any malaria

Crude estimates: 33% (95% CI: 22-43), $p < 0.001$ in children with anemia; 38% (95% CI: 11-57), $p = 0.010$ in children with severe anemia

Adjusted on country: 35% (95% CI: 23-45), $p < 0.001$ in children with anemia; 39% (95% CI: 12-58), $p = 0.009$ in children with severe anemia

Severe malaria

Adjusted on country: 42% (95% CI: 17-59), $p = 0.003$ in children with anemia; 51% (95% CI: 10-73), $p = 0.021$ in children with severe anemia.

11.4.5.2. Averted cases based on Total Effect

The cumulative number of *P. falciparum* cases averted 1 year after Dose 4 from Dose 3 (30 months duration) was calculated by summing the number of cases averted for each 3-month follow-up period (Table 11.26).

- The cumulative number of any malaria (uncomplicated+severe malaria) cases averted per 1000 children vaccinated was 231.55.
- The cumulative number of hospitalizations due to malaria averted per 1000 children vaccinated was 17.68.
- The low number of all-cause death and deaths due to malaria averted per 1000 children vaccinated reflects the low number of deaths reported in the study (see Section 11.4.4.4).

Table 11.26 Cases averted (RTS,S vaccinated versus unvaccinated) based on Total Effect of RTS,S/AS01E vaccine on incidence of any Malaria 1 year after Dose 4 from Dose 3 by 3-monthly periods - Cluster design comparison – Active Surveillance - Impact Analysis set

Endpoint	N1	N2	n1	n2	RTS,S vaccinated N=12634		
					n	95% CI	
						LL	UL
Any Malaria	12634	17128	10837	17182	231.55	155.05	319.67
Uncomplicated malaria	12634	17128	10733	16985	227.48	150.32	315.57
Severe malaria	12634	17128	104	197	4.07	1.35	7.03
Hospitalization due to malaria	12634	17128	793	1387	17.68	9.43	25.47
All-cause death	NA	NA	NA	NA	0.31	-1.79	2.31
Death due to malaria	NA	NA	NA	NA	-0.11	-1.45	1.04

N1 = number of vaccinated participants; N2 = number of unvaccinated participants

n1 = number of events reported during the follow-up period among vaccinated participants; n2 = number of events reported during the follow-up period among unvaccinated participants

N = total number of participants; n = difference between RTS,S vaccinated and unvaccinated group in the incidences of any Malaria per 1000 persons followed up during the defined follow-up period.

NA = not available due to very few cases averted and not statistically significant vaccine effectiveness

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

95% Confidence interval obtained through 1000 resampling with the size equal to the number of participants, resampling with replacement, computation of the cases averted in each of the 1000 samples and taking the 2.5% and 97.5% percentiles

Source: Table 16.5.1 (26FEB2026 5:30 GMT), Table 16.5.2 (26FEB2026 5:44 GMT), Table 16.5.3 (26FEB2026 5:37 GMT), Table 16.5.4 (26FEB2026 5:15 GMT), Table 16.5.5 (26FEB2026 5:08 GMT), Table 16.5.6 (26FEB2026 5:22 GMT), Table 16.8.25 (31MAR2026 20:30 GMT), Table 16.8.26 (31MAR2026 20:44 GMT), Table 16.8.27 (31MAR2026 20:37 GMT), Table 16.8.28 (31MAR2026 20:23 GMT)

11.4.5.3. Vaccine Impact (Total Effect) accounting for Malaria Transmission Intensity estimated in the EPI-MAL-005 study

The Total Effect of RTS,S/AS01_E vaccine on the incidence of confirmed malaria cases, accounting for year and center-specific MTI, 2 years after Dose 4 from Dose 1, with baseline covariate balance adjusted by propensity score weights overlap, is summarized in [Table 11.27](#).

- The vaccine was effective (Total Effect) against any and severe malaria during the 24 month follow-up period after Dose 4/virtual Dose 4 from Dose 1/virtual Dose 1:

Any malaria

Estimates weighted by propensity scores using overlapping weights: 32%, p<0.001

Additionally adjusted on country and MTI: 24%, p<0.001

Severe malaria

Estimates weighted by propensity scores using overlapping weights: 25%, p=0.043.

Additional analyses of *P. falciparum* parasitemia prevalence of participants aged between 6 months to 5 years by center according to survey year from study EPI-MAL-005 by RTS,S/AS01_E vaccination status are presented in Section 16 Table 16.6.1, and baseline covariate balance by vaccination status in Section 16 Figure 16.6.2.

Table 11.27 Total Effect of RTS,S/AS01E vaccine on incidence of confirmed malaria cases (final diagnosis) accounting for year - and center - specific Malaria transmission intensity (MTI) 2 years after Dose 4 from Dose 1, with baseline covariate balance assessed using propensity score overlap weighting – Cluster design comparison – Active Surveillance - Impact Analysis set

Protocol definition	At-risk period	Vaccination Status	N	n	n*	Person-Years	Incidence rate per 100 000 person-years 95% CI			IR ratio* 95% CI				IR Ratio additionally adjusted on Country and MTI** 95% CI			
							Value	LL	UL	Value	LL	UL	P-value	Value	LL	UL	P-value
Any Malaria Per Protocol	24 months	Vaccinated	12640	6574	15830	43848.7	36101.4	35541.2	36668.3	0.68	0.66	0.70	<.001	0.76	0.74	0.79	<.001
		Unvaccinated	17170	8837	24117	58772.5	41034.5	40518.2	41555.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Vaccinated	12640	151	170	43848.7	387.7	331.6	450.6	0.75	0.57	0.99	0.043	0.79	0.59	1.05	0.103
		Unvaccinated	17170	280	290	58772.5	493.4	438.3	553.6	-	-	-	-	-	-	-	-

Confirmed cases = confirmed cases from hospitalization according to final diagnosis

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of evaluable participants with follow-up during at-risk period; n* = total number of events reported during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years estimated as $n^* / \text{Person-years}$

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

MTI = malaria transmission intensity

*IR ratio = estimation of risk ratio using Poisson or Negative binomial regression model with baseline covariate balance using propensity score overlap weighting and unvaccinated as reference status

**Adjusted Incidence Rate (IR) Ratio estimated with baseline covariate balance using propensity score overlap weighting and in addition adjusted using country as a fixed effect, MTI specific year and site estimates and unvaccinated as reference status.

Source: Table 16.6.3 (26FEB2026 7:35 GMT)

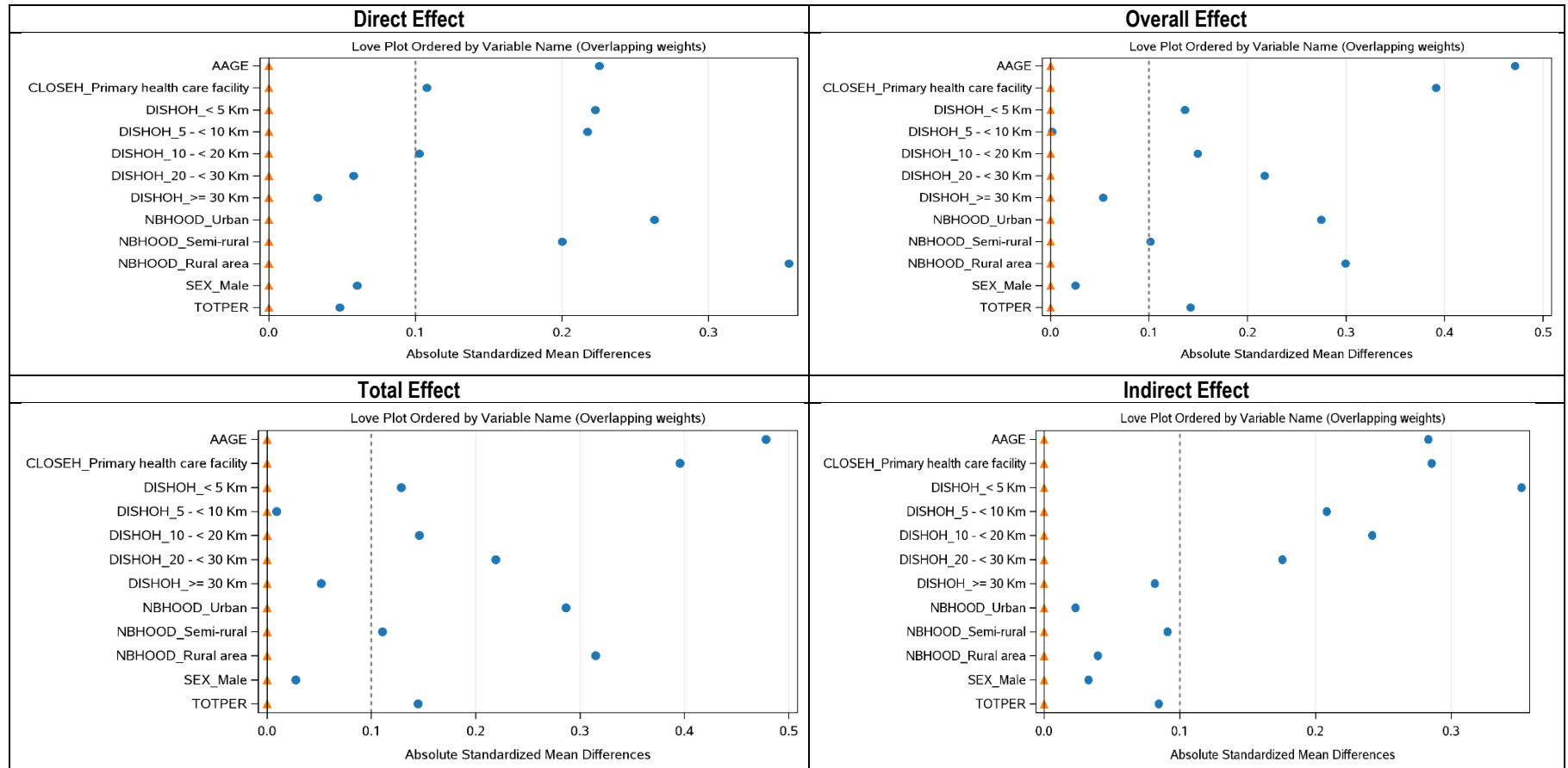
11.4.5.4. Vaccine effectiveness and impact against malaria and severe malaria – evaluation of baseline covariate balance

For some of the selected baseline variables, differences in absolute standardized means suggested imbalance between vaccinated and unvaccinated children (when estimating Direct and Total Effects), or between children from exposed and unexposed clusters (when estimating Indirect and Overall effects).

Exploratory analyses were conducted to understand the potential effect of participant differences between comparison groups, as captured by baseline covariates, and how these differences could influence effect estimates, through propensity score overlap weighting.

[Figure 11.3](#) and [Figure 11.4](#) show standardized mean differences before and after adjustment using propensity score overlap weighting, 1 year after Dose 4 from Dose 3 and 2 years after Dose 4 from Dose 4.

Figure 11.3 Baseline covariate balance by exposure status for Direct/Overall/Total/Indirect Effect of RTS,S/AS01E vaccine: A propensity score overlap weighting approach - 1 year after Dose 4 from Dose 3 - Cluster design comparison - Active Surveillance - Impact Analysis set

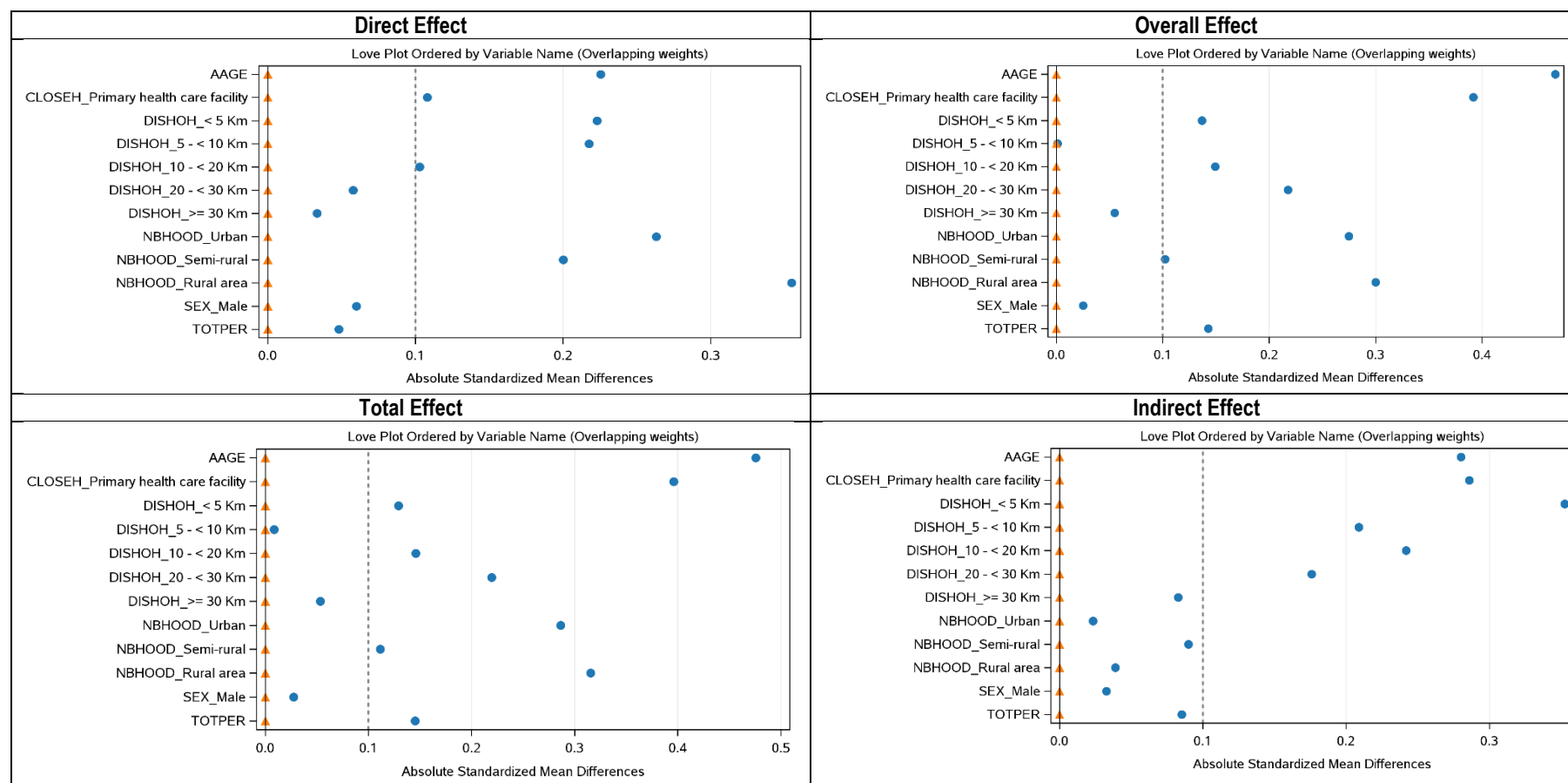


● = unadjusted; ▲ = adjusted

Covariates included are: Age at informed consent (AAGE), Closest health care facility (CLOSEH), Approximate distance between the study participant house and the closest health care facility (DISHOH), Neighbourhood of residence (NBHOOD), Gender (SEX) and Number of persons living in the household (TOTPER)

Source: Figure 16.8.1 (31MAR2026 20:13 GMT), Figure 16.8.2 (31MAR2026 20:12 GMT), Figure 16.8.3 (31MAR2026 20:12 GMT), Figure 16.8.4 (31MAR2026 20:11 GMT)

Figure 11.4 Baseline covariate balance by exposure status for Direct/Overall/Total/Indirect effect of RTS,S/AS01E vaccine: A propensity score overlap weighting approach - 2 years after Dose 4 from Dose 4 - Cluster design comparison - Active Surveillance - Impact Analysis set



● = unadjusted; ▲ = adjusted

Covariates included are: Age at informed consent (AAGE), Closest health care facility (CLOSEH), Approximate distance between the study participant house and the closest health care facility (DISHOH), Neighbourhood of residence (NBHOOD), Gender (SEX) and Number of persons living in the household (TOTPER)

Source: Figure 16.8.9 (31MAR2026 20:13 GMT), Figure 16.8.10 (31MAR2026 20:12 GMT), Figure 16.8.11 (31MAR2026 20:12 GMT), Figure 16.8.12 (31MAR2026 20:11 GMT)

IR and IRR of malaria

A summary of IR and vaccine impact and effectiveness (1-IRR), against malaria and severe malaria over the 1 year period after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and the 2 year period after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4 for any malaria and severe malaria, with baseline covariate balance assessed, is presented in [Table 11.28](#).

1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3

- The vaccine was effective against any, but not severe, malaria during the 12 month follow-up period after Dose 4 from Dose 3:

Any malaria

Vaccine effectiveness estimates weighted by propensity scores using overlapping weights: 33%, $p < 0.001$ (Overall Effect, Total Effect); 32%, $p < 0.001$ (Indirect Effect) Additionally adjusted on country: 32%, $p < 0.001$ (Overall Effect, Total Effect); 35%, $p < 0.001$ (Indirect Effect).

2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4

- The vaccine was effective against any, but not severe, malaria during the 24 month follow-up period after Dose 4 from Dose 4:

Any malaria

Vaccine effectiveness estimates weighted by propensity scores using overlapping weights: 29%, $p < 0.001$ (Overall Effect, Total Effect); 27%, $p < 0.001$ (Indirect Effect) Additionally adjusted on country: 28%, $p < 0.001$ (Overall Effect, Total Effect); 31%, $p < 0.001$ (Indirect Effect).

Vaccine effectiveness and impact of the RTS,S/AS01_E vaccine on the incidence of any malaria and severe malaria 2 years after Dose 4 from Dose 1 are presented in Section 16 Table 16.8.17 to Table 16.8.20.

Table 11.28 Effectiveness and impact analyses of RTS,S/AS01E vaccine on incidence of confirmed malaria and severe malaria cases (Final diagnosis) 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3 and 2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4, with baseline covariate balance assessed using propensity score overlap weighting - Cluster design comparison - Active Surveillance – Impact Analysis Set

Protocol definition	At-risk period	Exposure/ Vaccination Status				Incidence rate per 100 000 person-years				IR ratio*			IR Ratio* adjusted on Country				
			N	n	n*	Person- Years	Value	95% CI		Value	95% CI		P-value	Value	95% CI		P-value
								LL	UL		LL	UL			LL	UL	
1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3																	
DIRECT EFFECT																	
Any Malaria Per Protocol	12 months	Vaccinated	12634	5407	10842	28457.4	38099.0	37385.2	38823.1	0.96	0.83	1.10	0.519	1.02	0.89	1.18	0.762
		Unvaccinated	504	201	422	1142.3	36943.9	33502.7	40642.6	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Vaccinated	12634	98	105	28457.4	369.0	301.8	446.7	0.62	0.16	2.35	0.481	0.65	0.17	2.52	0.535
		Unvaccinated	504	6	6	1142.3	525.3	192.8	1143.3	-	-	-	-	-	-	-	-
OVERALL EFFECT																	
Any Malaria Per Protocol	12 months	Exposed	13138	5608	11264	29599.7	38054.5	37354.9	38763.8	0.67	0.65	0.69	<.001	0.68	0.65	0.70	<.001
		Unexposed	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Exposed	13138	104	111	29599.7	375.0	308.5	451.6	0.74	0.53	1.04	0.086	0.73	0.52	1.02	0.068
		Unexposed	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Any Malaria Per Protocol	12 months	Vaccinated	12634	5407	10842	28457.4	38099.0	37385.2	38823.1	0.67	0.65	0.69	<.001	0.68	0.65	0.70	<.001
		Unvaccinated	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Vaccinated	12634	98	105	28457.4	369.0	301.8	446.7	0.73	0.51	1.02	0.068	0.71	0.50	1.01	0.055
		Unvaccinated	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Any Malaria Per Protocol	12 months	Exposed	504	201	422	1142.3	36943.9	33502.7	40642.6	0.68	0.60	0.77	<.001	0.65	0.57	0.74	<.001
		Unexposed	17128	7544	17207	38934.9	44194.3	43536.4	44859.7	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	12 months	Exposed	504	6	6	1142.3	525.3	192.8	1143.3	0.97	0.31	3.02	0.956	0.87	0.28	2.75	0.817
		Unexposed	17128	194	197	38934.9	506.0	437.8	581.8	-	-	-	-	-	-	-	-

Protocol definition	At-risk period	Exposure/ Vaccination Status	Incidence rate per 100 000 person-years							IR ratio*			IR Ratio* adjusted on Country				
			N	n	n*	Person-Years	95% CI			95% CI			P-value	95% CI			
							Value	LL	UL	Value	LL	UL		Value	LL	UL	P-value
2 years after Dose 4/virtual Dose 4 from Dose 4/virtual Dose 4																	
DIRECT EFFECT																	
Any Malaria Per Protocol	24 months	Vaccinated	12621	4525	8197	24790.5	33065.0	32353.1	33788.7	0.94	0.80	1.11	0.470	1.01	0.85	1.18	0.950
		Unvaccinated	504	155	303	944.0	32098.5	28585.7	35923.8	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Vaccinated	12621	99	113	24790.5	455.8	375.7	548.0	1.84	0.33	10.40	0.488	1.77	0.30	10.22	0.526
	24 months	Unvaccinated	504	2	2	944.0	211.9	25.7	765.4	-	-	-	-	-	-	-	-
OVERALL EFFECT																	
Any Malaria Per Protocol	24 months	Exposed	13125	4680	8500	25734.5	33029.6	32331.1	33739.4	0.71	0.68	0.74	<.001	0.72	0.69	0.75	<.001
		Unexposed	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Exposed	13125	101	115	25734.5	446.9	368.9	536.4	0.85	0.60	1.20	0.358	0.83	0.58	1.17	0.280
		Unexposed	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-
TOTAL EFFECT																	
Any Malaria Per Protocol	24 months	Vaccinated	12621	4525	8197	24790.5	33065.0	32353.1	33788.7	0.71	0.68	0.74	<.001	0.72	0.69	0.75	<.001
		Unvaccinated	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Vaccinated	12621	99	113	24790.5	455.8	375.7	548.0	0.87	0.62	1.24	0.446	0.85	0.60	1.20	0.356
		Unvaccinated	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-
INDIRECT EFFECT																	
Any Malaria Per Protocol	24 months	Exposed	504	155	303	944.0	32098.5	28585.7	35923.8	0.73	0.63	0.85	<.001	0.69	0.59	0.80	<.001
		Unexposed	17071	5955	11905	32878.6	36208.9	35561.4	36865.3	-	-	-	-	-	-	-	-
Any Severe Malaria Cases	24 months	Exposed	504	2	2	944.0	211.9	25.7	765.4	0.38	0.07	2.05	0.261	0.35	0.06	1.89	0.221
		Unexposed	17071	163	168	32878.6	511.0	436.6	594.4	-	-	-	-	-	-	-	-

Confirmed cases = confirmed cases from hospitalization according to final diagnosis

Vaccinated = participants vaccinated with RTS,S/AS01E vaccine; Unvaccinated = participants not vaccinated with RTS,S/AS01E vaccine

N = number of evaluable participants with follow-up during at-risk period; n* = total number of events reported during the follow-up period at-risk; n = number of participants with at least one event reported during the follow-up period at-risk

Person-Years = sum of the follow-up periods at-risk of the participants (in years)

Incidence rate (IR) per 100 000 person-years = number of events per 100 000 person-years estimated as n* / Person-years

Adjusted IR ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status

95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)

*Incidence Rate (IR) Ratio estimated with baseline covariate balance using propensity score overlap weighting

Source: Table 16.8.13 (31MAR2026 20:16 GMT), Table 16.8.14 (31MAR2026 20:15 GMT), Table 16.8.15 (31MAR2026 20:15 GMT), Table 16.8.16 (31MAR2026 20:14 GMT), Table 16.8.21 (31MAR2026 20:16 GMT), Table 16.8.22 (31MAR2026 20:15 GMT), Table 16.8.23 (31MAR2026 20:15 GMT), Table 16.8.24 (31MAR2026 20:14 GMT)

11.5. Other analyses

11.5.1. Children with hemoglobinopathy and HIV-positive children

The number of children with hemoglobinopathy and HIV positive children in the Active Surveillance cohort is presented in [Table 11.29](#).

The number of participants and confirmed cases for the main safety endpoints (AESI, meningitis, cerebral malaria and death) for children with HIV from Active Surveillance are summarized in [Table 11.30](#).

In total 16 participants were positive for HIV. It should be noted that these HIV positive children were only those with known HIV status, i.e., they were not required to be tested per protocol and, if tested, this was only at site level. In addition, the parents/LARs were not required to disclose the child's HIV status if they chose not to. Therefore, the number of confirmed HIV cases, and of confirmed main endpoints, is low.

Table 11.29 HIV and Hemoglobinopathy status by study group - Active Surveillance - Analysis set

	AS DTP group N=41942		AS catch-up group N=2970		Total N=44912	
Characteristics	n	%	n	%	n	%
HIV positive status	14	0.03	2	0.1	16	0.04
Children with hemoglobinopathy	94	0.2	6	0.2	100	0.2

AS DTP group = Active surveillance DTP group; AS catch-up group = Active surveillance catch-up group

N = total number of participants; n = number of participants in a given category; % = percentage of participants in a given category

Source: Table 16.1.7.1 (03FEB2026 22:46 GMT)

Table 11.30 Summary of the number of participants and confirmed cases for the main endpoints by study group and study site – with HIV positive status – Active Surveillance - Analysis set

Study site	Title	AS DTP group N=14				AS catch-up group N=2				Total N=16			
		N*	n*	n	%	N*	n*	n	%	N*	n*	n	%
Overall exposed clusters	AESI	6	1	1	17	2	0	0	0	8	1	1	13
	Meningitis	6	0	0	0	2	0	0	0	8	0	0	0
	Any Malaria	6	1	1	17	2	9	2	100	8	10	3	38
	Cerebral Malaria	6	0	0	0	2	0	0	0	8	0	0	0
	Death all causes	6	1	1	17	2	1	1	50	8	2	2	25
	Death among Female	6	1	1	17	2	0	0	0	8	1	1	13
	Death among Male	6	0	0	0	2	1	1	50	8	1	1	13
Overall unexposed clusters	AESI	8	0	0	0	0	0	0	-	8	0	0	0
	Meningitis	8	0	0	0	0	0	0	-	8	0	0	0
	Any Malaria	8	9	3	38	0	0	0	-	8	9	3	38
	Cerebral Malaria	8	1	1	13	0	0	0	-	8	1	1	13
	Death all causes	8	3	3	38	0	0	0	-	8	3	3	38
	Death among Female	8	2	2	25	0	0	0	-	8	2	2	25
	Death among Male	8	1	1	13	0	0	0	-	8	1	1	13

Study site	Title	AS DTP group N=14				AS catch-up group N=2				Total N=16			
		N*	n*	n	%	N*	n*	n	%	N*	n*	n	%
Overall	AESI	14	1	1	7	2	0	0	0	16	1	1	6
	Meningitis	14	0	0	0	2	0	0	0	16	0	0	0
	Any Malaria	14	10	4	29	2	9	2	100	16	19	6	38
	Cerebral Malaria	14	1	1	7	2	0	0	0	16	1	1	6
	Death all causes	14	4	4	29	2	1	1	50	16	5	5	31
	Death among Female	14	3	3	21	2	0	0	0	16	3	3	19
	Death among Male	14	1	1	7	2	1	1	50	16	2	2	13

AS DTP group = Active surveillance DTP group ; AS catch-up group = Active surveillance catch-up group

N = total number of participants

n* = number of events reported

n = number of participants reporting at least one event

% = percentage of participants reporting the event at least once

At least one endpoint = at least one endpoint experienced regardless of the MedDRA Preferred Term

Confirmed cases = confirmed cases from hospitalization (and/or outpatient visits for Malaria endpoint only) according to final diagnosis

AESI = adverse event of special interest

Source: Table 16.1.1.11 (03FEB2026 22:50 GMT)

The number of participants and confirmed cases for the main safety endpoints (AESI, meningitis, cerebral malaria and death) for children with hemoglobinopathy from Active Surveillance are summarized in [Table 11.31](#).

In total, 100 participants presented with hemoglobinopathy, equally distributed in exposed and unexposed clusters. The low number of confirmed cases for the main endpoints was also evenly distributed between exposed and unexposed clusters.

Table 11.31 Summary of the number of participants and confirmed cases for the main endpoints by study group and study site – with hemoglobinopathy – Active Surveillance - Analysis set

Study site	Title	AS DTP group N=94				AS catch-up group N=6				Total N=100			
		N*	n*	n	%	N*	n*	n	%	N*	n*	n	%
Overall exposed clusters	AESI	43	0	0	0	6	0	0	0	49	0	0	0
	Meningitis	43	1	1	2	6	0	0	0	49	1	1	2
	Any Malaria	43	92	36	84	6	20	5	83	49	112	41	84
	Cerebral Malaria	43	0	0	0	6	0	0	0	49	0	0	0
	Death all causes	43	7	7	16	6	0	0	0	49	7	7	14
	Death among Female	43	3	3	7	6	0	0	0	49	3	3	6
	Death among Male	43	4	4	9	6	0	0	0	49	4	4	8
Overall unexposed clusters	AESI	51	1	1	2.0	0	0	0	-	51	1	1	2.0
	Meningitis	51	2	2	3.9	0	0	0	-	51	2	2	3.9
	Any Malaria	51	115	34	66.7	0	0	0	-	51	115	34	66.7
	Cerebral Malaria	51	0	0	0	0	0	0	-	51	0	0	0
	Death all causes	51	5	5	9.8	0	0	0	-	51	5	5	9.8
	Death among Female	51	2	2	3.9	0	0	0	-	51	2	2	3.9
	Death among Male	51	3	3	5.9	0	0	0	-	51	3	3	5.9
Overall	AESI	94	1	1	1.1	6	0	0	0	100	1	1	1.0
	Meningitis	94	3	3	3.2	6	0	0	0	100	3	3	3.0
	Any Malaria	94	207	70	74.5	6	20	5	83.3	100	227	75	75.0
	Cerebral Malaria	94	0	0	0	6	0	0	0	100	0	0	0

Study site	Title	AS DTP group N=94				AS catch-up group N=6				Total N=100			
		N*	n*	n	%	N*	n*	n	%	N*	n*	n	%
	Death all causes	94	12	12	12.8	6	0	0	0	100	12	12	12.0
	Death among Female	94	5	5	5.3	6	0	0	0	100	5	5	5.0
	Death among Male	94	7	7	7.4	6	0	0	0	100	7	7	7.0

AS DTP group = Active surveillance DTP group ; AS catch-up group = Active surveillance catch-up group

N = total number of participants

n* = number of events reported

n = number of participants reporting at least one event

% = percentage of participants reporting the event at least once

At least one endpoint = at least one endpoint experienced regardless of the MedDRA Preferred Term

Confirmed cases = confirmed cases from hospitalization (and/or outpatient visits for Malaria endpoint only) according to final diagnosis

AESI = adverse event of special interest

Source: Table 16.1.1.12 (03FEB2026 22:48 GMT)

A summary of the number of participants with HIV positive status, and participants with hemoglobinopathy, for confirmed cases for the main endpoints for the Enhanced Hospitalization Surveillance cohort is presented in Section 16 Table 16.1.1.15 and Table 16.1.1.16, respectively.

11.6. Adverse events/adverse reactions

No vaccination was administered per protocol. Any AE, which was serious and which, in the opinion of the investigator, was suspected to be related to the protocol required blood draw for any suspected AESI or meningitis case, was to be recorded in the Expedited Adverse Event screen in the eCRF. Other specific events, as defined in Protocol Section 11.3, were to be reported as expedited AEs.

No SAE related to a study procedure (blood collection in case of suspected AESI or meningitis) was reported.

Results for the cumulative number of expedited AEs according to final diagnosis with an available ICD10 code are presented in Section 16 Table 16.2.7.1 and Table 16.2.7.2 for Active Surveillance and Section 16 Table 16.2.7.3 and 16.2.7.4 for Enhanced Hospitalization Surveillance. Additional analyses to provide all expedited AEs, not requiring a final diagnosis, are presented in Section 16 Table 16.8.29 and Table 16.8.30 for Active Surveillance and Section 16 Table 16.8.31 and 16.8.32 for Enhanced Hospitalization Surveillance.

The cumulative number of expedited SAEs are presented in [Table 11.32](#) for Active Surveillance and in [Table 11.33](#) for Enhanced Hospitalization Surveillance. It should be noted that the numbers of cases/events with terms corresponding to AESIs or other safety endpoints may differ from those in the safety evaluations, as expedited AEs could be reported even if the event occurred outside the risk period, was not confirmed in hospital and did not have a final diagnosis with an ICD10 code which corresponded with a safety endpoint definition. In addition, although some safety endpoints required confirmation by the EEP (e.g., meningitis, cerebral malaria), these events could be reported as expedited AEs even if the diagnosis was not EEP confirmed.

Table 11.32 Cumulative number (%) of expedited serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term by study group - Active Surveillance - Analysis set

System Organ Class	Preferred Term	AS DTP group			AS catch-up group			Overall		
		Participants N=41942	Hospitalizations N=9843	Events N=748	Participants N=2970	Hospitalizations N=989	Events N=107	Participants N=44912	Hospitalizations N=10832	Events N=855
Any Events		560 (1.34%)	48 (0.49%)	748 (100%)	88 (2.96%)	3 (0.30%)	107 (100%)	648 (1.44%)	51 (0.47%)	855 (100%)
Blood and lymphatic system disorders	Anemia	13 (0.03%)	0	13 (1.74%)	2 (0.07%)	0	2 (1.87%)	15 (0.03%)	0	15 (1.75%)
	Hemolytic anemia	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Sickle cell anemia with crisis	4 (0.01%)	0	4 (0.53%)	0	0	0	4 (0.01%)	0	4 (0.47%)
	Thrombocytopenia	7 (0.02%)	0	7 (0.94%)	1 (0.03%)	0	1 (0.93%)	8 (0.02%)	0	8 (0.94%)
	Overall PT	24 (0.06%)	0	24 (3.21%)	4 (0.13%)	0	4 (3.74%)	28 (0.06%)	0	28 (3.27%)
Congenital, familial and genetic disorders	Cerebral palsy	8 (0.02%)	0	8 (1.07%)	3 (0.10%)	0	3 (2.80%)	11 (0.02%)	0	11 (1.29%)
	Congenital megacolon	2 (0.00%)	0	2 (0.27%)	1 (0.03%)	0	1 (0.93%)	3 (0.01%)	0	3 (0.35%)
	Heart disease congenital	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Sickle cell anemia	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Trisomy 21	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Ventricular septal defect	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	16 (0.04%)	0	16 (2.14%)	4 (0.13%)	0	4 (3.74%)	20 (0.04%)	0	20 (2.34%)
Gastrointestinal disorders	Abdominal mass	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Abdominal pain	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Acute abdomen	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Diarrhoea	3 (0.01%)	0	3 (0.40%)	1 (0.03%)	0	1 (0.93%)	4 (0.01%)	0	4 (0.47%)
	Ileus	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Intestinal obstruction	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Intussusception	6 (0.01%)	1 (0.01%)	6 (0.80%)	1 (0.03%)	0	1 (0.93%)	7 (0.02%)	1 (0.01%)	7 (0.82%)
	Vomiting	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Overall PT	17 (0.04%)	1 (0.01%)	17 (2.27%)	2 (0.07%)	0	2 (1.87%)	19 (0.04%)	1 (0.01%)	19 (2.22%)

System Organ Class	Preferred Term	AS DTP group			AS catch-up group			Overall		
		Participants N=41942	Hospitalizations N=9843	Events N=748	Participants N=2970	Hospitalizations N=989	Events N=107	Participants N=44912	Hospitalizations N=10832	Events N=855
General disorders and administration site conditions	Death	5 (0.01%)	0	5 (0.67%)	1 (0.03%)	0	1 (0.93%)	6 (0.01%)	0	6 (0.70%)
	Drowning	6 (0.01%)	0	6 (0.80%)	1 (0.03%)	0	1 (0.93%)	7 (0.02%)	0	7 (0.82%)
	Pyrexia	9 (0.02%)	0	9 (1.20%)	3 (0.10%)	0	3 (2.80%)	12 (0.03%)	0	12 (1.40%)
	Sudden death	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Sudden infant death syndrome	1 (0.00%)	0	1 (0.13%)	1 (0.03%)	0	1 (0.93%)	2 (0.00%)	0	2 (0.23%)
Hepatobiliary disorders	Overall PT	22 (0.05%)	0	22 (2.94%)	6 (0.20%)	0	6 (5.61%)	28 (0.06%)	0	28 (3.27%)
	Hepatic failure	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Overall PT	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
Immune system disorders	Allergy to vaccine	0	0	0	1 (0.03%)	0	2 (1.87%)	1 (0.00%)	0	2 (0.23%)
	Anaphylactic reaction	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Anaphylactic shock	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	4 (0.01%)	0	4 (0.53%)	1 (0.03%)	0	2 (1.87%)	5 (0.01%)	0	6 (0.70%)
Infections and infestations	Bacterial infection	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Bronchiolitis	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Cellulitis	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Cerebral malaria	11 (0.03%)	0	11 (1.47%)	3 (0.10%)	0	3 (2.80%)	14 (0.03%)	0	14 (1.64%)
	Complicated malaria	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Dysentery	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Encephalitis	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Encephalitis viral	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Epiglottitis	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	External ear cellulitis	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Gastroenteritis	41 (0.10%)	0	41 (5.48%)	4 (0.13%)	0	4 (3.74%)	45 (0.10%)	0	45 (5.26%)
	HIV infection	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Helminthic infection	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Herpes simplex	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Infection	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Injection site abscess	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Malaria	268 (0.64%)	0	296 (39.57%)	51 (1.72%)	0	52 (48.60%)	319 (0.71%)	0	348 (40.70%)

System Organ Class	Preferred Term	AS DTP group			AS catch-up group			Overall		
		Participants N=41942	Hospitalizations N=9843	Events N=748	Participants N=2970	Hospitalizations N=989	Events N=107	Participants N=44912	Hospitalizations N=10832	Events N=855
	Meningitis	14 (0.03%)	0	14 (1.87%)	0	0	0	14 (0.03%)	0	14 (1.64%)
	Meningitis bacterial	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Meningitis herpes	3 (0.01%)	1 (0.01%)	3 (0.40%)	0	0	0	3 (0.01%)	1 (0.01%)	3 (0.35%)
	Meningitis pneumococcal	1 (0.00%)	1 (0.01%)	1 (0.13%)	0	0	0	1 (0.00%)	1 (0.01%)	1 (0.12%)
	Meningitis streptococcal	1 (0.00%)	1 (0.01%)	1 (0.13%)	0	0	0	1 (0.00%)	1 (0.01%)	1 (0.12%)
	Plasmodium falciparum infection	5 (0.01%)	0	5 (0.67%)	0	0	0	5 (0.01%)	0	5 (0.58%)
	Pneumonia	44 (0.10%)	0	44 (5.88%)	4 (0.13%)	0	4 (3.74%)	48 (0.11%)	0	48 (5.61%)
	Respiratory tract infection	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Retroviral infection	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Sepsis	22 (0.05%)	3 (0.03%)	23 (3.07%)	3 (0.10%)	0	3 (2.80%)	25 (0.06%)	3 (0.03%)	26 (3.04%)
	Septic shock	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Upper respiratory tract infection	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	390 (0.93%)	6 (0.06%)	458 (61.23%)	64 (2.15%)	0	70 (65.42%)	454 (1.01%)	6 (0.06%)	528 (61.75%)
Injury, poisoning and procedural complications	Chemical poisoning	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Head injury	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Herbal toxicity	1 (0.00%)	0	1 (0.13%)	1 (0.03%)	0	1 (0.93%)	2 (0.00%)	0	2 (0.23%)
	Immunisation reaction	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Injury	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Poisoning	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Respiratory fume inhalation disorder	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Road traffic accident	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Soft tissue injury	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Thermal burn	10 (0.02%)	0	10 (1.34%)	1 (0.03%)	0	1 (0.93%)	11 (0.02%)	0	11 (1.29%)

System Organ Class	Preferred Term	AS DTP group			AS catch-up group			Overall		
		Participants N=41942	Hospitalizations N=9843	Events N=748	Participants N=2970	Hospitalizations N=989	Events N=107	Participants N=44912	Hospitalizations N=10832	Events N=855
Metabolism and nutrition disorders	Toxicity to various agents	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Venomous bite	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	22 (0.05%)	0	23 (3.07%)	3 (0.10%)	0	3 (2.80%)	25 (0.06%)	0	26 (3.04%)
	Dehydration	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Hypoglycaemia	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Hypokalaemia	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Kwashiorkor	3 (0.01%)	2 (0.02%)	3 (0.40%)	0	0	0	3 (0.01%)	2 (0.02%)	3 (0.35%)
	Malnutrition	34 (0.08%)	0	34 (4.55%)	5 (0.17%)	0	5 (4.67%)	39 (0.09%)	0	39 (4.56%)
Musculoskeletal and connective tissue disorders	Overall PT	39 (0.09%)	2 (0.02%)	42 (5.61%)	6 (0.20%)	0	6 (5.61%)	45 (0.10%)	2 (0.02%)	48 (5.61%)
	Muscular weakness	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Overall PT	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Retinoblastoma	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
Nervous system disorders	Arachnoiditis*	7 (0.02%)	7 (0.07%)	7 (0.94%)	0	0	0	7 (0.02%)	7 (0.06%)	7 (0.82%)
	Cerebral venous sinus thrombosis	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Diabetic coma	1 (0.00%)	1 (0.01%)	1 (0.13%)	0	0	0	1 (0.00%)	1 (0.01%)	1 (0.12%)
	Epilepsy	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Febrile convulsion	15 (0.04%)	3 (0.03%)	15 (2.01%)	0	0	0	15 (0.03%)	3 (0.03%)	15 (1.75%)
	Febrile status epilepticus	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Guillain-Barre syndrome	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Idiopathic generalised epilepsy	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Seizure	47 (0.11%)	0	49 (6.55%)	2 (0.07%)	0	2 (1.87%)	49 (0.11%)	0	51 (5.96%)
	Status epilepticus	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)

System Organ Class	Preferred Term	AS DTP group			AS catch-up group			Overall		
		Participants N=41942	Hospitalizations N=9843	Events N=748	Participants N=2970	Hospitalizations N=989	Events N=107	Participants N=44912	Hospitalizations N=10832	Events N=855
	Tonic convulsion	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	72 (0.17%)	9 (0.09%)	82 (10.96%)	2 (0.07%)	0	2 (1.87%)	74 (0.16%)	9 (0.08%)	84 (9.82%)
Renal and urinary disorders	Acute kidney injury	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Nephrotic syndrome	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Renal failure	5 (0.01%)	0	5 (0.67%)	1 (0.03%)	0	1 (0.93%)	6 (0.01%)	0	6 (0.70%)
	Overall PT	7 (0.02%)	0	7 (0.94%)	1 (0.03%)	0	1 (0.93%)	8 (0.02%)	0	8 (0.94%)
Respiratory, thoracic and mediastinal disorders	Asphyxia	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Aspiration	1 (0.00%)	0	1 (0.13%)	1 (0.03%)	0	1 (0.93%)	2 (0.00%)	0	2 (0.23%)
	Choking	2 (0.00%)	0	2 (0.27%)	1 (0.03%)	0	1 (0.93%)	3 (0.01%)	0	3 (0.35%)
	Dyspnoea	0	0	0	1 (0.03%)	0	1 (0.93%)	1 (0.00%)	0	1 (0.12%)
	Pneumothorax	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Respiratory distress	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Overall PT	6 (0.01%)	0	7 (0.94%)	3 (0.10%)	0	3 (2.80%)	9 (0.02%)	0	10 (1.17%)
Skin and subcutaneous tissue disorders	Rash	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
	Overall PT	2 (0.00%)	0	2 (0.27%)	0	0	0	2 (0.00%)	0	2 (0.23%)
Vascular disorders	Hypovolaemic shock	3 (0.01%)	0	3 (0.40%)	0	0	0	3 (0.01%)	0	3 (0.35%)
	Shock	1 (0.00%)	0	1 (0.13%)	0	0	0	1 (0.00%)	0	1 (0.12%)
	Overall PT	4 (0.01%)	0	4 (0.53%)	0	0	0	4 (0.01%)	0	4 (0.47%)
Suspected AE ruled out afterward	Suspected AE ruled out afterward	36 (0.09%)	36 (0.37%)	36 (4.81%)	3 (0.10%)	3 (0.30%)	3 (2.80%)	39 (0.09%)	39 (0.36%)	39 (4.56%)
	Overall PT	36 (0.09%)	36 (0.37%)	36 (4.81%)	3 (0.10%)	3 (0.30%)	3 (2.80%)	39 (0.09%)	39 (0.36%)	39 (4.56%)

AS DTP group = Active surveillance DTP group; AS catch-up group = Active surveillance catch-up group

Any events = at least one symptom experienced (regardless of the MedDRA Preferred Term)

Participants = number of participants reporting at least once the symptom after first dose; Hospitalizations = number of hospitalizations; Events = number of events

*Cases of arachnoiditis were evaluated as meningitis

AE = adverse event; PT = preferred term

MedDRA version 26.1

Source: Table 16.8.30 (31MAR2026 20:13 GMT)

Table 11.33 Cumulative number (%) of expedited serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term - Enhanced Hospitalization Surveillance - Analysis set

System Organ Class	Preferred Term	EHS		
		Participants N=32745	Hospitalizations N=12296	Events N=494
Any Events		401 (1.22%)	19 (0.15%)	494 (100%)
Blood and lymphatic system disorders	Anemia	5 (0.02%)	0	5 (1.01%)
	Sickle cell anemia with crisis	2 (0.01%)	0	2 (0.40%)
	Thrombocytopenia	9 (0.03%)	1 (0.01%)	9 (1.82%)
	Overall PT	15 (0.05%)	1 (0.01%)	16 (3.24%)
Cardiac disorders	Cardiac failure	1 (0.00%)	1 (0.01%)	1 (0.20%)
	Overall PT	1 (0.00%)	1 (0.01%)	1 (0.20%)
Congenital, familial and genetic disorders	Cerebral palsy	1 (0.00%)	0	1 (0.20%)
	Heart disease congenital	1 (0.00%)	0	1 (0.20%)
	Sickle cell anemia	1 (0.00%)	0	1 (0.20%)
	Overall PT	3 (0.01%)	0	3 (0.61%)
Gastrointestinal disorders	Diarrhoea	1 (0.00%)	0	1 (0.20%)
	Intussusception	6 (0.02%)	0	6 (1.21%)
	Overall PT	7 (0.02%)	0	7 (1.42%)
General disorders and administration site conditions	Drowning	1 (0.00%)	0	1 (0.20%)
	Pyrexia	2 (0.01%)	0	2 (0.40%)
	Sudden death	1 (0.00%)	0	1 (0.20%)
	Overall PT	4 (0.01%)	0	4 (0.81%)
Hepatobiliary disorders	Hepatic failure	3 (0.01%)	0	3 (0.61%)
	Overall PT	3 (0.01%)	0	3 (0.61%)
Infections and infestations	Cerebral malaria	8 (0.02%)	0	8 (1.62%)
	Encephalitis	1 (0.00%)	0	1 (0.20%)
	Encephalitis viral	1 (0.00%)	0	1 (0.20%)
	Gastroenteritis	11 (0.03%)	1 (0.01%)	12 (2.43%)
	Malaria	246 (0.75%)	0	272 (55.06%)
	Meningitis	16 (0.05%)	0	16 (3.24%)
	Meningitis bacterial	3 (0.01%)	0	3 (0.61%)
	Meningitis streptococcal	1 (0.00%)	0	1 (0.20%)
	Pneumonia	11 (0.03%)	0	11 (2.23%)
	Pneumonia aspiration	1 (0.00%)	0	1 (0.20%)
	Sepsis	12 (0.04%)	0	12 (2.43%)
	Staphylococcal scalded skin syndrome	1 (0.00%)	0	1 (0.20%)
	Varicella encephalitis	1 (0.00%)	0	1 (0.20%)
	Overall PT	300 (0.92%)	1 (0.01%)	340 (68.83%)
Injury, poisoning and procedural complications	Herbal toxicity	1 (0.00%)	0	1 (0.20%)
	Thermal burn	1 (0.00%)	0	1 (0.20%)
	Overall PT	2 (0.01%)	0	2 (0.40%)
Metabolism and nutrition disorders	Dehydration	3 (0.01%)	0	3 (0.61%)
	Failure to thrive	1 (0.00%)	0	1 (0.20%)
	Hypoglycaemia	2 (0.01%)	0	2 (0.40%)
	Malnutrition	15 (0.05%)	0	15 (3.04%)
	Overall PT	19 (0.06%)	0	21 (4.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cardiac neoplasm	1 (0.00%)	0	1 (0.20%)
	unspecified			
	Craniopharyngioma	1 (0.00%)	0	1 (0.20%)
	Nephroblastoma	1 (0.00%)	0	1 (0.20%)
	Overall PT	3 (0.01%)	0	3 (0.61%)

System Organ Class	Preferred Term	EHS		
		Participants N=32745	Hospitalizations N=12296	Events N=494
Nervous system disorders	Arachnoiditis*	2 (0.01%)	2 (0.02%)	2 (0.40%)
	Febrile convulsion	6 (0.02%)	1 (0.01%)	6 (1.21%)
	Hepatic encephalopathy	1 (0.00%)	0	1 (0.20%)
	Seizure	59 (0.18%)	0	62 (12.55%)
	Status epilepticus	1 (0.00%)	0	1 (0.20%)
	Tonic convulsion	1 (0.00%)	0	1 (0.20%)
	Overall PT	67 (0.20%)	3 (0.02%)	73 (14.78%)
Renal and urinary disorders	Renal failure	3 (0.01%)	0	3 (0.61%)
	Overall PT	3 (0.01%)	0	3 (0.61%)
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	1 (0.00%)	0	1 (0.20%)
	Respiratory distress	1 (0.00%)	0	1 (0.20%)
	Overall PT	2 (0.01%)	0	2 (0.40%)
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome	1 (0.00%)	0	1 (0.20%)
	Overall PT	1 (0.00%)	0	1 (0.20%)
Suspected AE ruled out afterward	Suspected AE ruled out afterward	15 (0.05%)	15 (0.12%)	15 (3.04%)
	Overall PT	15 (0.05%)	15 (0.12%)	15 (3.04%)

EHS group = Enhanced Hospitalization Surveillance group

Any events = at least one symptom experienced (regardless of the MedDRA Preferred Term); Participants = number of participants reporting at least once the symptom after first dose

Hospitalizations = number of hospitalizations; Events = number of events

*Cases of arachnoiditis were evaluated as meningitis

AE = adverse event; PT = preferred term

MedDRA version 26.1

Source: Table 16.8.32 (31MAR2026 20:14 GMT)

12. DISCUSSION

12.1. Key results

This Final Analysis included 44 998 children from Active Surveillance, uniformly distributed between exposed and unexposed clusters. In addition, 32 955 children were included from the Enhanced Hospitalization Surveillance cohort. The RTS,S/AS01_E vaccination coverage with at least 1 dose in the exposed clusters was 92.0% of participants in Active Surveillance, and 33.5% of participants in Enhanced Hospitalization Surveillance, the lower coverage in the latter cohort in part reflecting an older age group, with many not eligible for vaccination.

For the co-primary objectives, few cases of confirmed AESI and etiology-confirmed meningitis were reported in participants from Active Surveillance during the at-risk period. After the RTS,S/AS01_E vaccine/virtual full schedule (combining the RTS,S/AS01_E 4 doses/virtual doses), 8 cases of generalized convulsive seizure in the vaccinated group, 1 case of intussusception in the unvaccinated group and 1 case of thrombocytopenia in the unvaccinated group were reported. Of the 8 seizure cases in vaccinated participants, all cases occurred with events of pyrexia. Febrile convulsions are a known risk with RTS,S/AS01_E vaccination. Additionally, 5 cases reported concurrent infective events including pneumonia and gastroenteritis. The seizures did not recur in

participants that received subsequent doses. One case reported an event of status epilepticus, however, this was not witnessed by healthcare professionals and was reported to have spontaneously resolved, making it less likely to represent true status epilepticus. One case of etiology-confirmed meningitis was reported in each of the vaccinated and unvaccinated groups (crude IRR 1.06 [95% CI: 0.07-16.98], $p=0.966$). During the at-risk period after RTS,S/AS01_E vaccine/virtual Dose 4, 2 cases of generalized convulsive seizure in the RTS,S/AS01_E vaccinated group, 1 case of thrombocytopenia in the RTS,S/AS01_E unvaccinated group and no etiology-confirmed meningitis cases were reported.

For suspected cases of meningitis, lumbar puncture was to be performed according to routine medical practice for examination of CSF. However, in total 36/139 (25.9%) suspected meningitis cases had a CSF sample collected and 31/139 (22.3%) CSF samples were sent to a second line laboratory. Nonetheless, when considering protocol defined meningitis (etiology-confirmed, bacterial-confirmed, probable or clinically suspected meningitis), no statistically significant difference in IR in RTS,S/AS01_E vaccinated vs unvaccinated groups was observed.

After the vaccine/virtual full (4-dose) schedule, there were 5 cases of cerebral malaria in RTS,S/AS01_E vaccinated and 7 cases in RTS,S/AS01_E unvaccinated children, yielding a crude IRR of 0.76 (95% CI: 0.24-2.39; $p=0.637$). The all-cause mortality IR was 502.5 (95% CI: 434.8-577.8) per 100 000 PY in vaccinated vs 542.9 (95% CI: 474.4-618.5) per 100 000 PY in unvaccinated children. Similar mortality rates were observed in vaccinated children in both genders (females: IR 497.7 [95% CI: 403.2-607.8]; males: IR 507.1 [95% CI: 413.0-616.2]).

Amongst expedited AE, cases reported for participants enrolled via Active Surveillance, 1 case of Guillain-Barre Syndrome was reported which did not meet criteria for evaluation as an AESI as the event was not confirmed in hospital. Guillain-Barre Syndrome was considered possibly related to RTS,S/AS01_E by the investigator. However, the event occurred 4 days after vaccination, which is a short time-to-onset given the average time for development of post-vaccination Guillain-Barre Syndrome between 13 to 18 days as measured for other vaccines [Ha, 2023; Sah, 2024]. There was also insufficient information to meet any level of the Brighton Criteria case definition due to a lack of neurological examination performed and no evaluation of alternative causes for weakness performed.

Apart from these, 2 cases of febrile status epilepticus, 3 of status epilepticus, and 1 case of nephrotic syndrome were noted. The onset time was between 117 to 514 days and the events were not considered related by the investigator, with the exception of the event of status epilepticus mentioned earlier in the discussion on febrile convulsions, which occurred less than a day after administration of RTS,S/AS01_E.

Notable events in expedited AE cases reported for participants enrolled via Enhanced Hospitalization Surveillance include 1 case each of Stevens-Johnson syndrome, hepatic encephalopathy, status epilepticus, encephalitis and viral encephalitis. All events occurred with a long time-to-onset, between 108 to 493 days after administration of a dose of RTS,S/AS01_E. Additionally, 1 case of cardiac failure, occurring 17 days after administration of RTS,S/AS01_E, was noted. Cardiac failure was reported to be secondary to a congenital ventricular septal defect. These events were not considered to be related to RTS,S/AS01_E by the investigator.

Across both Active and Enhanced Hospital Surveillance, a small number of participants (20) experienced serious expedited AEs which were considered possibly related to vaccination by the investigator:

- Nine experienced events aligned to known risks (pyrexia, vomiting and febrile convulsions, including the case of suspected status epilepticus mentioned in the discussion on febrile convulsions).
- Two experienced fatal febrile seizures. One participant had concurrent meningitis (confirmed by the External Expert Panel). The other had cerebral palsy and was being treated for concurrent sepsis.
- Two experienced non-febrile seizures. One participant was known to have cerebral palsy. The remaining participant reported daily recurrent seizures 14 days following the first dose which resolved without intervention while this participant continued to receive further doses.
- One participant was reported to have vaccine allergy occurring 3 days following the first dose; a long duration for an immediate allergic reaction. The same participant also experienced a further “reaction” 1 day post third dose which was an event of pyrexia.
- Four participants were reported to have intussusception, 1 in Active Surveillance occurred outside the risk window. One fatal event in a participant in Active Surveillance was not confirmed by imaging or direct visualization (Brighton Criteria Level 2). The remaining 2 participants were in the Enhanced Hospitalization Surveillance group (Level 1). The numbers of participants here do not exceed the number of unvaccinated participants with intussusception in the Active Surveillance or Enhanced Hospitalization Surveillance groups.
- The remaining 2 participants experienced fatal events of Guillain-Barre Syndrome (the case discussed above) and malaria respectively.

Due to the imbalance in population size in RTS,S/AS01_E vaccinated vs unvaccinated participants in exposed clusters, vaccine effectiveness (Direct Effect) estimations should be interpreted with caution, therefore impact analyses of the Total Effect were summarized as more robust estimates which took into account a larger portion of the enrolled population. In the main analysis period 1 year after Dose 4/virtual Dose 4 from Dose 3/virtual Dose 3, the IR of any malaria was 38 099 (95% CI: 37 385-38 823) per 100 000 PY in vaccinated vs 44 194 (95% CI: 43 536-44 860) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 14% (95% CI: 12-16; $p<0.001$). The IR of severe malaria was 369.0 (95% CI: 301.8-446.7) per 100 000 PY in vaccinated vs 506.0 (95% CI: 437.8-581.8) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 27% (95% CI: 8-42; $p=0.009$). IR of malaria-attributed hospitalization was 2793.6 (95% CI: 2602.8-2994.8) per 100 000 PY in vaccinated vs 3564.9 (95% CI: 3379.8-3757.5) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 22% (95% CI: 14-28; $p<0.001$). IRs of all-cause mortality were 112.4 (95% CI: 76.9-158.7) per 100 000 PY in vaccinated vs 123.3 (95% CI: 90.9-163.5) per 100 000 PY in unvaccinated children, resulting in a statistically non-significant crude vaccine effectiveness of 9% (95% CI: -43-42; $p=0.687$). ORs of anemia were 0.069 (95% CI: 0.064-0.073) per 100 000 PY in vaccinated vs 0.087 (95% CI: 0.083-0.092) per 100 000 PY in unvaccinated children, resulting in a crude vaccine effectiveness of 23% (95% CI: 16-29; $p<0.001$). Vaccine effectiveness values for crude estimates were similar to country-adjusted estimates.

Exploratory analyses further confirmed robustness of findings. After adjustment for measured confounding using propensity score overlap weighting, the vaccine effectiveness estimate was 33%, $p<0.001$ (and 32%, $p<0.001$ when additionally adjusted on country), representing estimated Total Effect among individuals with overlapping baseline characteristics.

12.2. Limitations

- Study sample size may be limited for detection of very rare diseases for evaluation of safety of RTS,S/AS01_E. To address safety research with very rare outcomes, most epidemiological studies are based on existing disease-specific registries or large healthcare databases such as insurance claim databases. However, such detailed registries or databases do not exist in sub-Saharan Africa.
- AESI are individual diseases with different pathologies which were, by study design, closely monitored as individual AEs. Analyses of incidence rates of AESI by MedDRA body system used the longest at-risk period for the events in the system organ class. Assessment of AESI by body system is therefore not applicable.

- Some AESI and meningitis cases require specific diagnostic methods and such data may not be routinely collected, potentially leading to challenges with diagnostic certainty. These challenges are anticipated to be similar between vaccinated and unvaccinated participants. Specific training and monitoring of the field teams (community health workers, health care facilities' staff, physicians and hospital staff) was provided on diagnostic methods. All procedures were performed in line with the current national guideline recommendations in each of the participating countries. Additionally, the majority of AESI and meningitis are expected to be detectable via clinical signs/symptoms, such as neurological deficits, decreased conscious levels, mucocutaneous lesions, purpura/bleeding events, with the option for adjudication by the External Expert Panel for further confirmation.
- In total 36/139 (25.9%) suspected meningitis cases had a CSF sample collected and 31/139 (22.3%) CSF samples were sent to a second line laboratory. Although low CSF sampling affects identification of probable and etiology-confirmed meningitis, clinically suspected meningitis diagnosis did not solely rely on CSF samples analysis and contributed to the cases evaluated as part of protocol-defined meningitis, for which no statistically significant difference in IR in RTS,S/AS01_E vaccinated vs unvaccinated groups was observed.
- The scrutiny in detecting AESI and meningitis cases during EPI-MAL-003 might have been different between the exposed and unexposed clusters, for example due to different health care structures, different accesses to care, or different routine case ascertainment procedures, increased awareness among the public/parents/LARs and health care personnel to report any suspicious event/behavior in vaccinated children [Merrett, 2006].
- Longitudinal detection of events such as meningitis might be difficult to interpret because of the changing meningitis disease epidemiology; interpretation of differences in meningitis incidence rates should take into account the epidemiological context of each site.
- Because surveillance was conducted in study areas covering mainly rural areas, children who were severely ill might have died before being transported to hospital. In the event of death, the cause of death was systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital. However, ascertaining the cause of death remains a concern considering the limitation of the verbal autopsy methods in the field, and is the reason all-cause mortality is an important endpoint to consider in this study.
- Some study participants might have left the study area during the study period, but this was regularly documented through demographic census (scheduled at least once a year during the study periods).

- All efforts were made to standardize data collection, both in exposed and unexposed clusters. However, due to the long study duration, changes in diagnostic procedures, national healthcare systems performance and updates, implementation of malaria control measures, seasonality and year-to-year variations in transmission, and in treatment measures could have occurred and might potentially have impacted interpretation of the safety and effectiveness/impact data. Potential confounders were collected at the individual level during EPI-MAL-003 and at the community level during EPI-MAL-005.
- Potential differences in baseline characteristics between vaccinated and unvaccinated children in exposed and unexposed clusters were possible, therefore this possible source of confounding was investigated through propensity score overlap weighting (based on baseline covariates). The results of propensity score overlap weighting adjust vaccine effects estimates only on measured confounders, however, it is important to note methodological distinction between different vaccine effects when adjusted by propensity score overlap weights: for Total and Direct Effects the exposure is individual vaccination status and confounding arises from individual-level baseline covariates (e.g., age, comorbidities etc), whilst for Indirect and Overall vaccine effectiveness, the exposure is cluster vaccination coverage and confounding is primarily considered at the cluster level (e.g., socioeconomic context, population density, baseline transmission intensity, healthcare access etc). Even after propensity score overlap weighting adjustments for vaccine effectiveness estimates, it is possible that unmeasured confounding was still present at individual and/or cluster level.

Propensity score overlap weighting was selected to control for differences between comparison groups as it provided better covariate balance and greater stability than inverse probability of treatment weighting. Unlike inverse probability of treatment weighting, which targets the average treatment effect, overlapping weights targets the average treatment effect in the overlap population and this focus on participants in clinical equipoise may generate effect estimates that are not generalizable to the full study population

- A fixed number of clusters were included in the cluster design comparison (6 exposed clusters and 6 unexposed clusters) which did not allow for robust intra-cluster adjustment. Unexposed EPI-MAL-003 clusters were selected by the Ministry of Health based on the following characteristics: malaria transmission, geographic location, access to care, and population size. This limitation was reflected at the time of the Interim Analysis when it was observed that the random effect Poisson regression model with the study site as random effect was rarely converging and was therefore replaced by Poisson regression models with country as fixed effect for estimates of IRR.

12.3. Interpretation

Safety signals observed in Phase 3 were not confirmed by EPI-MAL-003 Final Analyses, after the RTS,S/AS01_E vaccine full schedule (combining the RTS,S/AS01_E 4 doses):

- Meningitis events were rare and evenly distributed in RTS,S/AS01_E vaccinated and unvaccinated groups.
- Cerebral malaria events were rare and occurred both in RTS,S/AS01_E vaccinated and unvaccinated groups.
- Deaths occurred at similar rates in males and females.

Effectiveness (Total Effect) against any malaria and severe malaria in the 1-year period after the full (4-dose) schedule was 14% and 27%, respectively. Effectiveness (Total Effect) against malaria-related hospitalization was 22%, and against hospitalized anemia 23%. The Final Analysis did not show an impact on reducing all-cause mortality. The imbalance in mortality rates between females and males was not observed.

Overall interpretation:

- Safety signals observed after Phase 3, i.e., increased risk of meningitis and higher mortality rate in RTS,S/AS01_E vaccinated females compared to males, were not observed following the full (4-dose) RTS,S/AS01_E vaccination schedule in this Final Analysis of the EPI-MAL-003 study.
- No new safety signal was observed, and there was no evidence of an association between vaccine exposure and any prespecified AESI.
- In this large observational study, 1 year after Dose 4 of RTS,S/AS01_E evaluated from Dose 3, for children who had received the 3 doses before 12 months of age and Dose 4 of RTS,S/AS01_E before 30 months of age, a positive impact against hospitalizations due to malaria, severe malaria and hospitalized anemia was observed.
- Even though some confounding was present, as assessed by propensity score overlap weighting, adjusted vaccine effectiveness estimates were robust and the observed effects were in the same direction as crude estimates, indicating that confounding was not detrimental to study results and conclusions.

12.4. Generalizability

In the framework of the WHO-led MVIP, the RTS,S/AS01_E malaria vaccine was introduced in selected areas in 3 sub-Saharan countries through routine national immunization programs. Within the MVIP areas, the EPI-MAL-003 disease surveillance study was conducted, which comprised prospective cohort event monitoring to evaluate the safety, effectiveness and impact of the RTS,S/AS01_E vaccine in young children in sub-Saharan Africa less than 5 years of age. This Final Analysis presents data up to 2 years after the full (4-dose) vaccination schedule with the RTS,S/AS01_E vaccine. The eligibility criteria for participation was very broad, with the only exclusion criterion not permitting a child in care to participate, leading to an extensive database comprising 45 998 study participants of which 44 912 were included in the Analysis Set.

Given the comprehensive prospective data collection to support detection of any/potentially vaccine-related event, in 3 sub-Saharan Africa countries, EPI-MAL-003 is the largest observational study conducted to date that actively followed 44 998 children under the age of 5 years and their health outcomes. The findings of this Final Analysis can be considered generalizable to other settings in sub-Saharan Africa with similar malaria burden of disease, health care systems and use of other prevention measures than vaccine.

13. OTHER INFORMATION

Not applicable.

14. CONCLUSION

Safety signals observed in Phase 3 were not confirmed by the EPI-MAL-003 Final Analysis, and no new signals were identified. Meningitis events were rare and evenly distributed over RTS,S/AS01_E vaccinated and unvaccinated groups. Cerebral malaria events were rare and occurred both in RTS,S/AS01_E vaccinated and unvaccinated groups. Deaths occurred at similar rates in males and females. There was no evidence of an association between vaccine exposure and any prespecified AESI. Over 1 year after the full (4-dose) vaccination schedule, a positive impact against hospitalizations due to malaria, any and severe malaria, and hospitalizations due to anemia was observed.

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16. POST-TEXT TABLES

Appendices

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1.	115056	06 May 2026	Annex 1: List of stand-alone documents
2.	115056	06 May 2026	Annex 2: Glossary of Terms
3.	115056	06 May 2026	Annex 3: Trademarks
4.	115056	06 May 2026	Annex 4: Case Definitions for Protocol Defined Adverse Events of Special Interest (AESI)
5.	115056	06 May 2026	Annex 5: Report Sign-off

ANNEX 2 GLOSSARY OF TERMS

Active surveillance: Screening for AESI and other diseases during study follow-up visits at the community level.

Adverse event of special interest (AESI): A predefined list of adverse events that are potentially associated with RTS,S/AS01_E, that have historically been associated with vaccines other than RTS,S/AS01_E, or may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines.

Adverse event: Any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Child in care: A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.

Cohort event monitoring:	A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time.
Cohort study:	A form of epidemiological study where study participants in a study population are classified according to their exposure status/disease and followed over time (prospective/retrospective) to ascertain the outcome(s).
DTP/HepB/Hib	This refers to Diphtheria, Tetanus, and Pertussis (DTP), or DTP-Hepatitis B (DTP-HepB tetravalent) or DTP-HepB-Haemophilus influenza type b (Hib) (DTP-HepB-Hib pentavalent) vaccines.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enhanced hospitalization surveillance:	Case detection during hospitalization through monitoring of medical records and registries.
Epidemiology study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all study participants at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
Veeva CTMS:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Exposed clusters	Study sites where the RTS,S/AS01 _E vaccine will be implemented at the beginning of the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI.
Hospitalization:	Study participants requiring overnight stay in a health care facility.
Interventional human subject research:	Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.
National EPI:	Routine vaccination programs, administered by the national EPI system in place, usually given at 6, 10 and 14 weeks of age (e.g. DTP/HepB/Hib vaccines. NOTE: in some countries the EPI schedule may differ by a few weeks).

Pharmacovigilance:	Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs) [WHO, 2012].
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Serious adverse event:	A serious adverse event (SAE) is any untoward medical occurrence that: a. results in death; b. is life-threatening; c. requires hospitalization or prolongation of existing hospitalization; d. results in disability/incapacity; Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.
Site monitor:	An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.
Study participant number:	A unique number identifying a study participant, assigned to each study participant consenting to participate in the study.
Study participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.

Unexposed clusters	Study sites where the RTS,S/AS01 _E vaccine will not be implemented in the pilot implementation program by Ministries of Health using an expanded schedule of their routine EPI.
Vaccine ineligible	Vaccine ineligible is defined as those study participants that on the basis of age would be ineligible for RTS,S/AS01 _E vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the label for RTS,S/AS01 _E vaccination in the country.

ANNEX 3 TRADEMARKS

The following trademarks are used in the present document.

Note: In the body of the document (including the abstract), the names of the vaccines are written without the superscript symbol TM or ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Mosquirix TM	<i>Plasmodium falciparum</i> and hepatitis B vaccine (recombinant, adjuvanted)
Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
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ANNEX 4 CASE DEFINITIONS FOR PROTOCOL DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Nerves and Central Nervous System		
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)	LEVEL 1 - Diffuse or multifocal demyelination revealed on histopathological sampling OR Focal or multifocal impairment of the central nervous system with ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, most often focal) - Sensory abnormalities	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	- Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). - Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus AND - On MRI: diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences AND - Monophasic character of the illness (absence of relapse within a minimum of 3 months of symptomatic nadir) LEVEL 2 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND Focal or multifocal impairment of the central nervous system with ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, most often focal) - Sensory abnormalities - Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry) - Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus AND - On MRI: Diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences AND - Follow up insufficient to confirm a monophasic nature of the illness (absence of relapse within a minimum of three months after the clinical nadir). LEVEL 3 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND Focal or multifocal impairment of the central nervous system with ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects	2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus. Exclusion criteria for all levels of diagnostic certitude • Authentication of an acute infection or of a differential diagnosis is compatible with the clinical picture • Relapse of the illness at any moment after a minimum period of three months of clinical improvement after the nadir of clinical symptoms. • MRI images or histopathology in the clinical diagnosis is compatible with the case definition with the diagnosis of ADEM. In Summary ADEM can be confirmed if: • The clinical diagnosis is compatible with the case definition. • All differentials diagnoses have been excluded • The CSF exam supports the diagnosis of ADEM. NB: Plan for diagnostic confirmation by a neurologist (and MRI if possible). Generally the illness completely resolves in a few months. The diagnosis must be confirmed by a clinical examination performed 3 months after the nadir of the clinical symptoms.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
ENCEPHALITIS	LEVEL 1 - Demonstration of acute inflammation of the central nervous system parenchyma (+/- the meninges) on histopathology LEVEL 2 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND <i>One or more of the following signs:</i> - Absent or diminished reflexes to external stimuli (such as a loud noise or painful stimuli) - Absent or markedly diminished eye contact - Inadequate or absent response to an external stimuli - Seizures with loss of consciousness OR Focal or multifocal impairment of the central nervous system with ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, more often focal) - Sensory abnormalities - Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) - Cerebellar dysfunction, such as ataxia, dysmetria, cerebellar nystagmus AND <i>Two or more of the following signs:</i> - Fever ($\geq 37.5^{\circ}\text{C}$) - CSF: Pleocytosis >15 leukocytes/ mm^3 in a child 2 months of age or younger >5 leukocytes/ mm^3 in a child 2 months of age or older - EEG signs compatible with an encephalitis - Cerebral imagery compatible with an encephalitis. LEVEL 3 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND <i>One or more of the following signs:</i>	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	- Absent or diminished response to external stimuli (such as a loud noise, painful stimuli) - Absent or markedly diminished eye contact - Inconsistent or absent response to an external stimuli - Seizures with associated loss of consciousness OR Focal or multifocal impairment of the central nervous system with ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, most often focal) - Sensory abnormalities - Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) - Cerebellar impairment, such as ataxia, dysmetria, cerebellar nystagmus AND One of the following signs: - Fever ($\geq 37.5^{\circ}\text{C}$) - CSF: Pleocytosis >15 leukocytes/ mm^3 in a child 2 months of age or younger >5 leukocytes/ mm^3 in a child 2 months of age or older - EEG signs compatible with an encephalitis - Cerebral imagery compatible with an encephalitis Evaluation Criteria - Exclude the presence of all diseases (cancer, toxic-metabolic encephalopathy, vascular problems, trauma, meningitis etc.) In Summary The diagnosis of encephalitis is confirmed if: - The clinical diagnosis is compatible with the case definition. AND - The CSF analysis is compatible with an encephalitis picture. AND - The differential diagnoses (especially meningitis) have been excluded.	
GUILLAIN-BARRÉ SYNDROME	LEVEL 1 Bilateral weakness (symmetric) with flaccid extremities	Sejvar JJ, Kohl KS, Gidudu J, et al. The Brighton

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	(usually of all 4 limbs) AND - Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND - Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase AND - Electromyography: Electrophysiological signs the clinical diagnosis is compatible with the case definition with GBS AND - Albuminocytologic dissociation: hyperproteinorachia (elevation of CSF protein) and normal CSF white cell count [< 50 cells/μl] AND - Absence of plausible differential diagnosis (to explain the motor weakness) LEVEL 2 - Bilateral AND flaccid weakness of the extremities AND - Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND - Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND - CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value) OR - If CSF not collected or results not available, electrophysiologic studies consistent with GBS AND - Absence of identified alternative diagnosis for weakness LEVEL 3 - Bilateral AND flaccid weakness of the extremities AND - Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND - Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of	Collaboration Guillain-Barré Syndrome Working Group. Guillain- Barré Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine. 2011; 29(3): 599– 612.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase AND - Absence of plausible differential diagnosis (to explain the motor weakness) In Summary The diagnosis of Guillain-Barre Syndrome can be confirmed if: - The clinical diagnosis is compatible with the case definition - The poliovirus is not isolated from the stool - The CSF examination is compatible with GBS: Hyperproteinorachia (elevation of CSF protein), absence of pleocytosis. - There is diagnostic confirmation by a neurologist.	
GENERALIZED CONVULSIVE SEIZURE	LEVEL 1 - Witnessed sudden loss of consciousness AND - Generalized tonic, clonic, tonic-clonic or atonic motor manifestations LEVEL 2 - Reported sudden loss of consciousness AND - Generalized tonic, clonic, tonic-clonic or atonic motor manifestations LEVEL 3 - Reported sudden loss of consciousness AND - Other generalized motor manifestations In Summary The diagnosis of generalized seizure can be confirmed if: - The clinical diagnosis is compatible with the case definition. - The history of present illness evokes seizure activity - The etiological work up is negative: (i.e. acute intoxication, trauma, severe malaria etc. have all been excluded).	Bonhoeffer J, Menkes J, Gold MS, et al; The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22:557-562.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
HYPOTONIC HYPORESPONSIVE EPISODE (HHE)	LEVEL 1 • Hypotonia (muscular weakness) AND • Reduction or absence of response to sensory or verbal stimuli AND • Pallor or cyanosis LEVEL 2 • Indeterminate muscle tone AND • Reduction or absence of response to sensory or verbal stimuli AND • Pallor or cyanosis OR • Hypotonia (muscular weakness) AND • Reduction or absence of response to sensory or verbal stimuli AND • Indeterminate skin color LEVEL 3 • Normal muscle tone AND • Reduction or absence of response to sensory or verbal stimuli AND • Pallor or cyanosis OR • Hypotonia (muscular weakness) AND • Indeterminate response to sensory or verbal stimuli AND • Palor or cyanosis.	Bonhoeffer J, et al. Brighton Collaboration HHE Working Group. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004; 22(5-6): 563–568.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Hepato-Gastrointestinal and Renal System		
HEPATIC FAILURE	Major criteria - Total serum bilirubin ≥ 1.5 times the upper limit of normal (ULN) OR - Elevation of the serum transaminases (ALT, AST ≥ 3 times the upper limit of normal [ULN]) AND - Coagulopathy unresponsive to vitamin K (prothrombin time (PT) ≥ 15 seconds or INR ≥ 1.5). In Summary The diagnosis of hepatic insufficiency can be confirmed if: - The diagnosis can be considered if the major criteria are present and confirmed on at least two blood draws. - The etiologies of the most frequent causes of jaundice and alterations of liver function tests and, the non-hepatic encephalopathies are excluded: viral hepatitis, malaria, sickle cell anemia, exposure to toxins and medicines. NB: In case of fortuitous discovery of a perturbation in the hepatic panel without clinical manifestations, it is recommended to do a follow up hepatic panel.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012;30(33): 5038–5058.
INTUSSUSCEPTION	I) Definition of criteria DIAGNOSTIC CRITERIA - Surgical criteria - Demonstration of intussusception during exploratory surgery - Imaging criteria - Demonstration of intussusception via non-barium or aircontrast enema; - Demonstration via ultrasound of an intra-abdominal mass with specific characteristics – target (or doughnut) sign on transverse images and pseudokidney or sandwich sign on longitudinal images – the reduction of these signs by hydrostatic enema is also confirmed by ultrasound. Major criteria - Symptoms and signs of intestinal obstruction: - History of vomiting bile AND - Clinical examination shows acute abdominal distention and abnormal or absent bowel sounds OR - Radiological examination (plain abdominal X-ray) shows air-fluid levels and loops of distended small bowel.	Bines JE, Kohl K, Forster J, et al and the Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:569–574.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	- Signs of intussusception, ≥ 1 following signs: - Abdominal mass - Rectal mass - Rectal prolapse - Plain abdominal X-ray shows a soft tissue mass - Abdominal ultrasound shows a soft tissue mass - Abdominal CT shows a soft tissue mass - Evidence of vascular compromise or venous congestion: - Anal bleeding OR - Currant jelly stools" OR - Blood detected during rectal examination Minor criteria - Predisposing factors: aged < 1 year, male - Abdominal pain - Lethargy - Pallor - Hypovolemic shock - Plain abdominal X-ray showing an abnormal and unspecific distribution of air in the intestines. II) Diagnostic certainty levels LEVEL 1 - Surgical criteria: The demonstration of invagination of the intestine at surgery; AND/OR - Radiologic criteria: The demonstration of invagination of the intestine by either air or liquid contrast enema; OR The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on postreduction ultrasound; AND/OR - Autopsy criteria: The demonstration of invagination of the intestine. LEVEL 2 - Clinical criteria: Two major criteria or One major criterion and three minor criteria. LEVEL 3 - Clinical criteria: Four or more minor criteria.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
RENAL INSUFFICIENCY	Major criteria Creatinine ≥ 1.5 times the upper limit of normal (ULN) or 1.5 times the patient's initial value. Minor criteria Urine production $<0.5\text{ml/kg/hour}$ In Summary Renal insufficiency can be confirmed if: - The major criteria is present and confirmed (at least two blood draws) - The etiological diagnosis has been carried out.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038–5058.
Skin and Mucous Membranes & Bones and Joints		
HENOC SCHÖNLEIN PURPURA	I) Definition of criteria MAJOR CRITERIA - Purpura (mandatory criterion) Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia - Abdominal pain Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding - Histopathology Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit - Arthritis or arthralgias Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. - Renal involvement Proteinuria $>0.3\text{ g/24 h}$ or $>30\text{ mmol/mg}$ of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or $\geq 2+$ on dipstick. MINOR CRITERIA - Other diagnoses unlikely (exclude meningitis) II) Diagnostic certainty levels LEVEL 1 - Purpura or petechiae (mandatory) with lower limb predominance	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND ≥ 1 following criteria - Abdominal pain - Histopathology - Arthritis or arthralgias - Renal involvement AND - Absence of thrombocytopenia LEVEL 2 - Purpura or petechiae (mandatory) with lower limb predominance AND - Absence of thrombocytopenia.	
JUVENILE CHRONIC ARTHRITIS	Juvenile Chronic Arthritis is defined by an evolution of symptoms of at least three months. The clinical examination often reveals a child with growth retardation. The different clinical forms are the following: 1. Pauciarticular form (the most common form between 1 and 3 years of age). Clinically this presents with: - Involvement of four or less joints - Symmetric involvement of the small joints - Tenosynovitis of the flexor tendons and erosive nodules (frequent) - Rheumatoid factor seronegativity These signs can be associated with: - A positive anti-nuclear antibody (among 40 to 75% of children) - Uveitis 2. Polyarticular form - Affects 5 or more joints - Rheumatoid factor IgM can be positive or negative - Hips, cervical spine, hands and feet are the joints the most often affected, followed by the knees, wrists and ankles. - Among the patients seronegative for the rheumatoid factor, an association of fever, hepatosplenomegaly and symmetrical arthritis has been described. 3. Systemic form - Accompanied by a fever up to 39.5°C during at least two weeks - A typical rash on the trunk and thighs can be seen - Frequent involvement of the wrists, knees, ankles as well as the temporomandibular joint, and the hands. - The illness typically lasts between 2 and 5 years before complete resolution.	Medical websites resources: e.g. http://www.arthritis.co.za/jra.htm; http://emedicine.medscape.com/article/1007276-overview; http://www.med.univ-rennes1.fr/etud/pediatric/arthritis_cique.htm

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty			References
	In Summary The diagnosis of Juvenile Chronic Arthritis (JCA) can be confirmed if: • The clinical diagnosis responds to the case definition • The biological panel shows signs of chronic inflammation • The most frequent differential diagnoses are excluded • If necessary, the diagnosis should be confirmed by a specialist. The symptoms must last at least 3 months before concluding JCA. A confirmation of the diagnosis requires a follow up visit 3 months after the beginning of the illness.			
STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)	Symptoms start by a feeling of malaise, fever, headache, cough and conjunctivitis. Then the macular eruption appears, rapidly transforming into confluent bullae over one to three days. Nails and eyebrows can be lost due to epidermal involvement. The diagnosis of Stevens-Johnson syndrome becomes evident with the appearance of cutaneous lesions, the rapid and expansive progression of symptoms, which include two mucosal sites.			Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129:92-6.
	Diagnosis	Lesion morphology	Body surface area detachment	
	SJS	Maculae, bullae, atypical target lesions	≤10%	
	SJS-TEN overlap	Maculae, bullae, atypical target lesions	10-30%	
	TEN with spots	Maculae, bullae, atypical target lesions	≥30%	
	In Summary The diagnosis of STEVENS-JOHNSON SYNDROME (SJS) can be confirmed if: • The clinical diagnosis responds to the case definition • The etiological research indicates exposure to a triggering element (medication, immunization, toxin, febrile state, virus) • In case of doubt, consultation of a specialist is necessary.			
KAWASAKI DISEASE	I) DEFINITION OF CRITERIA Major criteria • Fever ≥ 5 days • Clinical criteria: Signs of mucocutaneous inflammation: – Polymorphic exanthem – Non-exudative bilateral conjunctivitis – Involvement of the lips and oral cavity: erythema, cracked lips. “strawberry red” tongue. diffuse			Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	inflammation of the oral and pharyngeal mucosa – Involvement of the hands and feet: erythema of the palms and/or soles, oedema of the hands and/or the feet. Hand and/or foot periungual peeling skin (week 2-3 of disease course) – Usually unilateral neck lymphadenopathy (≥ 1.5 cm) Minor criteria • Erythrocyte sedimentation rate ≥ 40 mm/h or CRP ≥ 3 mg/dL • Echocardiogram showing coronary artery or heart involvement II) Diagnostic certainty levels LEVEL 1 • Fever ≥ 5 days AND • ≥ 4 clinical criteria: AND • Other diagnoses unlikely after clinical examination and laboratory tests LEVEL 2 • Fever ≥ 5 days AND • < 4 clinical criteria: AND • Erythrocyte sedimentation rate ≥ 40 mm/h OR CRP ≥ 3 mg/dL AND • Other diagnoses unlikely after clinical examination and laboratory tests LEVEL 3 • Fever ≥ 5 days AND • < 4 clinical criteria: AND • Normal erythrocyte sedimentation rate OR normal CRP AND • Coronary artery or heart involvement AND • Other diagnoses unlikely after clinical examination and laboratory tests.	Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Cardiovascular system and blood disorders		
ANAPHYLAXIS	For all levels of diagnostic certainty - Sudden onset AND - Rapid progression of signs and symptoms AND - Involving multiple (≥ 2) organ systems, as follows: LEVEL 1 ≥ 1 major dermatological criterion AND ≥ 1 major cardiovascular AND/OR ≥ 1 major respiratory criterion LEVEL 2 ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion OR ≥ 1 major cardiovascular OR respiratory criterion AND ≥ 1 minor criterion involving ≥ 1 different system (other than cardiovascular or respiratory systems) OR ≥ 1 major dermatologic AND ≥ 1 minor cardiovascular AND/OR minor respiratory criterion LEVEL 3 ≥ 1 minor cardiovascular OR respiratory criterion AND ≥ 1 minor criterion from each of ≥ 2 different systems/categories In Summary The diagnosis can be confirmed if: - The clinical diagnosis is compatible with the case definition (at least 2 major signs/criteria) - Symptom onset occurred after a short period of time (a few minutes to hours) after exposure to a food item, an insect sting, a vaccination, or contact with a product allergen (such as peanuts) - If the child reports a known allergy, one major sign/criteria following exposure to a known allergen is sufficient for a diagnosis of anaphylaxis.	Rüggeberg JU, Gold MS, Bayas JM et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-5684.
DIABETES MELLITUS TYPE 1	- Serum fasting glucose $\geq 7\text{mmol/L}$ ($> 126\text{ mg/dL}$) OR - Postprandial serum glucose $\geq 11.1\text{mmol/L}$ ($\geq 200\text{ mg/dL}$) 2 hours after ingesting 1.75 g/kg (max. 75g) of glucose (oral glucose tolerance test) OR - A1C Hemoglobin $\geq 6.5\%$ AND Hyperglycemia	WHO Definition and Diagnosis of diabetes mellitus and intermediate hyperglycaemia, 2006 and http://www.nlm.nih.gov/medlineplus/encyclopedia.html

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND No other cause of hyperglycemia In Summary The diagnosis of type 1 diabetes mellitus can be confirmed when a confirmed hyperglycemia responds to the case definition.	
THROMBOCYTOPENIA	LEVEL 1 - Platelet concentration < to $150 \times 10^6/\text{mL}$ AND - Confirmation par blood smear OR - Clinical signs of spontaneous bleeding (i.e. non traumatic)* LEVEL 2 - Platelet concentration < to $150 \times 10^6/\text{mL}$. <i>*Spontaneous bleeding (i.e. non traumatic), includes purpura (i.e. petechiae, purpura sensu stricto, ecchymoses) exudative hemorrhage, hematomas, hematemesis, occult bleeding par rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding, conjunctival bleeding, intracranial bleeding.</i> In Summary The diagnosis of thrombocytopenia can be confirmed if: - It corresponds to the level 1 of diagnostic certainty case definition - An etiological investigation was carried out.	Wise RP, Bonhoeffer J, Beeler J, et al. Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5717–5724.

ANNEX 5**REPORT SIGN-OFF**

1. PASS INFORMATION

Title:	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01 _E vaccine in young children in sub-Saharan Africa.
Protocol version identifier:	115056 EPI-MALARIA-003 VS AME
Date of last version of the protocol:	<i>Amendment 2: 15 October 2020</i>
EU PAS Register No:	EUPAS28541
Active substance:	RTS,S antigen and AS01 _E adjuvant
Medicinal product(s):	Mosquirix™
Product reference:	EMA/H/W/002300
Procedure number:	Not Allocated
Opinion Holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	Co-primary objectives: - To estimate the incidence of adverse events of special interest (AESI) in children vaccinated with RTS,S/AS01_E. - To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E. Objectives related to malaria are considered as secondary objectives.
Countries of study:	Sites in sub-Saharan African (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system. In October 2015, the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended the pilot implementations of RTS,S/AS01_E in 3-5

	distinct settings in SSA restricted to moderate-to-high transmission of malaria. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine was to be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GlaxoSmithKline (GSK) Phase IV studies were selected from the 3 countries where the RTS,S/AS01_E vaccine was to be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 (unexposed clusters) became exposed cluster study sites in study EPI-MAL-003.

2. OPINION HOLDER

Opinion holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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PAGE

24 Oct 2024

9.2.7.1.	Active surveillance.....	66
9.2.7.1.1.	Enrolment and follow-up	66
9.2.7.1.2.	Surveillance of AESI, meningitis and malaria during follow-up.....	68
9.2.7.1.3.	Surveillance of other AE leading to hospitalisation during follow-up.....	69
9.2.7.1.4.	Surveillance for death	69
9.2.7.1.5.	Study conclusion	69
9.2.7.1.6.	Outline of study procedures	70
9.2.7.2.	Enhanced hospitalisation surveillance	74
9.2.7.2.1.	Informed consent (for study participants not enrolled previously, i.e. for previous hospitalisation or for active surveillance)	74
9.2.7.2.2.	Check inclusion and exclusion criteria (for study participants not enrolled previously)	74
9.2.7.2.3.	Assign study participants study number (for study participants not enrolled previously)	74
9.2.7.2.4.	Collect demographic data (for study participants not enrolled previously)	75
9.2.7.2.5.	Record type of health care facility	75
9.2.7.2.6.	Record any serious delay in developmental milestones or physical disability (for study participants not enrolled previously and at study conclusion)	75
9.2.7.2.7.	Health history.....	75
9.2.7.2.8.	Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards.....	75
9.2.7.2.9.	Record standard vaccinations.....	76
9.2.7.2.10.	Record diagnosis.....	76
9.2.7.2.11.	Record haemoglobin measurement.....	76
9.2.7.2.12.	Record deaths	76
9.2.7.2.13.	Record cases of suspected AESI, other AE leading to hospitalisation, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations.....	76
9.2.7.2.14.	Record and report adverse events.....	77
9.2.7.2.15.	Study conclusion	77
9.2.7.2.16.	Outline of study procedures	77

9.2.7.3.	Biological sample handling and analysis.....	79
9.2.7.3.1.	Biological samples.....	79
9.2.7.3.2.	Laboratory assays	80
9.2.7.4.	Case ascertainment.....	80
9.2.7.4.1.	Meningitis cases	81
9.2.7.4.2.	AESI	82
9.2.7.4.3.	Death.....	83
9.2.7.4.4.	Other AE leading to hospitalization	83
9.2.7.4.5.	Malaria	83
9.2.7.5.	Management of AESI, other AE leading to hospitalisation, meningitis cases, malaria, abscess at injection site and foot positional deformations.....	84
9.2.7.6.	Package for standard of care.....	84
9.2.7.7.	Capacity building	84
9.2.8.	Study procedures during special circumstances	85
9.3.	Variables.....	86
9.3.1.	Co-primary endpoints.....	86
9.3.2.	Secondary endpoints	86
9.3.2.1.	Safety endpoints.....	86
9.3.2.2.	Effectiveness and impact endpoints	87
9.3.3.	Patient characteristics and potential confounding variables	87
9.3.3.1.	Recorded in EPI-MAL-002 and EPI-MAL-003.....	87
9.3.3.2.	Recorded in EPI-MAL-005.....	88
9.4.	Data sources	89
9.4.1.	HDSS (or equivalent surveillance system) databases.....	89
9.4.2.	Active surveillance and enhanced hospitalisation surveillance.....	89
9.4.3.	Baseline study EPI-MAL-002	91
9.4.4.	Malaria transmission intensity study EPI-MAL-005	91
9.5.	Study size	91
9.5.1.	Sample size for co-primary objectives.....	92
9.5.2.	Sample size for meningitis monitoring.....	94
9.5.3.	Sample size to estimate the risk associated with the vaccination.....	95
9.5.3.1.	Before-after design	95
9.5.3.2.	Cluster design	96
9.5.4.	Sample size for the effectiveness and impact on severe malaria.....	97
9.5.4.1.	Effectiveness (direct effect)	98
9.5.4.2.	Impact using the before-after design	99
9.5.4.3.	Impact using the cluster design	100
9.5.5.	Sample size for the effectiveness and impact on cerebral malaria.....	100
9.5.5.1.	Effectiveness (direct effect)	101
9.5.5.2.	Impact using the before-after design	101
9.5.5.3.	Impact using the cluster design	102
9.5.6.	Sample size for the effectiveness and impact on mortality rate, overall and per gender	103
9.5.6.1.	Effectiveness (direct effect)	103
9.5.6.2.	Impact using the before-after design	104
9.5.6.3.	Impact using the cluster design	104

9.6.	Data management	105
9.7.	Data analysis	105
9.7.1.	Study population	106
9.7.2.	Study participant disposition	106
9.7.3.	Demographics and characteristics at study entry	107
9.7.4.	Exposure description	107
9.7.5.	Analysis for co-primary objectives.....	108
9.7.5.1.	Analysis population.....	108
9.7.5.2.	Statistical approach	108
9.7.5.2.1.	Incidence rate of AESI	108
9.7.5.2.2.	Incidence rate of aetiology-confirmed meningitis.....	109
9.7.6.	Analysis for secondary safety objectives.....	110
9.7.6.1.	Analysis population.....	110
9.7.6.2.	Meningitis cases.....	110
9.7.6.2.1.	Incidence rate of aetiology-confirmed, probable and/or clinically suspected meningitis	110
9.7.6.2.2.	Meningitis cases monitoring.....	110
9.7.6.3.	Incidence rate of cerebral malaria.....	111
9.7.6.4.	Mortality rate.....	111
9.7.6.5.	Cause of hospitalisation due to AESI, meningitis or malaria and death in children < 5 years vaccinated with RTS,S/AS01 _E and unvaccinated children < 5 years	111
9.7.6.6.	Other AE leading to hospitalisation	111
9.7.6.7.	Comparison of vaccinated and unvaccinated populations	112
9.7.6.7.1.	Before-after comparison	112
9.7.6.7.2.	Cluster design comparison	113
9.7.6.7.3.	Exposed clusters comparison	113
9.7.6.8.	Febrile convulsion	114
9.7.6.9.	Surveillance indicator analysis.....	114
9.7.7.	Analysis for secondary effectiveness and impact objectives.....	114
9.7.7.1.	Analysis population.....	114
9.7.7.1.1.	Effectiveness (direct effect).....	115
9.7.7.1.2.	Impact using the before-after design.....	116
9.7.7.1.3.	Impact using the cluster design	117
9.7.7.2.	Comparison of incidence rate of effectiveness or impact endpoints	118
9.7.7.3.	Comparison of time to event of effectiveness or impact endpoints	119
9.7.7.3.1.	Effectiveness	119
9.7.7.3.2.	Impact using the before-after design.....	119
9.7.7.3.3.	Impact using the cluster design	120
9.7.8.	Statistical considerations	120
9.7.8.1.	Handling of missing data	120
9.7.8.2.	Descriptive statistics	120
9.7.9.	Statistical models.....	120

9.7.9.1.	Poisson regression model	120
9.7.9.1.1.	Fixed effect model	120
9.7.9.1.2.	Mixed regression	121
9.7.9.2.	Maximised sequential probability ratio tests (MaxSPRT)	121
9.7.10.	Conduct of analysis	123
9.7.11.	Sequence of analyses.....	123
9.7.12.	Statistical considerations for interim analyses.....	123
9.7.13.	Statistical analyses during special circumstances	123
9.8.	Quality control.....	123
9.8.1.	Monitoring by GSK Biologicals site monitors or delegates	124
9.8.2.	Archiving of data at study sites	124
9.8.3.	Audits	125
9.9.	Limitations of the research methods	125
10.	PROTECTION OF HUMAN SUBJECTS	130
10.1.	Regulatory and ethical considerations, including the informed consent process.....	130
11.	MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	131
11.1.	Safety definitions	131
11.1.1.	Definition of an adverse event.....	131
11.1.2.	Definition of a serious adverse event	132
11.2.	Detecting and recording adverse events.....	133
11.2.1.	Time period for detecting and recording adverse events.....	133
11.3.	Recording of adverse events via eCRF.....	133
11.3.1.	Evaluation of adverse events.....	134
11.3.1.1.	Assessment of intensity	134
11.3.1.2.	Assessment of causality	134
11.3.1.3.	Assessment of outcomes.....	135
11.4.	Reporting of adverse events not via eCRF.....	135
11.4.1.	Back-up system in case the electronic reporting system does not work	136
11.4.2.	Updating of adverse event information after removal of write access to the study participant's eCRF.....	136
11.4.3.	Regulatory reporting requirements for adverse events.....	136
11.5.	Follow-up of adverse events	136
12.	PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	137
13.	REFERENCES.....	138

LIST OF TABLES

		PAGE
Table 1	Meningitis cases observed in MALARIA-055 over 20 months post first dose (MedDRA preferred terms including meningitis and meningitis with any aetiologies)	33
Table 2	Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 5-17 month age category; from MALARIA-055 study)	35
Table 3	Summary of AESI by body system	57
Table 4	List of study procedures for participants in active surveillance.....	70
Table 5	List of study procedures to be conducted in the event of hospitalisation	77
Table 6	Estimation of the lower (LL) and upper (UL) limits of observed incidences of events following dose administration based on 20,250 study participants, different numbers of detected events, different risk periods and two scenarios for the 4 th dose uptake of RTS,S/AS01 _E	93
Table 7	Estimation of the lower (LL) and upper (UL) limits of observed incidences of events among all children less than 5 years of age based on 11,500 birth cohort, and different numbers of detected events	94
Table 8	Average length of surveillance* and power for the Poisson-based MaxSPRT [Kulldorff, 2011] for different true relative risks when alpha = 0.05	95
Table 9	Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]	96
Table 10	Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]	96
Table 11	Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005].....	97
Table 12	Detectable relative risk for mortality overall and by gender with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]	97

Table 13	Detectable direct effect for severe malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]	99
Table 14	Detectable total effect for severe malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]	99
Table 15	Detectable total effect for severe malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]	100
Table 16	Detectable direct effect in terms of relative risk for cerebral malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]	101
Table 17	Detectable total effect in terms of relative risk for cerebral malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]	102
Table 18	Detectable total effect in terms of relative risk for cerebral malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005].....	102
Table 19	Detectable direct effect in terms of mortality rate ratio, overall and per gender with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005].....	104
Table 20	Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]	104
Table 21	Detectable total effect in terms of mortality rate ratio, overall and per gender in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]	105
Table 22	Incidence rate and prevalence calculations for effectiveness and impact objectives (children enrolled in active surveillance).....	118

LIST OF FIGURES

	PAGE
Figure 1	Study design overview 46
Figure 2	Evaluation of safety, effectiveness and impact using data collected in studies EPI-MAL-002, EPI-MAL-003 and EPI-MAL- 005..... 48
Figure 3	Diagram on effectiveness (adapted from Halloran and Longini [Halloran, 1997])..... 115
Figure 4	Diagram on impact presenting the different vaccine effects for the before-after design (adapted from Halloran and Longini [Halloran, 1997])..... 116
Figure 5	Diagram on impact presenting the different vaccine effects for the cluster design (adapted from Halloran and Longini [Halloran, 1997])..... 117

LIST OF ANNEXES

	PAGE
Annex 1	List of stand-alone documents..... 145
Annex 2	Glossary of terms 146
Annex 3	Trademarks..... 149
Annex 4	Sponsor Information 150
Annex 5	Case definitions for protocol-defined AESI and Surveillance Indicators 151
Annex 6	Study specific guidance document 172
Annex 7	Amendment to the protocol 174
Annex 8	Protocol Amendment 3 Sponsor Signatory Approval 252
Annex 9	Protocol Amendment 3 Investigator Agreement 253
Annex 10	ENCePP Checklist for study protocols 254

LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalo-Myelitis
AE	Adverse Event
AESI	Adverse Event Of Special Interest
AIC	Akaike's Information Criterion
AMP	Agence de Médecine Préventive
AS01	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome
ATP	According-To-Protocol
BOD	Burden Of Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLS	Clinical Laboratory Services
CRP	C-Reactive Protein
CS	Circumsporozoite
CSF	Cerebrospinal fluid
DTP	Diphtheria, Tetanus, Pertussis
DTPa	Diphtheria, Tetanus, Pertussis (acellular) vaccine
DTPw	Diphtheria, Tetanus, Pertussis (whole cell) vaccine
DTPwHepB/Hib	Diphtheria-tetanus- pertussis (whole cell)-hepatitis B-Haemophilus influenza type b pentavalent vaccine
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPI	Expanded Programme on Immunisation
ESR	Erythrocyte Sedimentation Rate
EU PAS	European Union Post-Authorisation Studies
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface Antigen
HDSS	Health and Demographic Surveillance System
HHE	Hypotonic Hyporesponsive Episode
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee

MPL	3-O-desacyl-4'-monophosphoryl lipid A (produced by GSK)
MTI	Malaria Transmission Intensity
MVIP	Malaria Vaccine Implementation Programme
NRA	National Regulatory Authority
OPV	Oral Poliovirus Vaccine
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
pIMD	Potential immune-mediated disorder
PT	Preferred Term
PY	Person-Years
QS-21	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc, a Delaware, USA corporation)
RAFT	Réseau en Afrique Francophone pour la Télémédecine
RDT	Rapid Diagnostic Test
RMP	Risk Management Plan
RR	Relative Risk
RTS	Hybrid protein comprising HBs (hepatitis B surface antibody) and CS protein portions
RTS,S	Particulate antigen, containing both RTS and HBs antigen (S) proteins
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAP	Statistical Analysis Plan
SCCS	Self-Controlled Case-Series
SDV	Source Document Verification
SOC	System Organ Class
SPM	Study Procedures Manual
SPRT	Sequential Probability Ratio Tests
SSA	Sub-Saharan Africa
VS	Vaccine Safety
WHO	World Health Organization

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

PPD [REDACTED] (*PhD; PPD [REDACTED] – Epidemiology – Malaria*) and PPD [REDACTED] (PhD; PPD [REDACTED] – Epidemiology – Malaria) are the GSK Biologicals designated contact persons for this study.

4. ABSTRACT

Title	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01_E vaccine in young children in sub-Saharan Africa. 115056 (EPI-MALARIA-003 VS AME)
Main authors	PPD [REDACTED] (PhD; PPD [REDACTED] – <i>Epidemiology– Malaria</i>) and PPD [REDACTED] (PhD; PPD [REDACTED] - <i>Epidemiology Malaria</i>).
Rationale and background	GlaxoSmithKline (GSK) Biologicals has developed a pre-erythrocytic <i>Plasmodium (P.) falciparum</i> malaria vaccine, RTS,S/AS01_E, for routine immunisation of children living in malaria-endemic countries of sub-Saharan Africa (SSA). RTS,S/AS01_E is the first vaccine to be implemented for the prevention of malaria and it is the first AS01-adjuvanted vaccine to be implemented in the paediatric population. The vaccine antigen, RTS,S, consists of sequences of the <i>P. Falciparum</i> circumsporozoite (CS) protein and hepatitis B surface antigen (HbsAg). The antigen is adjuvanted with the AS01_E Adjuvant System, which consists of two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (Quillaja saponaria Molina, fraction 21), in a liposomes suspension. The World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5–9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine was to be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GSK Phase IV studies were selected from the 3 countries where the RTS,S/AS01_E vaccine was to be implemented. Sites from Ghana and Kenya that were part of the completed pre-implementation (i.e., before vaccine implementation) surveillance study, EPI-MALARIA-002 VS AME (115055) (referred to as EPI-MAL-002 in the remainder of the protocol) are exposed clusters in EPI-MAL-003. The first vaccine introduction started in April 2019 in Malawi and Ghana, and in September 2019 in Kenya. The RTS,S/AS01_E vaccine contains

new components, including a novel adjuvant that is not present in currently licensed vaccines. ***In 2021, the WHO recommended widespread use of the RTS,S/AS01_E malaria vaccine for children living in regions with moderate to high P. falciparum transmission, based on the MVIP results [WHO recommends groundbreaking malaria vaccine for children at risk. October 2021].***

The safety and efficacy of RTS,S/AS01_E have been evaluated during pre-authorisation clinical trials conducted mainly in SSA. Study EPI-MALARIA-003 VS AME (115056) (referred to as EPI-MAL-003 in the remainder of the protocol) will further evaluate the safety, effectiveness and impact of the vaccine during initial implementation.

The EPI-MAL-002 ***study*** measured the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, ***was*** also estimated.

EPI-MAL-003 is intended primarily as a post-implementation safety study, as reflected in the co-primary and secondary objectives. Additionally, vaccine effectiveness and impact estimations are included as secondary objectives.

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MALARIA-005 BOD AME [116682], referred to as EPI-MAL-005 in the remainder of the protocol) is ***being*** conducted to measure malaria transmission intensity and other malaria control interventions as confounding factors in the study site areas.

The three studies are ***being/were*** conducted in similar if not identical settings and with the same methodology for identification and characterisation of the events of interest. A strong capacity development component ***was*** included in the baseline study EPI-MAL-002 ***and EPI-MAL-003***.

**Research
question and
objectives****Co-primary objectives**

- To estimate the incidence of AESI¹ in children vaccinated with RTS,S/AS01_E.
- To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E.

Secondary objectives**Safety**

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E):

- To estimate the incidence of aetiology-confirmed and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.
- To estimate the incidence of other AEs leading to hospitalisation*.
- To describe the causes of hospitalisation (including AESI, meningitis and malaria)*.
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during ***the 3-day period and*** the 7-day period following each dose of RTS,S/AS01_E *.

¹ Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, Hypotonic Hyporesponsive Episode (HHE), generalised convulsive seizure
Intussusception, hepatic failure or renal insufficiency
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E)^{**}:

- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and AESI, by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.
- To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.

****Analyses of Other AE leading to hospitalisation, cause of hospitalisation and incidence of febrile convulsions will only be***

conducted for the Interim Analysis and not for the Final Analysis.

*****Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

Effectiveness and impact

- To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria diagnosed by RDT and/or microscopy.
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on:
 - the prevalence of anaemia among hospitalised children.
 - the incidence of hospitalisations attributed to malaria (including *P. falciparum*).
 - the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]) overall and by gender.

Study design

- A disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; ***Interim Analysis only***) and concurrent (cluster design comparison of exposed and unexposed clusters; ***Interim Analysis and Final Analysis***)² comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters.
- The design includes active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities) and enhanced hospitalisation surveillance (continuous monitoring of hospitalisations) in both exposed and unexposed clusters.

² **Exposed clusters:** Study sites where the RTS,S/AS01_E vaccine will be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.

Unexposed clusters: Study sites where the RTS,S/AS01_E vaccine will not be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.

The enrolment to active surveillance was completed on 06 April 2021.

Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

- The study **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 in exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants **would** receive three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.
- The diseases under surveillance for safety include AESI, other AE leading to hospitalisation, meningitis, and severe malaria including cerebral malaria. They will be monitored among the vaccinated and unvaccinated children, enrolled in active surveillance and in enhanced hospitalisation surveillance. The mortality rate, overall and by gender, will be estimated. The potential association, overall and by gender, between vaccination and death will also be assessed. The effectiveness (direct effect) of the RTS,S/AS01_E vaccine will be investigated by monitoring all malaria (including severe and cerebral malaria) related events in the vaccinated and unvaccinated children of the exposed clusters, enrolled in active surveillance. The impact (indirect, total and overall effect) of the vaccine will be investigated, in the active surveillance, firstly by comparing the incidence of all malaria (including severe and cerebral malaria) events in EPI-MAL-002 to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect)*. Secondly, the impact will also be investigated in the active surveillance, by comparing the incidence of all malaria (including severe and cerebral malaria) events in children of the unexposed clusters in EPI-MAL-003 to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in

EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect).

****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

- The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months. Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) ***given at a maximum age of 30 months.***

**Population,
including the
setting and study
population**

The study population is defined as study participants < 5 years of age living in a geographically limited area with a demographic surveillance system in place, and a well-developed infrastructure to monitor population health and vaccination programmes.

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01_E in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria enrolled ***participants*** for EPI-MAL-002 (Ghana [Kintampo and Navrongo], Kenya [Kombewa], and Burkina Faso [Sapone, Nouna]), ***and the study has completed.***

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ***was to*** be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. In order to align with the MVIP, the study sites for the GSK Phase IV studies ***were*** selected from the 3 countries where the RTS,S/AS01_E vaccine ***was to*** be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 (***unexposed clusters***) ***became exposed cluster*** study sites in EPI-MAL-003.

Variables

Co-primary endpoints

In children in active or enhanced hospitalisation surveillance:

- Occurrence of AESI.
- Occurrence of aetiology-confirmed meningitis.

Secondary endpoints*Safety endpoints*

In children in active or enhanced hospitalisation surveillance:

- Occurrence of probable meningitis (final classification).
- Occurrence of clinically suspected meningitis (final classification).
- Occurrence of meningitis cases identified at site level (first line laboratory).
- Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- Occurrence of hospitalisation (including those attributed to an AESI, meningitis or malaria)*.
- Occurrence of other AE leading to hospitalisation*.
- Occurrence of febrile convulsions during ***the 3 day period (days 0-3) and*** the 7-day period (Days 0-6) following each dose of RTS,S/AS01_E*.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation*.

****Occurrence of hospitalisation, other AE leading to hospitalisation, febrile convulsions and quality indicators will only be conducted for the Interim Analysis and not for the Final Analysis.***

Effectiveness and impact endpoints

In children in active surveillance:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
 - Any malaria (including *P. falciparum* malaria);
 - Severe malaria (including *P. falciparum* malaria);
 - Cerebral malaria.
- Occurrence of anaemia at hospital entry among hospitalised children.
- Occurrence of hospitalisation*

- All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.
- Occurrence of death
 - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death).
 - AE attributed deaths.

****Occurrence of all-cause hospitalisation will only be conducted for the Interim Analysis and not for the Final Analysis.***

Data sources

HDSS (or equivalent surveillance system)

- Listings of all children living in the study area based on the demographic census;
- Total number of children < 5 years of age (according to year and gender) recorded at the beginning of the study, at least once a year during the study duration and at the end of the study;
- Other demographic data (cause and date of deaths, migrations), if available;
- Information related to vaccination, if available.

Active surveillance (enrolment)

- Socio-demographic data;
- Active participation in any trial with an investigational product.

Active surveillance (home visits)

- Vaccination types and dates;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;
- Verbal autopsy report.

Active surveillance (outpatient visits and hospitalisations at all health care facilities)

- Data on visits at primary health care facilities and hospitals since enrolment or last home visit.

Enhanced hospitalisation surveillance (hospitalisations)

- Socio-demographic data;
- Active participation in any trial with an investigational product;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;
- Type of health care facility;
- Final diagnosis for the hospitalisation visit on discharge for all children;
- Data relevant to the diagnosis of AESI, other AE leading to hospitalisation, meningitis and malaria (including cerebral malaria);
- Vaccination types and dates;
- Autopsy report.

Study conclusion (home visit)

- Vital status;
- Verbal autopsy report;
- Vaccination types and dates;
- Health history since last visit.

Baseline study EPI-MAL-002

- Baseline incidence rates of AESI, other AE leading to hospitalisation, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality.

Malaria Transmission Intensity Study EPI-MAL-005

- Estimation of annual parasite prevalence;
- Changes in diagnostic practices;
- Malaria control and prevention measures at the community and individual level.

Study size

- The study **targeted** enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children **were**

estimated to be enrolled in active surveillance, assuming that the distribution according to the administration of RTS,S/AS01_E in the exposed clusters **would** be 10% without any dose (2,250 unvaccinated children), 10% with an incomplete primary schedule (i.e. 1 or 2 doses; 2,250 partially vaccinated children), 80% with the full primary schedule (i.e. 3 doses; 18,000 vaccinated children). ***The enrolment to active surveillance was completed on 06 April 2021.***

- For some of the AESI, the incidence could be very rare (around 1/100,000 person-years [PY]) and the period at risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis. The 95% confidence interval (CI) around the observed incidence of 15.5 per 100,000 PY (1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], with 50% of the study participants receiving the 4th dose, based on 20,250 study participants) will be [0.4, 86.1].
- With the before-after design*, assuming 10 as the cumulative number of meningitis cases in EPI-MAL-002, based on cohort size and period of follow-up of 1 year following dose 3, a true relative risk (RR) = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters in a follow-up time corresponding to an observed RR equal to 3.
- With the before-after design*, and depending on the follow-up, the total effect for severe malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, ranges from 16% to 23%, and the direct effect, from 23% to 33%.
- With the before-after design*, and depending on the follow-up, the total effect for cerebral malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, expressed as RR ranges from 1.51 to 1.82, and the direct effect, from 1.55 to 1.88.

****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

Data analysis

Analysis of the co-primary objectives:

- The incidence rate of each AESI will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable.

- The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first RTS,S/AS01_E vaccination for the vaccinated study participants and virtual vaccination corresponding to the week before first visit for the unvaccinated study participants) and the end of the at-risk period or the earliest of the followings:
 - Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis);
 - Date of end of study period;
 - Date when child reaches 5 years;
 - Date of last contact (lost-to follow-up, defined as two unsuccessful attempts to visit the child at home within the month of the scheduled visit);
 - Date of death.
- Each AESI will be grouped after case ascertainment (for both confirmed and non-confirmed cases).
- The incidence rate of aetiology-confirmed meningitis and of cerebral malaria will be computed with 95% CI using the same approach as described above.

For the analysis of the secondary objectives, all comparisons will be performed separately for each of the two designs (i.e. before-after design and cluster design). As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters; and the cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters.

Note: Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

Milestones

The milestones will be adapted based on the timing of vaccine introduction in the intended study sites in the target SSA countries.

Progress reports will be generated every 6 months. An interim epoch analysis is planned to be performed one year after the 3rd dose of RTS,S/AS01_E in the last study participant from exposed clusters.

5. AMENDMENTS AND UPDATES

Amendment 1 Final: 24 April 2019.

Amendment 2 Final: 15 October 2020.

Amendment 3 Final: 24 Oct 2024.

The rationales for protocol amendment 1, protocol amendment 2 **and protocol amendment 3** are provided in [Annex 7](#).

6. MILESTONES

The target population for the introduction of the RTS,S/AS01_E vaccine are children living in sub-Saharan Africa (SSA). The age group **for** the vaccine **administration** is 5 to 17 months of age.

The milestones below **are** based on the timing of vaccine introduction in the intended study sites in the target SSA countries and the selected immunisation schedule (3-doses primary with a 4th dose). The World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose [[WHO, 2015\(a\)](#)]. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. This programme initially planned to make the RTS,S/AS01_E vaccine available in selected areas, starting in 2018 [[WHO, 2017](#)], but the RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries in 2019.

The study **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants **would** receive three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact (see [Annex 2](#) for definitions of exposed and unexposed clusters). The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports.

The protocol might be adapted according to feedback from the European Medicines Agency (EMA) and the National Regulatory Authorities (NRAs), and the Institutional Review Boards (IRBs) in the countries of the study; the WHO recommendations will also be taken under consideration.

Milestone	Planned date
Draft 1 protocol submitted to EMA as part of an EU "Article 58 procedure"	June 2014
Draft 2 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the consolidated list of questions	March 2015
Draft 3 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the list of outstanding issues	June 2015
Draft 4 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the list of outstanding issues	July 2015

Milestone	Planned date
Draft 5 protocol prepared with updates to enable synergy with WHO Pilot Implementation, and submitted as part of a Type II variation	February 2017
Draft 6 protocol prepared with updates to answer the request for supplementary information, and submitted as part of a Type II variation	July 2017
Final protocol submitted to NRAs in the first country of the study, as applicable according to local regulatory guidance, either as part of the marketing authorisation applications or after granting of marketing authorisation	Q4 2017
Protocol Amendment 1	April 2019
Protocol Amendment 2	October 2020
Protocol Amendment 3	April 2024
Start of data collection	Q1 2019
End of data collection	Q2 2025
Study progress reports	1 progress report every 6 months
Interim epoch analysis	Q2 2024
Registration in the EU PAS register	23 March 2019 Updated 17 March 2023
NCT Number	27 February 2019
Statistical analysis completed	Q4 2025
Final report of study results	Q1 2026

7. RATIONALE AND BACKGROUND

7.1. Background

GSK Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01_E, for routine immunisation of children living in malaria-endemic countries of SSA. RTS,S/AS01_E is the first vaccine to be implemented for the prevention of malaria and it is the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

The vaccine antigen, RTS,S, consists of sequences of the *P. falciparum* circumsporozoite (CS) protein and hepatitis B surface antigen (HbsAg). The antigen is adjuvanted with the AS01_E Adjuvant System, which consists of two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (Quillaja saponaria Molina, fraction 21), in a liposomes suspension.

The pre-authorisation clinical development has been conducted mainly in SSA countries. The main clinical study supporting efficacy and safety is the large Phase III study, MALARIA-055, conducted at 11 study sites in 7 countries across SSA, which enrolled 15,459 children. This clinical trial was conducted in two age categories: infants aged 6-12 weeks at first dose and children aged 5-17 months at first dose. Infants aged 6-12 weeks at first dose received RTS,S/AS01_E, in co-administration with other childhood vaccinations (diphtheria-tetanus-whole-cell pertussis-hepatitis B- *Haemophilus influenza* type b pentavalent vaccine [DTPwHepB/Hib] and oral poliovirus vaccine [OPV]), within the context of the Expanded Programme on Immunization (EPI). The comparator group received meningococcal C conjugate vaccine in co-administration with the same EPI vaccines. At Month 20, infants vaccinated with RTS,S/AS01_E in

co-administration with other childhood vaccinations received either a fourth dose of RTS,S/AS01_E with OPV, or meningococcal C conjugate vaccine with OPV. Infants in the comparator group received meningococcal C conjugate vaccine with OPV. Children aged 5-17 months at first dose received RTS,S/AS01_E without co-administration of other vaccines. The comparator group received human diploid-cell rabies vaccine. At Month 20, children vaccinated with RTS,S/AS01_E received either a fourth dose of RTS,S/AS01_E or meningococcal C conjugate vaccine. Children in the comparator group received meningococcal C conjugate vaccine at the time of the fourth dose. Children aged 5 to 17 months at first dose were followed for approximately 48 months after Dose 1 and infants aged 6 to 12 weeks at first dose for approximately 38 months after Dose 1.

In most SSA countries endemic for malaria, pharmacovigilance reporting systems are either in development phase, poorly functional or non-existent. As RTS,S/AS01_E will be distributed in SSA countries, GSK Biologicals deems crucial to expand the data on vaccine safety without relying solely on a passive reporting system once the vaccination **is** implemented. Therefore, GSK Biologicals developed a Post Approval Plan **comprising** of a set of complementary prospective studies **to** be conducted in similar if not identical settings.

The pre-implementation (i.e. before vaccine implementation) surveillance study EPI-MAL-002, measured the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, **was** estimated. The events measured in EPI-MAL-002 **were** based on data generated from MALARIA-055 described below (see Section 7.2 and Section 7.3), or **were** events that have historically been associated with vaccines other than RTS,S/AS01_E, or may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines. The EPI-MAL-002 study started in Q4 2015. The RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries (Ghana, Kenya and Malawi) in 2019. As the vaccine **became** available in the study sites that are exposed clusters, EPI-MAL-003 **was** initiated. EPI-MAL-002 and EPI-MAL-003 **were** partly run concomitantly in the same study sites.

EPI-MAL-003 is intended primarily as a post-implementation safety study as reflected in the co-primary and secondary objectives. Additionally, vaccine effectiveness and impact estimations are included as secondary objectives. **The protocols for** EPI-MAL-002 and -003 **include** the same methodology for identification and characterisation of the events of interest. A strong capacity development component **was** included in the baseline study EPI-MAL-002 **and -003**.

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MAL-005) is **being** conducted to measure malaria transmission intensity (MTI) and other malaria control interventions as confounding factors in the study site areas.

The three studies **were/are being** conducted in similar if not identical settings. Site selection **was** done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO [WHO, 2017] (refer also to Section 9.2.1), in order to

ensure synergy between the latter and those three studies. The MVIP encompasses all aspects of the pilot implementation of the malaria vaccine:

1. The implementation of the RTS,S/AS01_E malaria vaccine in selected areas in each of the participating countries (Ghana, Kenya and Malawi),
2. The WHO-led evaluations of feasibility, impact and safety of the malaria vaccine, as described in the Malaria Vaccine Pilot Evaluation protocol (*An evaluation of the cluster-randomised pilot implementation of RTS,S/AS01_E through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa*) and the Program for Appropriate Technology in Health (PATH)-led health utilization study and economic analyses.
3. The GSK-led evaluation of the malaria vaccine consisting of the EPI-MAL-002 baseline study in the MVIP pilot countries prior to vaccine implementation and the EPI-MAL-003 Phase 4 study conducted in a sub-set of vaccination and comparator areas of the three MVIP pilot countries following vaccine implementation.

Through this programme, the malaria vaccine **is being** routinely delivered in sub-national areas of the pilot implementation countries by Ministries of Health (MoH) using an expanded schedule of their routine EPI contacts, building on the national immunization programmes which routinely deliver vaccines to young children living in SSA countries. According to the MVIP, the RTS,S/AS01_E vaccine **is** given as a four dose schedule with the first dose administered as soon after 5 months of age as possible, followed by doses two and three at approximately one month intervals, and a fourth dose 15-18 months after dose three. ***After study start, Mosquirix was prequalified by the WHO on 15 July 2022, with the WHO recommendation for administration from 5 months of age, as a 3-dose primary schedule with a minimum interval of 4 weeks between doses and a fourth dose provided approximately 12–18 months after the third dose. The recommendations also allow for flexibility in the schedule to optimize delivery, e.g. to align the fourth dose with other vaccines given in the second year of life.***

Vaccine implementation **was** based on a cluster-randomized design, in which some areas (clusters) introduced RTS,S/AS01_E at the beginning of the programme and other clusters, initially without RTS,S/AS01_E, acted as comparison areas. In terms of vaccine evaluation, GSK monitors vaccine safety, effectiveness and impact in some of those clusters while the WHO monitored vaccine safety, effectiveness/impact and programmatic feasibility in the remaining ones (see Malaria Vaccine Pilot Evaluation protocol sections 7.6.5, 9.1, 9.5, 10.1 and 10.10 for more details regarding number and distribution of clusters for vaccine evaluation component). The division of clusters into intervention or comparison areas **was** randomized; with the exception of sites where the EPI-MAL-002 and EPI-MAL-003 **studies were** running, which **was** purposely selected by the MoHs according to WHO guidance. From each pilot country, about 256,000 children **were** expected to be included into the pilot implementation programme (about 128,000 children in the RTS,S/AS01_E clusters [exposed clusters] and about 128,000 in the comparison arm [unexposed clusters]). Identical monitoring systems **were** set up to record the outcomes of interest in both intervention and comparison areas.

7.2. Safety results of the clinical development of RTS,S/AS01_E

In the large, pivotal Phase III study (MALARIA-055), serious adverse events (SAEs) were collected throughout the trial in all study participants regardless of causal relationship. Seizures occurring within 7 days after vaccination were collected proactively and were analysed according to Brighton Collaboration Guidelines. Potential immune-mediated disorders (pIMDs) were collected as SAEs throughout the trial. Information was collected on all unsolicited reports of AEs that occurred within 30 days after vaccination and on reactogenicity within 7 days after vaccination among the first 200 children in both age categories at each study site. This study was overseen by an Independent Data Monitoring Committee. Safety results are shown below for the intention-to-treat population.

In the 5-17 month old group at Month 20 post Dose 1, at least one SAE was reported in 1,108 children out of 5,949 vaccinated with RTS,S/AS01_E (18.6%; 95% confidence interval [CI]: 17.6, 19.6) and in 676 children out of 2,974 who received the rabies vaccine (control group) (22.7%; 95% CI: 21.1, 24.3) [The RTS,S Clinical Trials Partnership, 2014]. At least one SAE related to vaccination (judged by the study investigator) was reported in 10 children (0.2%) vaccinated with RTS,S/AS01_E and in one child (0.0%) receiving the rabies vaccine.

Over the same surveillance period in the 6-12 week old group, at least one SAE was reported in 959 infants among 4,358 who were vaccinated with RTS,S/AS01_E (22.0%; 95% CI: 20.8, 23.3) and in 503 infants among 2,179 who received the meningococcal C conjugate vaccine (control group) (23.1%; 95% CI: 21.3, 24.9) [The RTS,S Clinical Trials Partnership, 2014]. SAEs were judged to be related to vaccination by the study investigator for 4 children (0.1%) vaccinated with RTS,S/AS01_E and 3 infants (0.1%) receiving the meningococcal C conjugate (control group).

Pneumonia, gastroenteritis, malaria, anaemia and febrile convulsions were the most frequently reported SAEs in both study groups.

Up to study end, in the 5-17 month old group, at least one SAE was reported in 720 children out of 2,976 vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E (24.2%; 95% CI: 22.7, 25.8), in 752 children out of 2,972 vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose (25.3%; 95% CI: 23.7, 26.9) and in 846 children among 2,974 who received the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (control group) (28.4%; 95% CI: 26.8, 30.1). At least one SAE related to vaccination was reported in 8 children vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E, in 4 children vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and in one child receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015].

In the 6-12 week old group, over the same surveillance period, at least one SAE was reported in 580 infants among 2,180 who were vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E (26.6%; 95% CI: 24.8, 28.5), in 602 children among

2,178 who were vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose (27.6%; 95% CI: 25.8, 29.6), and in 619 infants among 2,179 who received meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose (control group) (28.4%; 95% CI: 26.5, 30.4). At least one SAE related to vaccination was reported in 6 infants vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E, in one infant vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and in 3 infants receiving the meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [[The RTS,S Clinical Trials Partnership](#), 2015].

Potential immune-mediated disorders (pIMDs)

In the 5-17 month old group and up to Month 20 post Dose 1, 3 cases of pIMDs were reported among children vaccinated with RTS,S/AS01_E (2 cases of encephalitis, one case of erythema multiforme) and 2 cases among children receiving the rabies vaccine (2 cases of encephalitis). In the 6-12 week old group, 3 cases were reported among infants vaccinated with RTS,S/AS01_E (encephalitis, glomerulonephritis acute, Langerhans' cell histiocytosis) and 2 cases among children receiving the meningococcal C conjugate vaccine (encephalitis, glomerulonephritis).

Post 4th dose of RTS,S/AS01_E/ meningococcal C conjugate vaccine, no case of pIMD was reported in the 6-12 week old group, and 6 cases were reported in the 5-17 month old group: 3 cases among children vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E (2 cases of encephalitis and one case of encephalomyelitis), 1 case among children vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose (encephalitis), and 2 cases among children receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (vitiligo, Stevens-Johnson syndrome).

Meningitis

An imbalance was observed for meningitis in the 5-17 months category ([Table 1](#)). During the 20 months period post Dose 1, in children aged 5-17 months, 16 meningitis cases (9 no aetiology, 4 meningococcal meningitis, 1 meningitis viral, 1 meningitis pneumococcal, 1 *Haemophilus influenza* meningitis) occurred in the RTS,S/AS01_E group and 1 (no aetiology) in the control vaccine group (Relative Risk [RR] = 8.0 [95% CI: 1.1, 60.3]). Among infants aged 6-12 weeks, 9 meningitis cases (3 no aetiology, 3 meningitis pneumococcal, 3 meningitis due to salmonella) occurred in the RTS,S/AS01_E group and 3 (2 no aetiology, 1 meningitis pneumococcal) in the control group (RR = 1.5 [95% CI: 0.4, 5.5]) [[The RTS,S Clinical Trials Partnership](#), 2014]. Most of the meningitis cases were observed during the 12 months period post-Dose 3 (23 out of 29 cases, 79.3%), no clear risk window was identified in study MALARIA-055. The meningitis cases were mainly observed in 2 trial sites, Lilongwe in Malawi and Kombewa in Kenya.

Table 1 **Meningitis cases observed in MALARIA-055 over 20 months post first dose (MedDRA preferred terms including meningitis and meningitis with any aetiologies)**

Analysis available	Follow up (post dose 3)	Age category	Number of cases in RTS,S/AS01 _E group (Number of RTS,S/AS01 _E study participants)	Number of cases in control group (Number of control study participants)	RR	95% CI
June 2014	18 months	6-12w	9 (4358)	3 (2179)	1.5	0.4-5.5
		5-17m	16 (5949)	1 (2974)	8.0	1.1-60.3

Between administration of the 4th dose of RTS,S/AS01_E/ meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 2 meningitis cases occurred among children vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E, and 3 cases among children vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No case occurred in the control vaccine group (rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose). In infants aged 6-12 weeks, 2 meningitis cases occurred among infants vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 3 cases among infants receiving meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [[The RTS,S Clinical Trials Partnership, 2015](#)]. Therefore, meningitis was considered as a potential risk.

Febrile convulsions

Among children aged 5-17 months, the occurrence of generalised convulsive seizures with fever within 7 days following primary vaccination in RTS,S/AS01_E recipients was 1.04 case/1000 doses compared to recipients of control vaccine (0.57 case/1000 doses). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 0.16 case/1000 doses of RTS,S/AS01_E vaccine versus 0.47 case/1000 doses of control vaccine. Although the increase in febrile convulsions was observed within 7 days of vaccination in children, the overall rate of febrile convulsions reported as a SAE was not increased in the RTS,S/AS01_E group compared to the control group over 30 days post vaccination (0.8% in RTS,S/AS01_E versus 0.8% in control) and over 18 months of follow-up (3.8% in RTS,S/AS01_E versus 3.8% in controls) [[The RTS,S Clinical Trials Partnership, 2011](#)]. The incidence of febrile convulsions after administration of the 4th dose of RTS,S/AS01_E/ meningococcal C conjugate vaccine was 2.5 cases/1000 doses in children aged 5-17 months, vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E, 1.2 case/1000 doses in children vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 0.4 case/1000 doses in the control vaccine group (rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 2.2 cases/1000 doses in infants vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E, no case/1000 doses in infants vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose and 0.5 case/1000 doses in the control vaccine group [[The RTS,S Clinical Trials Partnership, 2015](#)]. Therefore, febrile convulsions were considered as an identified risk.

Severe malaria including cerebral malaria

In the MALARIA-055 study there was a higher susceptibility to severe malaria in 5-17 months child recipients of a primary course of RTS,S/AS01_E without a 4th dose (R3C) relative to the control group (C3C) after Month 20. This finding was considered to be related to a potential rebound effect and has been included in the Risk Management Plan (RMP) as a potential risk. In order to further investigate this finding, an additional analysis was conducted in MALARIA-055 to examine clinical syndromes and outcomes of cases of severe malaria.

The cases of severe malaria disease according to the secondary case definition 1 (*P. falciparum* > 5000 parasites per μ L AND with one or more marker(s) of disease severity including co-morbidities: pneumonia, meningitis, sepsis, gastroenteritis) were classified by syndrome using the markers of severe malaria disease. GSK Biologicals has considered the definition for cerebral malaria cases as: parasitaemia > 5000 per μ L, Blantyre Coma Score $\leq$ 2 and haemoglobin level of $\geq$ 5 g/dL. It should be noted that whereas this is a commonly used definition, low coma score can be the outcome of many diseases processes and is not pathognomic of sequestration of parasitized red cells in the cerebral microvasculature.

In a post-hoc analysis of the Phase III study MALARIA-055, the distribution of the markers of severity used in the case definition of severe malaria were analysed by study group. Of the 1038 severe malaria cases according to the secondary case definition 1, 73 cases met the definition of cerebral malaria (parasitaemia > 5000 per μ L, Blantyre Coma Score $\leq$ 2 and haemoglobin level of $\geq$ 5 g/dL) in both age categories over the entire study period. An imbalance was observed for cerebral malaria in the 5-17 month category ([Table 2](#)).

Table 2 Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 5-17 month age category; from MALARIA-055 study)

Time Period	Syndrome	RTS,S group (R3C + R3R) N=5948		Control group (C3C) N=2974			
		N	Died	N	Died		
M0-M20	All Cases	205	6	158	2		
	Cerebral	16	3	5	1		
	Cerebral + Anaemia	6	1	1	0		
	Anaemia	25	0	29	1		
	Other	157	2	123	0		
	Missing	1	0	0	0		
Time period	Syndrome	3-dose schedule (R3C) N=2719		4-dose schedule (R3R) N=2681		Control (C3C) N=2702	
		N	Died	N	Died	N	Died
M21-SE	All Cases	103	6	76	3	76	2
	Cerebral	9	4	11	2	2	0
	Cerebral + Anaemia	0	0	1	0	2	1
	Anaemia	18	1	11	0	17	0
	Other	75	1	53	1	54	1
	Missing	1	0	0	0	1	0

R3C group: children and infants to receive 3 doses of RTS,S/AS01_E on a 0-1-2-month schedule + a dose of a meningococcal C conjugate vaccine at study Month 20

R3R group: children and infants to receive 3 doses of RTS,S/AS01_E on a 0-1-2-month schedule + a 4th dose of RTS,S/AS01_E at study Month 20

C3C group: children and infants to receive 3 doses of a control vaccine on a 0-1-2-month schedule + a dose of a control vaccine at study Month 20. Note that it is only for the 5-17 months age category

SE = Study end (Month 48)

All cases: Secondary case definition 1 (> 5000 parasites/μL and at least 1 marker of severe disease, including comorbidities)

Cerebral: > 5000 parasites/μL and BCS ≤ 2 and a haemoglobin level of ≥ 5 g/dL

Anaemia: > 5000 parasites/μL and BCS > 2 and a haemoglobin level of < 5 g/dL

Cerebral+Anaemia: > 5000 parasites/μL and BCS ≤ 2 and a haemoglobin level of < 5 g/dL

Other severe disease: >5000 parasites/μL, a BCS >2, a haemoglobin level of ≥ 5 g/dL and another marker of severe disease (prostration, respiratory distress, seizures, hypoglycemia [< 2.2 mmol/L], acidosis [BE ≤ -10.0 mmol/L], lactate ≥ 5.0 mmol/L)

Missing: Haemoglobin or BCS unavailable so syndrome classification could not be determined

- During the 20 months period post Dose 1, in children aged 5-17 months, 16 cerebral malaria cases (parasitaemia > 5000 per μL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL) occurred in the RTS,S/AS01_E group, among 5948 children, and 5 cerebral malaria cases occurred in the control vaccine group, among 2974 children. In addition, cerebral malaria and anaemia (parasitaemia > 5000 per μL, Blantyre Coma Score ≤ 2 and haemoglobin level of < 5 g/dL) were observed for 6 subjects in the RTS,S/AS01_E group and 1 subject in the control vaccine group.
- Between administration of the 4th dose of RTS,S/AS01_E / meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 9 cerebral malaria cases occurred among 2719 children vaccinated with RTS,S/AS01_E and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No cerebral malaria with anaemia was observed in this group. 11 cerebral malaria cases occurred among

2681 children vaccinated with RTS,S/AS01_E and receiving a 4th dose of RTS,S/AS01_E (plus one case of cerebral malaria with anaemia), and 2 cerebral malaria cases occurred among 2702 children receiving rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose (plus 2 cases of cerebral malaria with anaemia).

Taking into consideration the fact that the numbers were small, that no clinical diagnosis was performed by the investigators (no clinical case definition used), that there is no known biological plausibility of a pre-erythrocytic vaccine to directly cause cerebral malaria, the most likely explanation of the imbalance is a possible rebound effect and/or shift of age linked to the efficacy of the intervention. Therefore, GSK Biologicals considers cerebral malaria as a safety concern that requires further evaluation, and has therefore categorized it as an important potential risk in the RMP.

Overall mortality by gender

Ad-hoc analysis of mortality by gender based on the completed Phase III study MALARIA-055 data was performed at the request of WHO, in the context of their policy making pertaining to the potential use of *Mosquirix* in SSA [WHO, 2016(a); WHO, 2016(b)].

In this analysis all-cause mortality in the girls who received RTS,S/AS01_E was $\approx$ 2-fold higher than in the girls who received the control vaccine (123/5091 [2.4%] versus 33/2603 [1.3%]; for both age categories pooled); while in boys, all-cause mortality was slightly lower in the group that received RTS,S/AS01_E compared to the boys in the control group (95/5215 [1.8%] versus 55/2550 [2.2%]).

It is GSK's position that this should not be considered a safety signal because:

- Low fatality rate overall in study MALARIA-055 compared to what could be expected: 1 to 2% in each group, while in real-life setting mortality under 5 years old in SSA is estimated to be 5% (World bank);
- An investigator-initiated case control study in one site showed a 70% reduction in all-cause mortality in children enrolled in the study, as compared to children living in the same area but not enrolled in MALARIA-055;
- Background mortality rates per gender vary significantly across SSA countries. Under circumstances where boys and girls have the same access to resources such as food and medical care, boys have higher mortality rates than girls during childhood.
- The overall trend for differences in mortality rates in girls between the RTS,S/AS01_E and control groups is also observed in the subgroup analyses of the potential confounding factors including administration of recommended EPI vaccines (measles, yellow fever, etc), human immunodeficiency virus (HIV) status and different access to medical care and/or proper nutrition. These differences are in-line with the observed imbalance in overall mortality and it is difficult to understand whether they actually contributed to the overall mortality differences between girls in the RTS,S/AS01_E treatment groups and girls in the control group. Therefore, these additional analyses only seem to support the hypothesis that the observed imbalance

in mortality in girls (i.e. active versus control) is likely to be a chance finding (given the small numbers involved and the fact that clinical trials are not designed to evaluate impact on mortality, especially for a disease like malaria that is perfectly treatable).

However, GSK Biologicals considers that gender-specific mortality requires further evaluation, and has therefore categorized it as missing information in the RMP.

In summary, meningitis is considered/reported as a potential risk in the RMP of RTS,S/AS01_E. The occurrence of febrile convulsions is considered/reported as an identified risk associated during the 7 days following vaccination with RTS,S/AS01_E. The imbalance observed for cerebral malaria following a post-hoc analysis of the MALARIA-055 study is considered as a safety concern that requires further evaluation and is therefore categorized as an important potential risk in the RMP. At present, GSK Biologicals does not consider excess/increased mortality in females as a potential risk. Additional data need to be generated; for now it has been categorized in the RMP as missing information.

7.3. Efficacy results of the clinical development of RTS,S/AS01_E

Efficacy results of the Phase III study, MALARIA-055, are shown below for the intention-to-treat population. Efficacy against all episodes of clinical malaria in children aged 5 to 17 months over 12 months after Dose 3 was estimated to be 55.1% (95% CI: 50.5, 59.3) [[The RTS,S Clinical Trials Partnership](#), 2011]. Over 18 months after Dose 3 it was estimated to be 45.1% (95% CI: 41.4, 48.7) [[The RTS,S Clinical Trials Partnership](#), 2014]. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 12 months was 32.9% (95% CI: 26.3, 38.8) [[The RTS,S Clinical Trials Partnership](#), 2012] and over 18 months was 27.0% (95% CI: 21.1, 32.5) [[The RTS,S Clinical Trials Partnership](#), 2014].

In both age groups, vaccine efficacy for clinical malaria waned over time (Schoenfeld residuals $p < 0.001$). In children 5-17 months, the reduction in malaria by 6 month time intervals following Dose 3 was reported as: 68% (95% CI: 64, 72) over the first 6 months of follow-up; 41% (95% CI: 36, 46) over the subsequent 6 months of follow-up; and 26% (95% CI: 19, 33) over the last 6 months of follow-up [[The RTS,S Clinical Trials Partnership](#), 2014]. In infants 6-12 weeks, the corresponding reduction was reported to be 47% (95% CI: 39, 54), 23% (95% CI: 15, 31), and 12% (95% CI: 1, 21), respectively [[The RTS,S Clinical Trials Partnership](#), 2014].

Long-term follow-up efficacy data and data following administration of a 4th dose of RTS,S/AS01_E 18 months post Dose 3 show a decline in efficacy against clinical and severe malaria with time in both children and infants who did not receive a 4th dose of the RTS,S/AS01_E vaccine. Administration of a 4th dose of RTS,S/AS01_E enhanced protection against clinical malaria in infants and children as well as the efficacy against severe malaria in children. In children aged 5 to 17 months who did not receive a 4th dose of RTS,S/AS01_E, efficacy against all episodes of clinical malaria over 30 months post Dose 3 was estimated to be 35.2% (95% CI: 30.5, 39.5). In children who were administered a 4th dose of RTS,S/AS01_E, efficacy against all episodes of clinical malaria over 30 months was 43.9% (95% CI: 39.7, 47.8). For severe malaria, efficacy over 30

months in children aged 5 to 17 months was 4.5% (95% CI: -20.6, 24.5) when no 4th dose of RTS,S/AS01_E was administered and 34.9% (95% CI: 15.6, 50.0) when a 4th dose of RTS,S/AS01_E was administered. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 30 months was 20.3% (95% CI: 13.6, 26.5) without administration of a 4th dose of RTS,S/AS01_E and 27.8% (95% CI: 21.7, 33.4) with administration of a 4th dose of RTS,S/AS01_E. Efficacy against severe malaria over 30 months was 7.9% (95% CI: -23.3, 31.2) without administration of a 4th dose of RTS,S/AS01_E and 11.9% (95% CI: -18.3, 34.5) with administration of a 4th dose of RTS,S/AS01_E [The RTS,S Clinical Trials Partnership, 2015]. These data support the benefit of a 4th dose of RTS,S/AS01_E administered 18 months post Dose 3.

A potential rebound effect was observed in children aged 5-17 months. Throughout the period 18 months post Dose 3 to study end, an increased incidence of severe malaria was observed in children who did not receive a 4th dose of RTS,S/AS01_E, compared to controls: efficacy was -41.0% (95% CI: -98.5, -0.8). Among children who were administered a 4th dose of RTS,S/AS01_E, efficacy against severe malaria throughout the same period was -4.0% (95% CI: -50.0, 27.8). In infants aged 6-12 weeks, efficacy against severe malaria during the period 18 months post Dose 3 to study end was 11.2% (95% CI: -31.3, 40.2) when no 4th dose of RTS,S/AS01_E was administered and 32.4% (95% CI: -3.2, 56.2) when a 4th dose of RTS,S/AS01_E was administered. In contrast, clinical malaria disease showed no period of increased incidence compared to controls. The impact of RTS,S/AS01_E against clinical malaria and severe malaria varied substantially by study site and the rebound effect was mainly observed in medium and high transmission settings [The RTS,S Clinical Trials Partnership, 2015].

In three trial sites (Korogwe, Tanzania; Nanoro, Burkina Faso and Kombewa, Kenya) of the MALARIA-055 study, children were followed for 3 additional years to further document the long-term incidence of severe malaria in RTS,S/AS01_E and control groups (study MALARIA-076). Secondary objectives included evaluation of the incidence of clinical malaria, parasite prevalence, and serious adverse events of special interest.

The incidence of severe malaria was very low in each of the three study sites and was consistent with the epidemiology of the disease in high transmission areas – showing a decreased incidence of severe malaria with increasing age during childhood. There was no indication of rebound of severe malaria during the three additional years of follow-up in children who received either 3, or 4 doses of RTS,S/AS01_E.

In Nanoro (Burkina Faso), the site with highly seasonal malaria transmission, an increased susceptibility to uncomplicated malaria was observed. This increase did however not outweighing the initial benefit offered by the RTS,S/AS01_E vaccine, and most importantly did not appear to result in an increase of severe malaria cases.

In all three sites vaccine efficacy estimates against clinical malaria and the impact in terms of clinical cases averted remained positive over the six- to seven-year period, starting from the first vaccine dose in study MALARIA-055 until the end of follow-up in study MALARIA-076.

Overall vaccine efficacy over the 7-year follow-up period was:

- against clinical malaria: 4 doses: 24% (95% CI: 16, 31); 3 doses: 19% (95% CI: 11, 27)
- against severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32) [Tinto, 2019].

7.4. Summary of the study rationale

In July 2015, the EMA issued a positive opinion for the RTS,S/AS01_E vaccine [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)], and in October 2015 recommendations about RTS,S/AS01_E were issued by the WHO's SAGE and the MPAC [WHO, 2015(a)] (see Section 9.2.1).

The EMA issued a positive opinion for the RTS,S/AS01_E vaccine with the following indication: “*Mosquirix* is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *P. falciparum* and against hepatitis B. The use of *Mosquirix* should be based on official recommendations considering *P. falciparum* malaria epidemiology in different geographical areas” [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)]. These policy recommendations will be defined by the WHO and public health authorities in the malaria endemic SSA countries where the vaccine would be used.

The WHO's SAGE and MPAC recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. They did not recommend the use of the malaria vaccine in the 6–12 weeks age group [WHO, 2015(a)]. In this post-implementation safety study EPI-MAL-003, only the 5-17 months age group **was** kept. The first vaccine introduction occurred in 2019 after approval and recommendation by local health authorities. The RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries and the RTS,S/AS01_E vaccination programme **was expanded** to the unexposed areas/clusters from 2023.

The safety profile of RTS,S/AS01_E has been evaluated during pre-authorisation clinical trials conducted mainly in SSA. The EPI-MAL-003 study will further evaluate the safety of the vaccine during initial implementation by monitoring for rare AEs such as protocol-defined AESI (potentially associated with RTS,S/AS01_E, historically associated with vaccines other than RTS,S/AS01_E, or which may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines), other AE leading to hospitalisation and meningitis (potential risk) among a minimum of 20,250 vaccinated study participants from exposed clusters.

In addition to the efficacy data provided by the MALARIA-055, evidence on the impact and effectiveness of RTS,S/AS01_E when administered post-implementation most close to routine medical practice is needed. Although primarily designed as a post-implementation safety study to detect potential rare and uncommon AEs following

vaccination with RTS,S/AS01_E, the secondary objectives of EPI-MAL-003 also aim to evaluate the effectiveness (direct effect) and impact (indirect, total and overall effects) of RTS,S/AS01_E when administered **in a setting matching** routine medical practice in SSA. Estimation of effectiveness and impact will be done by comparison of a vaccinated cohort and an unvaccinated cohort (see Section 9.7.7.1 for diagrams of vaccine effects [direct, indirect, total and overall]).

It is important to note that background data on AEs are limited for malaria-endemic countries in SSA. This makes the assessment of risks potentially associated with the new vaccine following its implementation challenging. More specifically, the incidence and onset of autoimmune diseases and some of the other AESI are not known for African populations. Thus, an epidemiological study (EPI-MAL-002) to collect AESI data **was** initiated in Q4 2015 in the same study sites. The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation), of approximately 30,000 children in several sites in SSA countries (with at least 20,000 children enrolled where the RTS,S/AS01_E vaccine will be implemented), measured the baseline incidence of AESI, other AE leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, **was** also estimated. In addition, EPI-MAL-005 **is being** conducted in parallel to EPI-MAL-002 and EPI-MAL-003, to measure MTI and record malaria control interventions at **the** community level in the study site areas on a yearly basis.

As much as possible, sites **were** selected for EPI-MAL-002 and EPI-MAL-005 based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system. The capacity of the study sites to detect AESI and meningitis **was** strengthened early in EPI-MAL-002. This should ensure improved sensitivity and specificity of case detection and should also enable standardised calculation of incidence rates. EPI-MAL-003 is conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005.

GSK Biologicals **intended** to enrol 30,000 unvaccinated study participants in EPI-MAL-002 (with at least 20,000 in sites where the RTS,S/AS01_E vaccine will be implemented). The EPI-MAL-003 study **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 children in the exposed clusters; with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact (assuming that 80% of the 22,500 study participants in the exposed clusters **would** receive three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose; see Section 9.2.7.1.1 for details of procedures if a child selected to be unvaccinated receives RTS,S/AS01_E vaccine); and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact. **The enrolment to active surveillance was completed on 06 April 2021.**

Considering the limited number of sites where the safety study **could have been** performed and following feasibility assessment with respect to recruitment target and practical conduct of the study, GSK **considered** that a sample size of around 45,000 study participants **was** the highest possible.

GSK acknowledges the limitations of these studies in terms of sample size, the difficulties to diagnose and characterise rare diseases such as auto-immune diseases in young children, the potential biases introduced by the sequential generation of data between EPI-MAL-002 and EPI-MAL-003 studies, as well as the unpredictable occurrence of meningitis cases and paucity of data on other rare diseases of special interest in those settings. GSK also acknowledges the uncertainties of vaccine uptake and coverage at each of these studies sites, and therefore the feasibility of recruiting and following unvaccinated children in the exposed clusters. However, the proposed approach is believed to be the best possible taking into account ethical considerations and practical limitations of the SSA setting. The potential biases and limitations are detailed in Section 9.9.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To estimate the incidence of AESI³ in children vaccinated with RTS,S/AS01_E.
- To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E.

8.2. Secondary objectives

8.2.1. Safety

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E):

- To estimate the incidence of aetiology-confirmed and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy).
- To estimate the incidence of other AE leading to hospitalization*.
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.

³ Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode (HHE), generalised convulsive seizure
Intussusception, hepatic failure or renal insufficiency
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria)*.
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following each dose of RTS,S/AS01_E*.

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E)**:

- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and AESI by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.

****Analyses of Other AE leading to hospitalisation, cause of hospitalisation and incidence of febrile convulsions will only be conducted for the Interim Analysis and not for the Final Analysis.***

*****Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

8.2.2. Effectiveness and impact

- To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria diagnosed by RDT and/or microscopy.
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on:
 - the prevalence of anaemia among hospitalised children.
 - the incidence of hospitalisations attributed to malaria (including *P. falciparum*).
 - the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]) overall and by gender.

9. RESEARCH METHODS

9.1. Study design

The EPI-MAL-003 study is a disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; ***Interim Analysis only***) and concurrent (cluster design comparison of exposed and unexposed clusters; ***Interim and Final Analysis***) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters. The design includes active surveillance (corresponds to a prospective cohort monitoring) and enhanced hospitalisation surveillance ([Figure 1](#)) in both exposed and unexposed clusters (see [Annex 2](#) for definitions).

Active surveillance: First, a cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children, ***was expected to*** be recruited in the exposed clusters (assuming that 80% of the 22,500 vaccinated study participants ***would*** receive three doses of RTS,S/AS01_E, 10% ***would*** receive one or two doses and 10% ***would*** not have any dose). Second, a cohort of at least 22,500 children ***was expected to*** be recruited in the unexposed clusters. In both exposed and unexposed clusters, the children ***are*** actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Parents/ legally acceptable representative(s) (LARs) (according to local requirements) ***were*** invited to enrol their child into the active surveillance as follows:

- **DTP group:** Children identified at any administration of DTP/HepB/Hib (usually given at 6, 10 and 14 weeks of age) or at hospitalisation before administration of 3rd dose of DTP/HepB/Hib and vaccinated with at least one dose of DTP/HepB/Hib. That group includes both RTS,S/AS01_E vaccinated and unvaccinated children (from exposed or unexposed clusters);

- **Catch-up group:** Children identified at 1st RTS,S/AS01_E dose administration (schedule **dependent** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and **were** older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group includes only RTS,S/AS01_E vaccinated children from exposed clusters. Indeed, the objective of this catch-up **was** to include all the children who **would** receive the RTS,S/AS01_E vaccine and who could not be recruited at the time of DTP/HepB/Hib administration because the study had not yet started.

There **was** no predefined number of study participants to be enrolled in each group. All children meeting the inclusion criteria **were** expected to be enrolled in the study within the recruitment period.

All children enrolled in the active surveillance will be followed-up through home visits (Figure 1, see also Section 9.2.7.1). Children receiving at least one dose of RTS,S/AS01_E will be defined as the vaccinated study participants. For these children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01_E vaccine, up to 2 years after the last dose. For children not vaccinated with RTS,S/AS01_E, visits will be scheduled at equal points in time. Note that, in practice, it is possible to find RTS,S/AS01_E vaccinated children in an unexposed cluster (e.g. parents/LARs from an unexposed cluster can decide to have their child vaccinated in another cluster where the vaccine is available) or RTS,S/AS01_E unvaccinated children in an exposed cluster (e.g. parents/LARs from an exposed cluster can decide not to have their child vaccinated). A last home visit will be conducted at study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). In addition to the home visits, in children enrolled in the active surveillance, all visits to health care facilities (primary health care and hospital level) for any diseases, signs and symptoms will be reported to the study staff up to the end of the active follow-up period for each individual child (2 years after the last RTS,S/AS01_E dose or equal point in time for unvaccinated) (Figure 1, see also Section 9.2.7.1). Thereafter there will be continuous monitoring of hospitalisations only, up to study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Note: *The enrolment to active surveillance was completed on 06 April 2021.*

Enhanced hospitalisation surveillance: All children who are at least 6 weeks and <5 years of age, within the study areas in both exposed and unexposed clusters, not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance at the time of hospitalisation, are eligible for enrolment in enhanced hospitalisation surveillance (Figure 1, see also Section 9.2.7.2). A home visit will be conducted at study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Since the MoHs of the countries participating in the MVIP according to the SAGE/MAPC recommendation **planned** to expand the RTS,S/AS01_E vaccine implementation to the unexposed clusters from 2023, clusters that were initially unexposed **became** exposed with regards to RTS,S/AS01_E vaccination. This change in

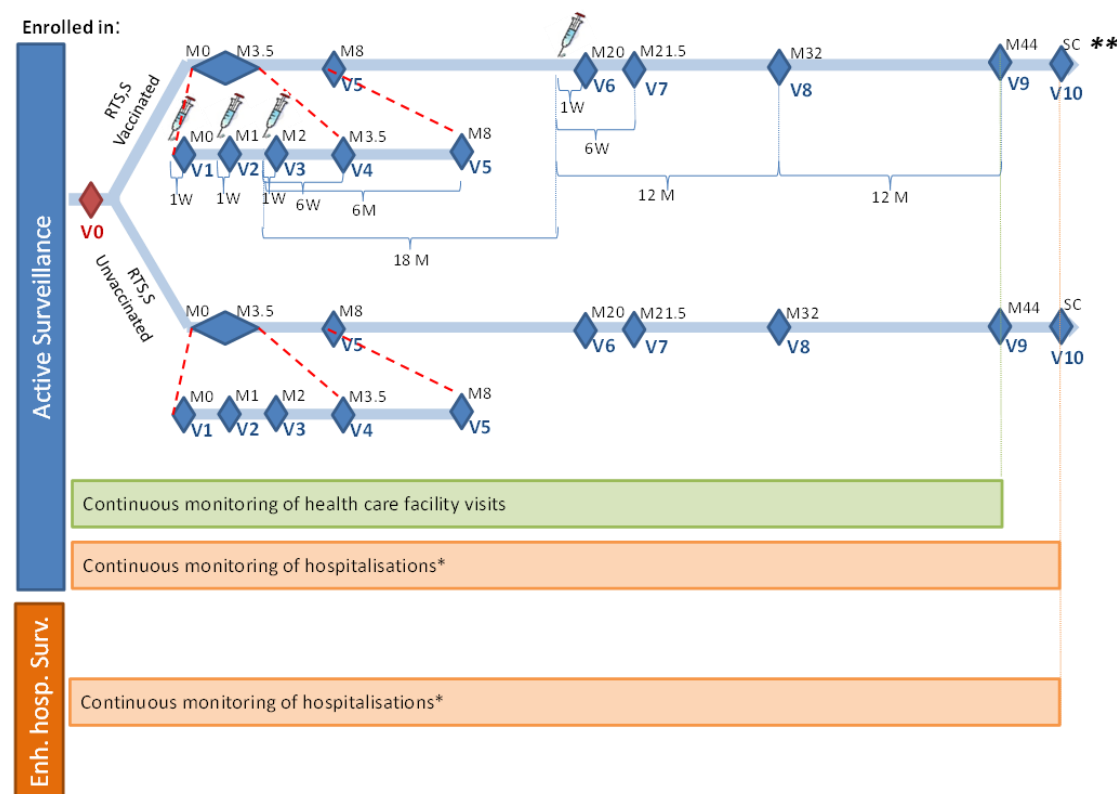
vaccine implementation directly **impacted** the current study plan. Therefore, the enrolment of subjects in the enhanced hospitalisation surveillance **was** stopped **on 01 November 2022** in clusters that were not involved in the EPI-MAL-002 study (i.e. all clusters in Malawi; unexposed clusters in Ghana and 1 exposed and 2 unexposed clusters in Kenya) as from 01 **November 2022**. Subjects already enrolled in EHS continued to be followed, in order to capture information on their subsequent hospitalisations. Study conclusions **are being** conducted in a timely manner from 01 January 2023. **Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.**

Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months (see Section 9.2.5; i.e. 24 months after the 4th dose of RTS,S/AS01E).

Figure 1 Study design overview

Distribution of vaccinated and unvaccinated children among the clusters		
Study groups in active surveillance	RTS,S/AS01 _E exposed clusters	RTS,S/AS01 _E unexposed clusters
DTP	RTS,S/ AS01 _E vaccinated and unvaccinated children	RTS,S/ AS01 _E vaccinated and unvaccinated children
Catch-up	RTS,S/ AS01 _E vaccinated children	-



* Hospitalisation is defined as spending at least one night at a health care facility

V0 = 1st dose of RTS,S/AS01_E vaccine for catch-up group; 1st identification of the child at any DTP/HepB/Hib, or during hospitalisation before 3rd dose of DTP/HepB/Hib (for children who already received at least 1 dose of DTP/HepB/Hib) for DTP group.

V = visit; W = week(s); M = month(s); SC = study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first).

The RTS,S/AS01_E vaccinated children will be either included in the DTP group (exposed or unexposed clusters) or in the catch-up group (exposed clusters) according to the abovementioned active surveillance study group characteristics.

The unvaccinated children will be included in the DTP group only and will be from either the exposed or the unexposed clusters.

For the children enrolled in active surveillance in the DTP group, enrolment is at any administration of DTP/HepB/Hib vaccine or at hospitalisation before 3rd administration of DTP/HepB/Hib vaccine and vaccinated with at least one dose of DTP/HepB/Hib. This group includes both RTS,S/AS01_E vaccinated and unvaccinated children from exposed or unexposed clusters.

The catch-up group of the active surveillance will include a group of children identified at 1st RTS,S/AS01_E dose administration (schedule depends on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group includes RTS,S/AS01_E vaccinated children from exposed clusters.

For the children vaccinated with RTS,S/AS01_E, the home visits will take place approximately 1 week after administration of each dose of primary schedule of RTS,S/AS01_E (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after

administration of the third dose; and 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after administration of the 4th dose of RTS,S/AS01_E.

For the children not vaccinated with RTS,S/AS01_E, the home visits will be scheduled at equal points in time.

A last home visit (V10) will be conducted at study conclusion.

Continuous monitoring of outpatient visits at health care facilities will be done up to the end of active follow-up for children enrolled in active surveillance.

For active surveillance, continuous monitoring of hospitalisations will be done throughout the whole study period.

For EHS, the continuous monitoring of hospitalisations will be done for clusters involved in EPI-MAL-002 study. For the other clusters not involved in EPI-MAL-002 study, enrolment into EHS **was** stopped and study conclusion conducted in a timely manner from 01 **November 2022**.

****Enrolment to EHS will stop following site Ethics Committee approval of Protocol Amendment 3.**

The diseases under surveillance for safety include AESI, other AE leading to hospitalisation, meningitis, and severe malaria including cerebral malaria. They will be monitored among the vaccinated and unvaccinated children, enrolled in active surveillance and in enhanced hospitalisation surveillance. The potential association, overall and by gender, between vaccination and death will also be assessed.

The effectiveness (direct effect) of the RTS,S/AS01_E vaccine will be investigated by monitoring all malaria (including severe and cerebral malaria) related events in the vaccinated and unvaccinated children of the exposed clusters, enrolled in active surveillance. This will be achieved by collecting data on any malaria and severe malaria (including cerebral malaria) from all health care facilities, including outpatient visits and hospitalisations. The impact (indirect, total and overall effect) of the vaccine will be investigated, in the active surveillance, firstly by comparing the incidence of all malaria (including severe and cerebral malaria) cases in EPI-MAL-002 to the incidence of all malaria (including severe and cerebral malaria) cases in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect)*. Secondly, the impact will also be investigated in the active surveillance, by comparing the incidence of all malaria (including severe and cerebral malaria) cases in children of the unexposed clusters in EPI-MAL-003 to the incidence of all malaria (including severe and cerebral malaria) cases in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect) (see also Section 9.7.7 and [Figure 3](#), [Figure 4](#) and [Figure 5](#)).

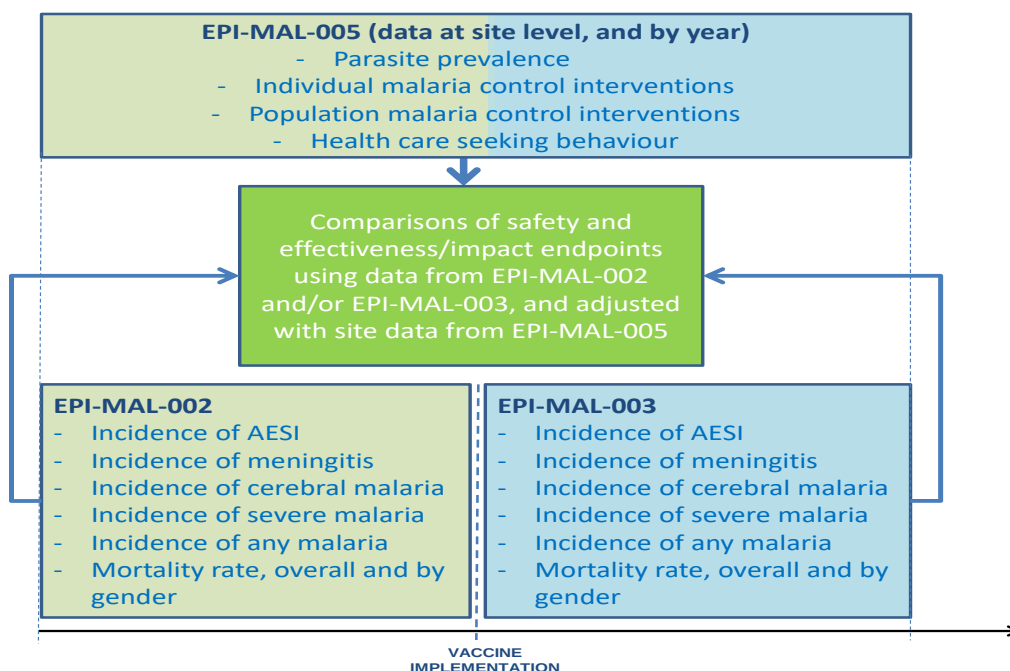
****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

9.1.1. Rationale for the study design

The RTS,S/AS01_E vaccine will be implemented only in part of malaria endemic countries of SSA. Most of these countries have no baseline incidence data on rare diseases such as those that may be reported in temporal association with vaccination. Therefore assessment of causality between adverse events and RTS,S/AS01_E may be difficult. As there are no baseline incidence rates for the AESI in the target population and in order to respond to potential safety concerns emerging during the introduction of the RTS,S/AS01_E vaccine, baseline incidence rates must be generated before vaccination. Additionally, many countries do not have standardised malaria surveillance systems in place. Both of these are required to evaluate the safety of the RTS,S/AS01_E vaccine.

GSK Biologicals has developed a set of studies to address the paucity of data regarding AE following vaccination with RTS,S/AS01_E, and to evaluate effectiveness and impact (Figure 2). Study EPI-MAL-003 is **being** conducted in similar if not identical settings as **the** EPI-MAL-002 and EPI-MAL-005 studies. The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation) **measured** the baseline incidence of AESI, other AE leading to hospitalisation, meningitis, and malaria morbidity and mortality. The mortality rate, overall and by gender, **was** also estimated. **Study** EPI-MAL-003 **is** collecting data in a similar manner **as in study EPI-MAL-002** to ensure their comparability. Capacity building of sites **was** provided before **the** start of EPI-MAL-002 and throughout the studies, to strengthen early case finding and diagnosis of the events of interest. **In parallel to studies EPI-MAL-002 and EPI-MAL-003, study** EPI-MAL-005 aims to estimate the annual parasite prevalence and record malaria control measures, providing information on potential confounding factors relevant to interpreting EPI-MAL-002/-003 malaria outcome measures. In addition, as the vaccine **was to** be implemented using a cluster design (sites in Kenya and Ghana where the EPI-MAL-002 **was conducted were expected to** become part of the intervention areas, and new sites **were** selected to be part of the comparison areas of the EPI-MAL-003 **study**), a concurrent unvaccinated cohort **was** added as a comparator. For study sites of EPI-MAL-003 which are unexposed clusters of EPI-MAL-003 and where the EPI-MAL-002 was not conducted, the same capacity building **was** provided before **the** start of EPI-MAL-003 and throughout the study.

Figure 2 Evaluation of safety, effectiveness and impact using data collected in studies EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005



Note: comparison of endpoint data between EPI-MAL-002 and EPI-MAL-003 will only be conducted for the Interim Analysis and not for the Final Analysis.

Active surveillance

Note: as the last participant enrolled to active surveillance on 06 April 2021, some of the below protocol instructions are no longer applicable.

In order to detect the events of interest within a wide range of time to onset intervals after RTS,S/AS01_E vaccination (from a few hours to several weeks or months), active surveillance of the enrolled children will be conducted through home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities. See Section 9.1 for details of home visits for vaccinated children receiving at least one dose of RTS,S/AS01_E and visits for children who do not receive RTS,S/AS01_E vaccine. The home visits will take place approximately 1 week after administration of each dose of the primary schedule of RTS,S/AS01_E (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose, and 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after the 4th dose of RTS,S/AS01_E (see details in Section 9.2.7.1). These home visits at 12 months and 24 months after the last dose will help to capture protocol-defined diseases that may have long risk window periods and that may not have been identified if the study participant did not visit a health care facility, and to monitor the occurrence of malaria episodes for evaluation of vaccine effect. In case the 4th dose of RTS,S/AS01_E was missed, a visit will be conducted approximately 24 months after the last dose received.

In addition to the home visits, any diseases, signs and symptoms in children enrolled in the active surveillance will also be reported to the study staff by all health care facilities (primary health care and hospital level) up to the end of the active follow-up period for each individual child.

If no SAE is detected in the enrolled child, active follow-up will cease and any diseases, signs and symptoms in children enrolled in the active surveillance will be reported to the study staff through monitoring of hospitalisations only, up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). If a SAE (AESI or meningitis or severe malaria including cerebral malaria) is detected in the child, he or she will be followed for an additional 12 months to further characterise the event. A last home visit (V10) will be conducted at study conclusion. Follow-up for the SAE disposition is described in Section 11.5.

An important function of the active surveillance component is to ensure referral of sick children to the health care facilities. Due to EPI-MAL-002 activities, the active surveillance processes should already ***have been*** effective when EPI-MAL-003 ***began*** enrolment, allowing for identification of AEs at an early stage of this study. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building ***was*** provided before ***the*** start of EPI-MAL-003 and throughout the study.

Enhanced hospitalisation surveillance

Note: following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

For the purpose of this study, enhanced hospitalisation surveillance corresponds to case detection during hospitalisation through monitoring of medical records and registries. Enhanced hospitalisation surveillance is included to supplement the active surveillance for several reasons: 1) it may capture AESI, other AE leading to hospitalisation, meningitis, and severe malaria including cerebral malaria in children who may have been vaccinated but declined enrolment in active surveillance, or who were not enrolled in active surveillance as recruitment had been completed or were not eligible for active surveillance; 2) it will provide supplemental information regarding these events in unvaccinated children (from either the exposed or the unexposed clusters) not enrolled in active surveillance, complementing data generated from EPI-MAL-002. Including those unvaccinated children ensures continuity with EPI-MAL-002 and captures events that may be occurring in the community (see Section 9.9 for the potential biases and limitations). All hospitalised children who are at least 6 weeks and <5 years of age within the study areas who are not already enrolled in the active surveillance (because parents/LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance, are eligible for enrolment in enhanced hospitalisation surveillance, to allow for data collection regarding that hospital visit and any subsequent hospitalisations until study conclusion. Children already enrolled in active surveillance will have hospitalisations monitored as part of the procedures related to the active surveillance and will therefore not be enrolled in enhanced hospitalisation surveillance.

To assess the operational conduct of both active surveillance and enhanced hospitalisation surveillance, two control outcomes have been included in the study protocol, as for EPI-MAL-002. Abscess at injection site (after any vaccination) is included as a positive control and positional foot deformation is included as a negative control (see case definitions in Section 9.2.6.10). These conditions are relatively easy to diagnose and will be used to assess changes in the performance of health care systems to diagnose disease.

Selected study sites **were** expected to have a HDSS or equivalent surveillance system in place. If a site **did** not have a HDSS in place, the ***International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH)*** procedures for demographic census **could have been** implemented to ensure consistency across study sites. In addition, being part of the INDEPTH (or seeking membership to INDEPTH) is an asset to ensure standard health and demographic surveillance practices, thereby enabling standardised calculation of incidence rates.

9.2. Setting

9.2.1. Study population

The three studies EPI-MAL-002, -003 and -005 **were** anchored when possible on the INDEPTH health and demographic survey platform (<http://www.indepth-network.org>) or equivalent surveillance system to provide both population and health facility linkage [INDEPTH]. For this study, the HDSS (or equivalent surveillance system) provides the population and its characteristics, from which a cohort may be identified. The cohort will be a subset of the total eligible population of children specified within the geographic catchment area of the study sites. The cohort is considered dynamic, as infants and immigrants are included in the cohort and the birth or in-migration date is recorded. Similarly, deaths and outmigrations are recorded.

The process begins with a census of the population and proceeds with regularly scheduled (at least once a year) monitoring of vital events (births, deaths), migration, selected health outcomes, and other demographic and lifestyle variables. The census serves as the source document for the initial screening for study population eligibility.

Note: If a site **was** not part of the INDEPTH network, the INDEPTH procedures for demographic census **could have been** implemented to ensure consistency across study sites.

Initially, seven sites in five SSA countries were chosen to participate in the EPI-MAL-002 study. Following SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01_E in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria [WHO, 2015(a)], some of the initially chosen sites located in low-endemicity settings had to be terminated. For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01_E vaccine **was** planned to be implemented according to MVIP, were added to the already defined study sites for EPI-MAL-002 as described below.

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through MVIP. The 3 countries were selected to participate in the pilot programme based on the following criteria: high coverage of long-lasting insecticidal-treated nets; well-functioning malaria and immunisation programmes, a high malaria burden even after scale-up of long-lasting insecticidal-treated nets, and participation in the Phase III RTS,S/AS01_E malaria vaccine trial. Each of the 3 countries **were to** decide on the districts and regions to be included in the MVIP. High malaria burden areas **were to** be prioritized [WHO, 2017]. In order to align with the MVIP, the study sites for the GSK's baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) **were** selected as follows:

- Sites **were** selected from the 3 countries where the RTS,S/AS01_E vaccine **was to** be implemented in the framework of the MVIP. Burkina Faso sites that started EPI-MAL-002 early terminated the study activities on 06 June 2018 (with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI). Burkina Faso sites **were** not included in EPI-

MAL-003 because the MVIP **was** not **planned to** take place in the country. Their data will therefore not be included neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies, nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study (e.g. background incidence of meningitis for study sample size and the exposure to other vaccines). Considering the RTS,S/AS01_E vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site.

- As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 (**unexposed clusters**) **became exposed clusters** study sites in EPI-MAL-003.
- Currently, as per MVIP and WHO guidance, 4 study sites (corresponding to 4 clusters of the MVIP) in each of the 3 countries selected for the RTS,S/AS01_E pilot implementation programme (12 study sites/clusters in total) **were** planned to be part of EPI-MAL-003: 2 of them **to** become exposed clusters and 2 of them **to** become unexposed clusters. **As** Phase IV vaccine evaluation **was** fully embedded in the MVIP, selection of the unexposed clusters included in study EPI-MAL-003 **depended** on the cluster identification process led by the MoH in collaboration with the WHO. Of note, the clusters, once pre-identified by the MoHs **were** submitted to a comprehensive scientific and operational study site assessment conducted by GSK, which determined study feasibility in those sites. Exposed and unexposed clusters **were to** be comparable in terms of malaria transmission, health facilities level, geographical region and population size.
 - As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 (**unexposed clusters**) **became exposed cluster** study sites in EPI-MAL-003.
 - Selection of the remaining study sites/clusters included in the EPI-MAL-003 study **was** fully embedded in the MVIP.
- In summary: currently, a total of 3 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa]) enrolled study participants in the EPI-MAL-002 study. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 sites have become exposed study sites/clusters in EPI-MAL-003. Selection of the remaining study sites/clusters included in the EPI-MAL-003 study **was** fully embedded in the MVIP. Study feasibility in all sites/clusters **was** assessed through a comprehensive scientific and operational study site assessment.

Taking into account a global birth cohort of 23,000 children at the time of EPI-MAL-002 study preparation, and the refusal rate of parents for their children to join the study, an expected number of at least 45,000 children, including 22,500 children in the exposed

clusters (with minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children) and 22,500 children in the unexposed clusters **were planned to** be part of the active surveillance of the study. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports.

9.2.2. Eligible population

The eligible study population is defined as those children living in the study areas.

The WHO's SAGE on Immunization and the MPAC recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. At the start of the malaria vaccine implementation, children aged 5-12 months **were** eligible for dose 1 of RTS,S/AS01_E. In some countries a large number of children aged 5-12 months may therefore **have been** vaccinated at the start of the pilot implementation programme. Once the malaria vaccine implementation **reached a** steady state, the majority of children receiving dose 1 **would** have only **just** grown into the eligible age range. Co-administration could **have happened** such as measles or yellow fever vaccines, scheduled in older infants at 9 months of age.

For the active surveillance, children from both exposed and unexposed clusters **were** enrolled. At least 22,500 children in the exposed clusters, including a minimum of 20,250 children vaccinated with RTS,S/AS01_E, and a minimum of 2,250 unvaccinated children, **were** targeted to be enrolled (assuming that 80% of study participants **would** receive at least three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose). At least 22,500 children in the unexposed clusters **were to** be enrolled into the active surveillance when presenting for administration of DTP/HepB/Hib vaccine. Parents/ LARs **were** invited to enrol their child into the active surveillance when children **were** presenting for administration of DTP/HepB/Hib vaccine (DTP group), regardless **of** whether they subsequently decided to vaccinate their child with RTS,S/AS01_E or not. In addition, parents/ LARs **were** invited to enrol their child into the active surveillance when children **were** presenting for 1st administration of RTS,S/AS01_E vaccine and who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and **were** older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start (catch-up group).

The enrolment to active surveillance was completed on 06 April 2021.

For enhanced hospitalisation surveillance, parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are at least 6 weeks and <5 years of age and who can be linked to the HDSS or equivalent surveillance system, will be approached to enrol their child into this study:

- If a child, who **was** first identified during hospitalization by study staff, **fulfilled** the eligibility criteria for enrolment in active surveillance (within the recruitment period), enrolment in active surveillance **was** proposed. If the parents/LARs declined enrolment in active surveillance and if the child **fulfilled** the eligibility criteria for

enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance **was** proposed.

- If a child, who **was** first identified during hospitalization by study staff, **was** not eligible for enrolment in active surveillance but **fulfilled** the eligibility criteria for enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance **was** proposed.

Note: ‘first identified during hospitalization by study staff’ means ‘not already enrolled in the study’.

Hospitalisation is defined as spending at least one night at a health care facility. Some primary care facilities have beds available for overnight monitoring; these stays are considered to be “hospitalisations” for protocol purposes. Additionally, some tertiary hospitals may offer primary health care services. So the more general term, “health care facility” is used in the protocol to include the spectrum of health care service access points, from primary health care clinics to tertiary hospitals. There may be a difference in the degree of severity of cases admitted in the hospital and those hospitalised at primary health care facilities as the latter may include children with non-severe disease who live too far to be sent home on the same day. On the other hand, hospitalisations in primary health care facilities may also include cases that under European conditions would normally be referred to the hospital, such as: parental refusal to refer the child to a hospital, difficulties of transport or local standard practice.

Children **who were** enrolled in active surveillance of EPI-MAL-002, and **were** not eligible for RTS,S/AS01_E vaccination or **declined** RTS,S/AS01_E vaccination, **were continued** to be followed up to the study conclusion visit in EPI-MAL-002. Children enrolled in active surveillance of EPI-MAL-002, and vaccinated with RTS,S/AS01_E, **had** their study conclusion of EPI-MAL-002. Thereafter, these children **could have been** enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

For children enrolled in enhanced hospitalisation surveillance of EPI-MAL-002, **the** study conclusion of EPI-MAL-002 **was** done at start of study EPI-MAL-003 (as the vaccine **became** available in the study sites that **were** exposed clusters). Thereafter, these children **could have been** eligible and enrolled in active surveillance or in enhanced hospitalisation surveillance of EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

Note: Enrolment to EHS will stop following site Ethics Committee approval of Protocol Amendment 3.

9.2.3. Inclusion criteria

Note: the enrolment to active surveillance was completed on 06 April 2021; reference to inclusion criteria at study entry to active surveillance is no longer applicable.

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or study participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All study participants must satisfy ALL the following criteria at study entry:

- Study participants' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written informed consent provided from either the parent(s) or LAR of the study participant.
- Study participant living in the HDSS or equivalent surveillance system area.
- For enrolment in the active surveillance – DTP group: children must be aged < 18 months, identified at any administration of DTP/HepB/Hib (or at hospitalisation before 3rd dose of DTP/HepB/Hib in case of hospitalisation and vaccinated with at least one dose of DTP/HepB/Hib). (This group will include children from exposed and unexposed clusters.)

OR

For enrolment in the active surveillance – Catch-up group: children must be aged < 18 months, received at least one dose of DTP/HepB/Hib vaccine, whose age corresponds to the age after the 3rd dose of DTP/HepB/Hib vaccine, (=who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start) and identified at 1st RTS,S/AS01_E dose administration (This group will include children from exposed clusters only).

OR

For enrolment in the enhanced hospitalisation surveillance: children must be aged at least 6 weeks and <5 years at the time of hospitalisation at any time during the study. (This group will include children from exposed and unexposed clusters.)

Parents/LARs of children meeting all eligibility criteria for active surveillance, not having completed the visits for DTP/HepB/Hib, and first identified during hospitalisation, must first be proposed enrolment in active surveillance (if recruitment is not completed).

Children already enrolled in active surveillance will have hospitalisation monitored as part of the procedures related to the active surveillance and can therefore not be enrolled in enhanced hospitalisation surveillance.

9.2.4. Exclusion criteria

The following criterion should be checked at the time of study entry. If the exclusion criterion applies, the study participant must not be included in the study:

- Child in care
Please refer to [Annex 2](#) for the definition of child in care.

9.2.5. Study period

Taking into account a global birth cohort of 23,000 children at the time of EPI-MAL-002 study preparation (11,500 children in the exposed clusters, and 11,500 children in the

unexposed clusters), a period of approximately 18 months **was** assumed to be sufficient to enrol at least 45,000 children in active surveillance of EPI-MAL-003, including 22,500 children in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children assuming that 80% **would** receive three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose) and 22,500 in the unexposed clusters. The vaccine coverage in the exposed clusters and enrolment **were** monitored through the progress reports.

The recruitment period **was to** be adapted according to the birth cohorts of the different sites at the time of study start. The duration of the recruitment **was also to** be adjusted according to the recommended schedule of the vaccine and the vaccine coverage in the exposed clusters, the time the participating countries started implementing the vaccine (which may **have been** different between countries), and potential unanticipated logistical issues.

The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months. Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) **given at a maximum age of 30 months**. (Children reporting a SAE due to study procedure might have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months).

Note: **Due to the** overlap of studies EPI-MAL-002 and EPI-MAL-003, some children enrolled in EPI-MAL-002 **had** the possibility to be part of EPI-MAL-003. First, the study conclusion of EPI-MAL-002 for children enrolled in enhanced hospitalisation surveillance **was** done at the start of study EPI-MAL-003 (as the RTS,S/AS01_E vaccine **became** available in the sites that are exposed clusters; See Section 9.2.2). In addition, children enrolled in active surveillance of EPI-MAL-002, and vaccinated with RTS,S/AS01_E, **had** their study conclusion of EPI-MAL-002. Thereafter, these children **could have been** enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

9.2.6. Case definitions

9.2.6.1. AESI

Adverse events of special interest (AESI) are protocol-defined diseases corresponding to AEs that are potentially associated with RTS,S/AS01_E, that have historically been associated with vaccines other than RTS,S/AS01_E, or may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines.

The list of AESI has been developed in collaboration with a group of paediatricians working in SSA. This group of paediatricians has been consulted following an opportunity to receive scientific advice with the EMA in 2011. Indeed, the Committee for Medicinal Products for Human Use (CHMP) suggested seeking advice from relevant

paediatric clinicians on which additional AESI (particularly autoimmune disorders) may be of most relevance for SSA countries as well as the surveillance indicators. In addition, GSK had considered four diseases which have been identified as potential AE with other vaccines and has added these to this list (Intussusception, Kawasaki diseases, Henoch-Schonlein Purpura and Hypotonic Hyporesponsive Episode [HHE]).

When available, the Brighton Collaboration Working Groups case definitions are used. These aim to define levels of diagnostic certainty of reported events following immunisation. Their global use enhances data comparability within and across clinical trials and surveillance systems and allows the adaption of the diagnosis based on the health facility's settings. Each case definition is structured in two or three levels of diagnostic certainty, each level being defined by a set of clinical and/or additional diagnostic criteria.

- Level 1 of diagnostic certainty: most specific and least sensitive level
- Level 2 of diagnostic certainty: intermediate level of specificity and sensitivity
- Level 3 of diagnostic certainty: most sensitive but lowest level of specificity.

Job Aids are field guides that act as a reference tool for study staff. For this study, Job Aids have been developed to standardise the definition of each AESI during a collaborative initiative between GSK, Agence de Médecine Préventive (AMP) and Réseau en Afrique Francophone pour la Télémédecine (RAFT). RAFT physicians will provide support for case diagnosis through virtual consultation infrastructure.

The predefined list of AESI and associated clinical information is provided in [Table 3](#) and case definitions are provided in [Annex 5](#).

Table 3 Summary of AESI by body system

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
Nerves and Central Nervous System				
ADEM	0.6 to 0.8/100,000 PY [Karussis, 2014]; 0.2/100,000 PY (in < 18 yr olds, Canada) [Banwell, 2009]; 0.40, 0.27 and 0.30/100,000 PY (10-14 yr olds, 15-19 yr olds, 20-29 yr olds, respectively, China) [Xiong, 2014]; 0.03/100,000 PY (10-16 yr olds, Germany) [Pohl, 2007]; 0.2/100,000 PY (< 18 yr olds, The Netherlands) [Ketelslegers, 2012]; 0.34/100,000 PY (1-15 yr olds, UK) [Absoud, 2012]; 0.3/100,000 PY (≤18 yr olds, US) [Langer-Gould, 2011];	1-2 per million following vaccination against measles, 0.2 per 100,000 following vaccination against Japanese encephalitis, 1 per 300 to 1 per 7,000 following administration of neural vaccine against rabies [Tenenbaum, 2007]	NA	BC

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
	0.4/100,000 PY (< 20 yr olds, US) [VanLandingham, 2010]			
Encephalitis	11.1 (95% CI: 10.1, 12.1) and 4.7 (95% CI: 4.3, 5.1) encephalitis-associated hospitalisations /100,000 PY (in <1 yr and 1-4 yr olds, US, respectively) [Vora, 2014]	1396 cases (mean age 23.4 yrs, range 0-89 yrs) in the US from 1990 to 2010 [Al Qudah, 2012]	Onset within 6 wks and 2 wks after vaccination: 65.2% and 50.7% of patients, respectively [Al Qudah, 2012]	BC
Guillain-Barré Syndrome	0.7/100,000 PY (in 12-29 yr olds, Tanzania) [Howlett, 1996]; 0.38/100,000 PY (in 0-4 yr olds, China) [Chen, 2014]; 0.62/100,000 PY (95% CI: 0.52, 0.75) in 0-9 yr olds in a meta-analysis from studies in North America and Europe [Sejvar, 2011]	1 additional case per 10 ⁶ doses with influenza vaccination in US, 1992-1994 [Lasky, 1998] Calculated RR in different studies on influenza vaccination from 1978 to 2005 produced RR values ranging from 0.4 to 1.7 [Sejvar, 2011]	Ranges from 3-5 days to 6-10 wks, and up to a few months and even years [Sejvar, 2011]	BC
Generalised convulsive seizure	Unknown	1.04 per 1,000 (95% CI: 0.62, 1.64) after primary vaccination with RTS,S/AS01 in children 5-17 months at first dose [The RTS,S Clinical Trials Partnership, 2012]; 2.5 per 1,000 and 2.2 per 1,000 after 4 th dose of RTS,S/AS01 in children 5-17 months at first dose, and in children aged 6-12 weeks at first dose, respectively [The RTS,S Clinical Trials Partnership, 2015]	0-7 days after RTS,S/AS01	BC
Hypotonic Hypo-responsive syndrome	NA	Reported rates following whole-cell and acellular pertussis component combination vaccines range from 21 to 71 episodes and 7 to 36 episodes per 100,000 doses and 36 to 250 episodes and 4 to 140 episodes per 100,000 children, respectively [Buettcher, 2007]	3-4h but ranges from immediately to 48h post vaccination	BC
Hepato-Gastrointestinal and Renal System				
Intussusception	Average rate 1 case per 3,300; yearly variations 1:2,500 to 1:5,000 (<1 yr old, Panama) [Sáez-Llorens, 2004]; <5/100,000 PY (<9 wks), 62/100,000 PY (26-29 wks), 26/100,000 PY (52 wks) (US) [Tate, 2008];	Overall estimate of risk of IS within 7 days is estimated at 5.4 (95% CI: 3.9-7.4) after 1 st dose Rotarix and 5.5 (95% CI: 3.3-9.3) after 1 st dose RotaTeq. Small increase after dose 2 for both vaccines [Carlin, 2013; Rosillon, 2015]	1 to 7 days after 1 st and 2 nd doses of Rotarix and RotaTeq vaccines	BC

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
	8.1/100,000 PY (<1 yr Australia) [Justice, 2005]			
Hepatic insufficiency	Unknown	NA	1-10 days	BC
Renal insufficiency	Unknown	NA	1-10 days	BC
Skin and Mucous Membrane & Bone and Joints				
Juvenile chronic arthritis	18/100,000 PY (in ≤16 yr olds, Canada) [Feldman, 2009]; 7/100,000 PY (Germany); 24/100,000 PY (Australia) [Begg, 2007]	NA	≤ 6 months	P
SJS and TEN	SJS: 1-6 per million PY [Roujeau, 1995]; TEN: 0.4-1.2 per million PY [Roujeau, 1995]	NA	1-3 weeks	P
Henoch Schonlein purpura	Peak at 70/100,000 PY (in 4-6 yr olds, UK) [Gardner-Medwin, 2002]	NA	NA	P
Kawasaki disease	About 215/100,000 PY (in <5 yr olds, Japan) [Nakamura, 2010]; 20/100,000 PY (in <5 yr olds, US); 17/100,000 PY (in <5 yr olds, African Americans) [Holman, 2010]; 6.4/100,000 PY (in <5 yr olds, Israel) [Bar-Meir, 2011]	Reporting to VAERS in the US, from 1990 through mid-October 2007: Hib (31 cases of Kawasaki disease), PVC-7 (29 cases), MMR (22 cases), diphtheria and tetanus toxoids and acellular pertussis (21 cases), inactivated polio (17 cases), rotavirus (16 cases), diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated polio combined (16 cases), hepatitis B (13 cases). 0.65 and 0.37 reports /100,000 PY for <i>RotaTeq</i> and <i>Pediarix</i> , respectively, before label revision of <i>RotaTeq</i> , and 2.78 and 2.44/100,000 PY for <i>RotaTeq</i> and <i>Pediarix</i> , respectively, after label revision [Hua, 2009] PCV-7: 4.6 per 100,000 doses, PCV-13: 5.4 per 100,000 doses [Tseng, 2013] PCV-13: 1 case in 233 vaccinated children, considered not to be related to vaccination [Gutierrez Brito, 2013] Electronically captured health insurance claims in the US, from 2006 to 2007: <i>RotaTeq</i> : 1	1 month after vaccination	P

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
		case within 30 days, 2 cases between 31 and 60 days after vaccination in North Wales. DTaP: 1 case [Loughlin, 2012]		
Systemic Disease and Haematology				
Diabetes mellitus type 1	0.06/100,000 PY (0.0, 0.13) (in 0-4 yr olds, Tanzania) [Swai, 1993]; 0.9/100,000 PY (in 0-4 yr olds, Sudan) [Karvonen, 2000]; 2.3 to 6.3/100,000 PY (in 0-4 yr olds, Tunisia) [Karvonen, 2000]; 9.06/100,000 PY (0-4 yr olds, Cyprus), 14.15/100,000 PY (5-9 yr olds, Cyprus) [Skordis, 2012]; 3.1/100,000 PY (in <18 yr olds, Egypt) [El-Ziny, 2014]; 12.9/100,000 PY (0-5 yr olds, Germany), 18.7/100,000 PY (5-10 yr olds, Germany) [Galler, 2010]; 8.59/100,000 PY (0-4 yr olds, Israel), 13.29/100,000 PY (5-9 yr olds, Israel) [Sella, 2011]; 17.1/100,000 PY (0-4 yr olds, Saudi Arabia), 10.9/100,000 PY (5-9 yr olds, Saudi Arabia) [Habeeb, 2011]; 4.3/100,000 PY (0-4 yr olds, Turkey), 9.1/100,000 PY (5-9 yr olds, Turkey) [Demirbilek, 2013]	NA	≤6 months	P
Thrombo- cytopenia	2.2/100,000 PY (in <16 yr olds, Germany) [Sutor, 2001]	NA	12-25 days median (range 1-83 days)	BC
Anaphylaxis	70/100,000 PY (in 0-19 yr olds, Minnesota, US) [Decker, 2008]	Monovalent measles (12 per 100,000 doses), MMR (1 per 100,000 doses), HPV bivalent (1.4 per million doses) or HPV quadrivalent (from 2.6 per 100,000 to 1.7 per million doses) [Vanlander, 2014] 0.65 (95% CI: 0.21, 1.53) per million doses for the most common vaccines for children and adolescents [Bohlke, 2003]	0-48 hours [Bohlke, 2003]	BC

ADEM= Acute Disseminated Encephalo-Myelitis; AE = adverse event; Hib = *Haemophilus influenzae* type B; HPV = human papilloma virus; MMR = measles, mumps, rubella; PCV = pneumococcal conjugate vaccine; SJS= Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis; NA = not available; PY = person years; RR = relative risk; VAERS = Vaccine Adverse Event Reporting System.

9.2.6.2. AE/SAE

Refer to Section 11.1 for the definition of AE and SAE.

9.2.6.3. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria)

These include all hospitalisations reported by the physician not due to an AESI (see Section 9.2.6.1) or to meningitis (Section 9.2.6.4) or to any malaria or to severe malaria (including cerebral malaria) (Section 9.2.6.6).

Collection of hospitalisations for an AE other than AESI or meningitis or any malaria or severe malaria (including cerebral malaria) **were** stopped as of 01 **November 2022** in subjects previously enrolled in EHS in sites not involved in EPI-MAL-002 study. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria) will continue to be collected as part of continuous monitoring for subjects enrolled in AS in all sites, or EHS in sites involved in **the** EPI-MAL-002 study **until enrolment to EHS is stopped following site Ethics Committee approval of Protocol Amendment 3.**

9.2.6.4. Meningitis

Of note, because meningitis was identified as a potential risk during RTS,S/AS01_E clinical development (see Section 7.2), the disease is identified separately from the other AESI.

- At the site level, a suspected meningitis case based on clinical symptoms and/or signs is defined as [adapted from WHO, 2003]:
 - A child with sudden onset of fever (> 38.0°C rectal or 37.5°C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

Lumbar puncture will be performed according to routine medical practice for examination of cerebrospinal fluid (CSF). Children with symptoms and/or signs of meningitis will be classified as follows based on first line laboratory results (for monitoring trends over time):

- If a CSF sample is available and a bacterial agent has been identified, as bacterial confirmed meningitis case;
- If a CSF sample is available, no bacterial agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels) or positive blood culture to a bacterial agent, as probable meningitis case;
- If a CSF sample is available and all examinations are normal at first line laboratory level, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.

- Based on second line laboratory results (see Section 9.2.7.3.1 and 9.2.7.3.2) and after external panel of experts review (see Section 9.2.7.4.1), final classification of meningitis cases will be as follows (for the statistical analyses):
 - If a CSF sample is available and any known aetiologic agent (bacterial or not) has been identified, as aetiology-confirmed meningitis case;
 - If a CSF sample is available, no aetiologic agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels), or positive blood culture to a bacterial agent as probable meningitis case;
 - If a CSF sample is available and all laboratory results are normal after second line laboratory results, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.

If none of the criteria (no specific clinical symptoms and/or signs or laboratory results) are fulfilled, after review by the external panel of experts, the case will be classified as a no meningitis case.

9.2.6.5. Febrile convulsions

- Adapted from Brighton case definition for generalised seizures (see Annex 5): generalised seizures with measured fever $\geq 37.5^{\circ}\text{C}$ (axillary) or reported history of fever.

9.2.6.6. Malaria

Case definitions according to the WHO will be used [WHO, 2015(b)]. Any malaria will include uncomplicated and severe malaria cases, including cerebral malaria.

- Uncomplicated malaria [WHO, 2015(b)]
Plasmodium parasitaemia > 0 detected by microscopy and/or RDT
AND
Presence of fever (temperature $\geq 37.5^{\circ}\text{C}$), as reported by the parent(s)/LAR(s) or recorded at the time of presentation
OR
Occurring in a child who is unwell and brought for treatment to a health care facility
AND
Without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.
- Severe falciparum malaria [adapted from WHO, 2015(b)]
P. falciparum parasitaemia > 0 detected by microscopy and/or RDT
AND

One or more of the following, occurring in the absence of an identified alternative cause:

- Impaired consciousness: a Glasgow coma score < 11 in children ≥ 2 years of age or a Blantyre coma score < 3 in children < 2 years of age;
- Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;
- Multiple convulsions: more than two episodes within 24 h;
- Acidosis: a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);
- Severe malarial anaemia: haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age with a parasite count > 10,000/μL;
- Renal impairment: plasma or serum creatinine > 265 μmol/L (3 mg/dL) or blood urea > 20 mmol/L;
- Jaundice: plasma or serum bilirubin > 50 μmol/L (3 mg/dL) with a parasite count > 100,000/μL;
- Pulmonary oedema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation;
- Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena;
- Shock: compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill);
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/μL).
- Severe vivax malaria is defined as for severe *falciparum* malaria but with no parasite density thresholds [WHO, 2015(b)].
- Cerebral malaria [adapted from WHO, 2015(b)]:

Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age);

AND

If malaria with seizure: coma persisting for > 30 min after the seizure.

Other treatable causes of coma should be excluded before diagnosing cerebral malaria (e.g. hypoglycaemia, bacterial meningitis).

Note: Suspected malaria cases routinely tested using RDT will have a blood smear for reading by microscopy in parallel, in order to measure sensitivity and specificity. This will be done for all suspected cases presenting at primary health care facilities one day per month during the first year of the study.

9.2.6.7. Anaemia

- All anaemia: haemoglobin <11g/dL [[Stoltzfus](#), 1993].
- Severe anaemia: haemoglobin <7g/dL [[Stoltzfus](#), 1993].

9.2.6.8. Hospitalisation

- Hospitalisation (all causes)
A study participant requiring overnight stay in hospital/inpatient facility.
- Hospitalisation for malaria (including *P. falciparum* malaria)
A hospitalised study participant with malaria (including *P. falciparum* malaria) and for whom malaria is the primary cause of hospitalisation.

9.2.6.9. Death

- Death – all cause
A fatality (of any cause).
- Malaria attributed death (including *P. falciparum* malaria)
A fatality for which malaria (including *P. falciparum* malaria) is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [[INDEPTH](#), 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.
- Deaths attributed to an AE
A fatality for which an AE is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [[INDEPTH](#), 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.

* If a site is not part of the INDEPTH network, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

Deaths, including malaria attributed deaths with an uncertain diagnosis after review by the GSK safety physician, will be reviewed by the expert panel to confirm the primary/secondary cause of death (see Section [9.2.7.4.3](#)).

9.2.6.10. Surveillance quality indicators

To ensure the quality of the surveillance that will be performed in the study sites, two surveillance quality indicators have been added based on discussion with African paediatricians (see also Section 9.9): abscess at injection site during the 7-day period (Days 0-6) after any vaccination and foot positional deformations.

Abscess at injection site after vaccination

The diagnosis and monitoring of abscess at the injection site will be used as a positive control, as this is an AE that is relatively frequently observed after routine vaccination in Africa, and is defined as:

- A localised collection of material in subcutaneous tissue, fat, fascia or muscle at the site of immunisation confirmed in spontaneous or surgical drainage of material from the mass or by presence of palpable fluctuance (defined as a wavelike motion on palpation due to liquid content). The abscess may be further classified as due to infectious aetiology, a sterile abscess or not-determined. Abscesses of infectious aetiology may be accompanied by fever/regional lymphadenopathy. Sterile abscesses are not accompanied by fever/regional lymphadenopathy.

Foot positional deformations

The diagnosis and monitoring of foot positional deformations as a birth defect will be used as a negative control (to assess changes in the performance of health care systems to diagnose disease), and is defined as:

- Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot
OR
- Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg
OR
- Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.

9.2.7. Study procedures

Supplementary study conduct information not mandated to be present in this protocol is provided in the Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the study participants.

In the event that a parent/LAR does not give consent for their child to participate in EPI-MAL-003, this decision will not influence their ability to access future vaccinations, including RTS,S/AS01_E.

9.2.7.1. Active surveillance

For the purposes of this study, study participants enrolled into active surveillance will be followed up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Study procedures to be conducted at scheduled study contacts/visits and during hospitalisations are detailed in [Table 4](#) and [Table 5](#). Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

Note: the enrolment to active surveillance was completed on 06 April 2021; the below instructions relating to enrolment and some of the protocol instructions are no longer applicable.

9.2.7.1.1. Enrolment and follow-up

- Parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine (V0) (any visit for DTP/HepB/Hib vaccine) or 1st RTS,S/AS01_E dose during the catch-up group enrolment period (Section [9.2.3](#)). In case the child is first seen during hospitalisation, meeting the inclusion criteria for active surveillance (DTP group), and not having completed the visits for DTP/HepB/Hib, the child can be enrolled in active surveillance during hospitalisation – See Section [9.2.3](#). The parent(s)/LARs will be informed about the study and the study procedures will be explained to them. They will be asked to provide signed or witnessed and thumbprinted informed consent, according to local requirements. Reasons for non-participating will be recorded.

Information on the cluster (exposed or unexposed), on the study participants' socio-demographic characteristics (e.g. date of birth and gender, the number of persons in the household) and active participation in any trial with an investigational product will be recorded at enrolment visit.

Each enrolled study participant will be assigned a study participant study number (study participant number) and will be provided with a study ID card and study specific stickers. The stickers can be used on the health care facility's registers if no other system is in place to indicate a study participants' visit and facilitate identification of data from enrolled study participants from the facility's register.

- Each child enrolled in active surveillance will be followed-up longitudinally through community based home visits.
 - For children receiving at least one dose of RTS,S/AS01_E (vaccinated children), these visits will take place approximately 1 week after administration of each dose of the primary schedule of RTS,S/AS01_E (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose. V6 will take place approximately 1 week after administration of the fourth dose of RTS,S/AS01_E (administered approximately 18 months after the third dose). This visit will be

followed by visits approximately 6 weeks (V7), 12 months (V8) and 24 months (V9) after the fourth dose as described in [Table 4](#). A last visit (V10) will take place at study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). If a child does not receive the complete primary schedule, V2 and/or V3 will not take place, but V4 will be done 6 weeks after the recommended scheduled visit for the third dose of RTS,S/AS01_E. If the child finally receives a delayed dose of the vaccine, the 1 week post vaccination visit (V2 and/or V3) will take place and V4 may take place again. If a child does not receive the 4th dose, a visit will take place approximately 24 months after the last dose received, and a last visit (V10) will take place at study conclusion.

- For unvaccinated children (i.e. children in the exposed clusters whose parents/LARs elect not to have them vaccinated with RTS,S/AS01_E or children in the unexposed clusters), visits will be scheduled at equal points in time. The visits will take place 1 week (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after the recommended scheduled visit for the primary series of RTS,S/AS01_E. Additional visits will be conducted at 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after the recommended scheduled visit for the 4th dose of RTS,S/AS01_E. A last visit (V10) will take place at study conclusion.
- If a child has been initially followed according to the schedule for the unvaccinated group, and finally receives a dose of RTS,S/AS01_E, the child will start the active follow-up of the vaccinated group as of V1, limited to a time period up to study end (which could be less than 2 years of follow-up after the last dose of RTS,S/AS01_E). This child will be considered unvaccinated until he/she receives the first dose of RTS,S/AS01_E.

Two attempts should be made to visit the child at home within the month of the scheduled follow-up visit/study conclusion visit before it is abandoned.

Information on dates of vaccine administered (RTS,S/AS01_E) and other vaccines as part of routine immunisation (administered concomitantly, or any time before, or prior to RTS,S/AS01_E during the study period) will be recorded at each home visit (see also [Section 9.3.3.1](#) for ascertainment of vaccine history).

Surveillance of AESI, other AE leading to hospitalisation, meningitis and malaria will be performed as described below.

Data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms (whether prescribed or self-medicated), and exposure to environmental hazards such as chemicals will be recorded at each visit. In addition, information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, and information on medication administered in anticipation of a reaction to the vaccination will be recorded (see [Section 9.3.3](#)).

- All health care facilities (primary health care and hospital level) will report to the study staff any diseases, signs and symptoms in children enrolled in the active surveillance, up to the end of the active follow-up period for each individual child.

After the home visit 2 years after last dose (or equal point in time for unvaccinated), there will still be continuous reporting of hospitalisations up to study conclusion. If a child is diagnosed with a SAE, the child will be followed for an additional 12 months to further characterise the event. Follow-up for the SAE disposition is described in Section 11.5.

9.2.7.1.2. Surveillance of AESI, meningitis and malaria during follow-up

The surveillance of AESI, meningitis and measures of malaria burden will be done at different levels in line with the surveillance strategy implemented for the EPI-MAL-002 study:

- **Scheduled home visits**

Active surveillance will be performed by trained community health workers through home visits. Medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies) will be recorded at the first visit (V1) and a basic physical examination will be performed at each visit. Community health workers will use visual aids and other training materials to detect any potential signs and symptoms indicating that the child is sick (such as change in food/milk intake, crying, identification of dehydration, bleeding, oedema, jaundice, neck stiffness). They will also be trained to recognise symptoms and signs of AESI and meningitis and be instructed to measure body temperature systematically of all children. Any signs and symptoms detected during examination or in the past 48 hours preceding the visit will be recorded in the electronic case report form (eCRF). Children who are sick, have an acute condition or with disabilities will be referred to health facilities for further assessment and care that will be dispensed according to routine medical practice, including consultation, laboratory tests and treatment. Any child with fever ($\geq 37.5^{\circ}\text{C}$) and symptoms suggestive of malaria will be referred to the primary health care facility or hospital where diagnosis of malaria will be ensured using RDT and/or microscopy. Referral will be recorded in the eCRF.

At follow-up visits 1 and 3, and at study conclusion, the parent/LAR will be asked for any noticed or previously diagnosed abnormalities while checking for developmental milestone delays and presence of physical disability using the study specific guidance document (see [Annex 6](#)).

In the event of death occurring at home, the cause of death will be systematically obtained through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire [[INDEPTH](#), 2003] as is routinely done in the study area.

If a site is not part of the INDEPTH network, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

- **Reporting by primary health care facilities and hospitals**

Health care staff serving paediatric patients in all the primary health care facilities and hospitals in the study area will inform the study staff about any diseases, signs and symptoms among children enrolled in active surveillance, up to the home visit 2 years after the last dose of RTS,S/AS01E, or equal point in time for unvaccinated. Thereafter there will still be continuous reporting of hospitalisations until the child

reaches 5 years of age, or study end, whichever comes first. Children reporting a SAE due to study procedure might have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months.

To maximise the possibility of capturing an AESI, meningitis, or malaria, an active search will be performed by the study staff through hospital rounds and by regular (at least 3 times a week) review of patient records at primary health care facilities.

The eCRFs for the reporting of AESI, meningitis, or malaria will allow timely reporting of the first signs and symptoms detected by the community health workers and health care staff and completion of diagnostic information, as more results from examination in hospitals with specialised care become available. Clinicians in charge of the patients may seek consultation with RAFT study physicians for case confirmation. Data entry is described in Section 9.6.

The maximum intensity (mild, moderate, severe) of each AESI, and meningitis recorded in the eCRFs will be assigned to categories.

In case a child enrolled in the active surveillance is hospitalised at any time during the study, then procedures should be followed as for hospitalisations of the children enrolled in the enhanced hospitalisation surveillance (see Section 9.2.7.2).

9.2.7.1.3. Surveillance of other AE leading to hospitalisation during follow-up

The surveillance of other AE leading to hospitalisation will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.

9.2.7.1.4. Surveillance for death

The surveillance of death will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.

9.2.7.1.5. Study conclusion

Study participants will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit), a record will be taken of any vaccinations received and of the study participants' health and vital status and any disability.

The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

9.2.7.1.6. Outline of study procedures**Table 4 List of study procedures for participants in active surveillance**

Epoch	1											
Type of contact	Enrolment V0 ¹	At time of each routine vaccination	V1	V2	V3	V4	V5	V6	V7	V8	V9	Study conclusion V10 ²
Visit days			1W (5-10 D) after 1 st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2 nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3 rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4 th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4 th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first (±2 W)
Time point (Month) ³			M0	M1	M2	M3.5	M8	M20	M21.5	M32	M44	
Informed consent	•											
Cluster specification (exposed/unexposed)	•											
Check inclusion/exclusion criteria	•											
Assign study participant study number	•											
Provide study ID card and study-specific stickers	○											
Record socio- demographic characteristics and active participation in any trial with an investigational product	•											
Record administration of RTS,S/AS01E ⁴			•	•	•			•				

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Protocol Amendment 3 Final

Epoch	1											
Type of contact	Enrolment V0 ¹	At time of each routine vaccination	V1	V2	V3	V4	V5	V6	V7	V8	V9	Study conclusion V10 ²
Visit days			1W (5-10 D) after 1 st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2 nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3 rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4 th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4 th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first (±2 W)
Time point (Month) ³			M0	M1	M2	M3.5	M8	M20	M21.5	M32	M44	
Record any other vaccination ⁵			•	•	•	•	•	•	•	•	•	•
Record brief medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies)			•									
Record any outpatient visits and hospitalisations at all health care facilities			•	•	•	•	•	•	•	•	•	
Conduct physical examination including systematic measurement of body temperature			•	•	•	•	•	•	•	•	•	

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Epoch	1											
Type of contact	Enrolment V0 ¹	At time of each routine vaccination	V1	V2	V3	V4	V5	V6	V7	V8	V9	Study conclusion V10 ²
Visit days			1W (5-10 D) after 1 st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2 nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3 rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4 th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4 th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first (±2 W)
Time point (Month) ³			M0	M1	M2	M3.5	M8	M20	M21.5	M32	M44	
Record any detected signs and symptoms including AESI, other AE, leading to hospitalisation, meningitis, malaria, abscess at injection site, foot positional deformations			•	•	•	•	•	•	•	•	•	
Refer sick children and children with disabilities to outpatient clinic or hospital according to clinical diagnosis			•	•	•	•	•	•	•	•	•	
Record information about malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards			•	•	•	•	•	•	•	•	•	
Record any serious delay in developmental milestones or physical disability			•		•							•

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115056 (EPI-MALARIA-003 VS AME)
Protocol Amendment 3 Final

Epoch	1											
Type of contact	Enrolment V0 ¹	At time of each routine vaccination	V1	V2	V3	V4	V5	V6	V7	V8	V9	Study conclusion V10 ²
Visit days			1W (5-10 D) after 1 st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2 nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3 rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4 th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4 th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first (±2 W)
Time point (Month) ³			M0	M1	M2	M3.5	M8	M20	M21.5	M32	M44	
If death, record verbal autopsy diagnosis ⁶			●	●	●	●	●	●	●	●	●	●
Study conclusion												●

● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF)

○ is used to indicate a study procedure that does not require documentation in the eCRF

1. Enrolment for the DTP group will be done during a visit for administration of DTP/HepB/Hib vaccine – see [Figure 1](#) for definition of V0. Completion of Enrolment visit procedures should be achieved within a maximum of 10 days after the administration of DTP/HepB/Hib vaccine for the DTP group or at Visit 1 for the catch-up group.
2. A last visit will be conducted at study end or when the child reaches 5 years of age, whichever occurs first.
3. Study months may be adapted according to the schedule implemented at each study site.
4. To be administered via EPI system at EPI clinics and/or outreach registers (for children in the vaccinated group).
5. Standard immunisations will be recorded.
6. Using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home and through medical records for children who died at a health care facility. If a site is not part of the INDEPTH network, INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

Note: the enrolment to active surveillance was completed on 06 April 2021; instructions relating to enrolment and some of the visit instructions are no longer applicable.

9.2.7.2. Enhanced hospitalisation surveillance

For the purposes of this study, study participants from both exposed and unexposed clusters enrolled in enhanced hospitalisation surveillance will have data collected from hospitalisation visits.

[Table 5](#) provides detail on the procedures to be conducted for children enrolled in enhanced hospitalisation surveillance at or around the time of hospitalisation.

Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

Note: following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

9.2.7.2.1. Informed consent (for study participants not enrolled previously, i.e. for previous hospitalisation or for active surveillance)

Freely given and written or witnessed and thumbprinted informed consent must be obtained from each study participant's parent(s)/LAR(s), as appropriate, prior to participation in the study. Refer to [Section 10.1](#) for the requirements on how to obtain informed consent.

In case routine procedures are performed before the informed consent form (ICF) signature, collection of those data for the study CRF will be done retrospectively once the ICF is signed or witnessed and thumbprinted. No study specific procedures will be performed before the ICF is signed or witnessed and thumbprinted.

9.2.7.2.2. Check inclusion and exclusion criteria (for study participants not enrolled previously)

Check all applicable inclusion and exclusion criteria as described in [Sections 9.2.3](#) and [9.2.4](#) before enrolment.

9.2.7.2.3. Assign study participants study number (for study participants not enrolled previously)

Provide study ID cards and assign study participant study number and record in the eCRF for all newly enrolled study participants (for study participants already enrolled - previous hospitalisation or for active surveillance - the same study participant study number applies). A holder will be provided for carrying the study participant's ID card/study stickers together with other records e.g. child growth record, immunisation record to avoid double enrolment.

In the event that a <18 months old child eligible for active surveillance (DTP group) is first detected during hospitalisation before the active surveillance recruitment is

completed, parents/ LARs (according to local requirements) will be invited to enrol their child in active surveillance. If consenting, they will be provided with study-specific stickers and a follow-up visit will be scheduled for active surveillance in the DTP group (see Section 9.2.7.1). For all study participants enrolled into active surveillance, study-specific stickers with the study participant's study number should be used at health care facilities to identify any visit of the study participant in the facility register if no other system is in place.

9.2.7.2.4. *Collect demographic data (for study participants not enrolled previously)*

Record cluster specification (exposed/unexposed), socio-demographic data (e.g. date of birth and gender, the number and age of persons in the household), and active participation in any trial with an investigational product in the study participants' eCRF.

9.2.7.2.5. *Record type of health care facility*

Record type of health care facility.

9.2.7.2.6. *Record any serious delay in developmental milestones or physical disability (for study participants not enrolled previously and at study conclusion)*

Perform an assessment of developmental milestones and physical disabilities according to the study specific guidance document (see [Annex 6](#)).

9.2.7.2.7. *Health history*

Record medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies), and perform a physical examination. Ask the parent/LAR for any noticed or previously diagnosed abnormalities. Record any pre-existing conditions present in a study participant prior to the start of the study.

9.2.7.2.8. *Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards*

Record data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated). Record also information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals (see Section 9.3.3).

9.2.7.2.9. Record standard vaccinations

Record all immunisations received, including type and dates, in the eCRF. Update if needed with vaccinations received since the last visit. See also Section 9.3.3.1 for ascertainment of vaccine history.

9.2.7.2.10. Record diagnosis

Record main diagnosis and any secondary diagnoses made by the physicians in the eCRF.

9.2.7.2.11. Record haemoglobin measurement

For all hospitalised study participants, measurement of haemoglobin concentration, if available, at hospital entry will be recorded in the eCRF.

9.2.7.2.12. Record deaths

In the event of death occurring at the hospital, the cause of death from the medical record or the death certificate will be recorded in the eCRF.

9.2.7.2.13. Record cases of suspected AESI, other AE leading to hospitalisation, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations

For all suspected AESI or any meningitis case, details of risk factors, medication history and results of the clinical examination and diagnostic testing ([Annex 6](#)) will be recorded in the eCRF. A blood sample will be taken for storage for all AESIs and meningitis (see Section 9.2.7.3). For all cases suspected of meningitis or neurological AESIs, a part of the CSF sample, collected according to routine practice, will be stored for further confirmatory testing (see Section 9.2.7.3.1). Final diagnosis will be recorded in the eCRF.

Children diagnosed with meningitis, cerebral malaria or with an AESI will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

For all hospitalisations, details of risk factors, medication history and results of the clinical examination as well as the final diagnosis will be recorded in the eCRF.

For suspected malaria, malaria microscopy and/or RDT or other results, such as retinoscopy for cerebral malaria (refer to Section 9.2.7.3.1) will be recorded in the eCRF.

For foot positional deformations and abscess at injection site after vaccination, record in the eCRF.

9.2.7.2.14. Record and report adverse events

Refer to Section 11.2 for the time period for the investigator to record AEs. Refer to Section 11.3 for guidelines on how to record AEs via eCRF.

The study participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the study participants manifest any signs or symptoms they perceive as serious.

9.2.7.2.15. Study conclusion

Study participants will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit), a record will be taken of the study participant's health and vital status, any disabilities and all vaccinations received. The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

Note: For subjects enrolled in EHS, data collection of other AE leading to hospitalisation **was** stopped as from 01 **November 2022** in sites not participating in EPI-MAL-002. For those subjects, a study conclusion visit **was to** be conducted in a timely manner from 01 **November 2022**. For subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge. **Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop in sites not participating in EPI-MAL-002, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.**

9.2.7.2.16. Outline of study procedures

Table 5 List of study procedures to be conducted in the event of hospitalisation

Type of contact	Hospitalisation visit	Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) (±2 W)
Study participants not enrolled previously (either in active surveillance or in enhanced hospitalisation surveillance)		
Informed consent	•	
Cluster specification (exposed/unexposed)	•	
Check inclusion/exclusion criteria	•	
Assign study participant study number	•	
Provide study ID card (to all study participants not enrolled previously) and study-specific stickers (only to eligible study participants <18 months not enrolled previously in DTP group and enrolled before the active surveillance recruitment is terminated)	○	

Type of contact	Hospitalisation visit	Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) (±2 W)
Record socio-demographic characteristics and active participation in any trial with an investigational product	●	
All study participants		
Record type of health care facility	●	
Record brief medical history	●	
Record information about malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards	●	
Record any serious delay in developmental milestones or physical disability	● ⁴	●
Record all vaccinations ¹	●	●
Identify if specific signs and symptoms present (standard for AESI screening among all hospitalisations)	●	
Record diagnosis with major symptoms and test results	●	
Record measurement of haemoglobin concentration	●	
Record any cases of death and cause of death	●	●
Record risk factors	●	
Record medication history	●	
Confirm diagnoses at discharge	●	
Only for study participants with suspected AESI, cerebral malaria or meningitis		
Consult specialised health care professional, if required ²	○	
Record clinical examination and additional testing according to clinical diagnosis for suspected AESI ³ , cerebral malaria or meningitis	●	
For each diagnosis of an AESI ³ or meningitis, collect approx. 5 mL of whole blood and store serum	●	
For each diagnosis of a neurological AESI ³ or meningitis, where a CSF sample has been taken as part of routine practice, store part of the CSF sample (minimum 500 µL)	●	
Record and report AEs	●	
Follow-up children up to study conclusion, by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge	●	
Only for study participants with suspected malaria		
For suspected malaria, record malaria microscopy and/or RDT or other result	●	
Study conclusion		●

● is used to indicate a study procedure that requires documentation in the individual eCRF

○ is used to indicate a study procedure that does not require documentation in the eCRF

¹ Standard immunisations will be recorded.

² See Study Procedures Manual (SPM)

³ See [Annex 5](#)

⁴ For study participants not enrolled previously

*For subjects enrolled in EHS in sites not participating in EPI-MAL-002, a study conclusion visit **was** conducted in a timely manner from 01 **November 2022**.

9.2.7.3. Biological sample handling and analysis

9.2.7.3.1. *Biological samples*

All enrolled study participants admitted to the hospital are expected to have routine laboratory tests performed according to good medical practice and routine practice (see Section 9.2.7.6), including, but not limited, to:

- All hospitalised children: haemoglobin concentration or full blood count.
- Malaria suspects: access to diagnosis of malaria using RDT and/or microscopy (according to routine practice) will be ensured for all children clinically suspected of malaria during active surveillance and at any of the health care facilities.
- Meningitis suspects: CSF examination (and blood culture if feasible) according to routine practice (first line testing).
- Neurological diseases such as seizures, encephalitis, Acute Disseminated Encephalo-Myelitis (ADEM), Guillain-Barre syndrome suspects: require neurological investigations (e.g. magnetic resonance imaging if available), eventually CSF analysis and other laboratory testing according to routine practice.
- Some AESI (such as diabetes mellitus, renal failure, hepatic failure, severe thrombocytopenia with bleeding): require laboratory testing for case management.

For all hospitalised children suspected of having an AESI or meningitis, a sample of approximately 5 mL of whole blood will be collected; a sample of at least 500 µL of CSF would be ideally collected for all cases of a suspected neurological AESI (seizures, encephalitis, ADEM, Guillain-Barre syndrome suspected) or meningitis, when a CSF sample is taken as part of routine practice.

Full details for obtaining, storing and shipment of biological samples will be provided in the SPM.

Samples will not be labelled with information that directly identifies the study participants but will be coded with the identification number for the study participant (study participant number).

Collected samples will be used for protocol mandated research. In addition, these samples may be used to perform research related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all study participants in countries where this is allowed will be invited to give another specific consent to allow GSK or a contracted partner to use the samples for future research including development of tests and their quality assurance. Future research will be

subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing, in the context of the study, will be done in line with the consent of the individual study participant's parent(s)/LAR(s).

Refer also to the Investigator Agreement ([Annex 9](#)), that notes that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last study participant performed the last study visit/contact), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the study participants consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

9.2.7.3.2. Laboratory assays

Any biological sample evaluation will be limited to the scope of this study and only related to assessment of study endpoints; it could include, for example, serology or deoxyribonucleic acid polymerase chain reaction (PCR) for infectious diseases or confirmatory tests for autoimmune diseases.

For all required biological sample evaluations, details of assay type, assay method, test kit/manufacturer and laboratory used, as applicable for the test conducted, will be recorded.

The principal investigator or designee of each study site/cluster will ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents. In case second line confirmatory testing is required (for instance PCR for meningitis or antibody testing for auto-immune AESI), samples will be sent to a qualified referral second line laboratory in South Africa (Clinical Laboratory Services [CLS]).

9.2.7.4. Case ascertainment

For the purpose of this study, a panel of experts **was** set up and a charter defined. As much as possible, the same experts will be involved in the case ascertainment process for studies EPI-MAL-002 and EPI-MAL-003, using the same rules and charter.

9.2.7.4.1. Meningitis casesMeningitis case identification

At the site level, a suspected meningitis case, based on clinical symptoms and/or signs is defined as [adapted from [WHO](#), 2003]:

- A child with sudden onset of fever ($> 38.0^{\circ}\text{C}$ rectal or 37.5°C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

Meningitis case characterisation

Further characterisation of a suspected meningitis case will imply performing a lumbar puncture for examination of CSF (and blood culture if feasible) and etiological (bacterial, viral, protozoal or fungal) search with a two-step laboratory approach.

Lumbar puncture will be performed according to routine medical practice. The diagnosis of bacterial meningitis will first be made on site, based on CSF macroscopic and microscopic examinations and blood culture if feasible (first line laboratory results). CSF tests will include selective culture for *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza* type b; latex agglutination tests for detection of bacterial antigens (*Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza* type b), Gram stain, white blood cell counts and cell differentiation and biochemistry testing (protein and glucose). Cryptococcal infection will be diagnosed using Indian ink, for HIV-positive children and those with unknown HIV-status, if feasible.

In addition, an external laboratory based in South Africa (CLS) is contracted to harmonize laboratory procedures, to provide Quality Assessment and Quality Control and to train laboratory technicians in all sites. If needed, in case of stock out, GSK will assess the need of supplementing reagents and consumables.

Based on these first examinations, the diagnosis of bacterial meningitis will be made by the physicians in charge of the children, with support from RAFT upon request from the investigators. Job Aids for medical staff and training on standardised diagnosis are put in place as in EPI-MAL-002 to improve the sensitivity and specificity of the case diagnosis for all meningitis. Decisions to start treatment of children with suspected meningitis will be based on the medical routine practice and should not be delayed by the second line laboratory investigations.

All collected CSF samples, regardless of first line testing outcome, will be shipped to a referral second line laboratory based in South Africa, CLS (unique for all sites) for identification of bacterial, viral, protozoal and fungal meningitis using molecular testing such as PCR.

Final meningitis case ascertainment

A specific subgroup of two experts will perform case ascertainment following strictly the definitions for meningitis as described in Section [9.2.6.4](#); the definition of aetiology-

confirmed meningitis being highly specific. Two experts will independently review all the cases. The experts will be blinded with regards to RTS,S vaccine exposure as much as possible. They will use all available medical information (including the first line and second line laboratory results) and classify the meningitis cases according to the case definitions (see Section 9.2.6.4). They will also be provided with all the data available in the eCRF (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records). If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

In parallel, monitoring trends over time of meningitis cases identified at site level (first line laboratory) will be done, and if GSK, with the support from the investigators, considers that the number of meningitis cases in vaccinated children is above the expected number (see Section 9.7.6.2.2), authorities will be informed as appropriate. The external panel of experts will be convened to assess the cases (using WHO methodology for case assessment [WHO, 2013]). This might trigger additional investigation on the potential association between use of the vaccine and onset of meningitis cases using methodology such as case control or self-controlled case series (SCCS). Final decision for further investigation will be also discussed with the local authorities, taking into account any additional surveillance data collected in the countries at the same period.

This section might be adapted according to the preliminary findings for EPI-MAL-002.

9.2.7.4.2. AESI

A panel of experts in the different fields **was** established and assessed whether the aetiology of the AESI is confirmed or not and whether the date of first symptoms of the disease falls within the risk period. For events (i.e. onset of the AESI) captured during active surveillance of vaccinated children, the observation period is defined as 1 year after the last dose of RTS,S/AS01_E. For events occurring in children enrolled only through enhanced hospitalisation surveillance or in unvaccinated children enrolled in active surveillance, the observation period will be defined as 1 year after the administration of last known dose of any vaccine.

The panel of experts will perform case ascertainment of AESI with an uncertain diagnosis and outcome after review by the GSK safety physician. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. The same procedures will be followed as for meningitis. Two experts will independently review the cases. The experts will be blinded with regards to RTS,S vaccine exposure as much as possible. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.1). Anonymized copies of the medical records including laboratory results might be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions

of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

9.2.7.4.3. Death

Death with an uncertain diagnosis after review by the GSK safety physician will be reviewed by the external panel of experts. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. Two selected experts will independently review and confirm the possible cause of death. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases according to the cause of death. Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

9.2.7.4.4. Other AE leading to hospitalization

Other AE leading to hospitalisation or with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts as described in Section [9.2.7.4.3](#).

9.2.7.4.5. Malaria

Enrolled children presenting at health facilities (outpatient and inpatient) with signs and symptoms of malaria will receive malaria testing (RDT and/or microscopy) as part of standard care in the country (see Section [9.2.7.6](#)). As part of good medical practice, the clinical staff will ensure that all study participants diagnosed with malaria will receive adequate care following national guidelines.

GSK will consider the following definition for cerebral malaria cases: severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age), and, if malaria with seizure: coma persisting for > 30 min after the seizure (see Section [9.2.6.6](#) [[WHO, 2015\(b\)](#)]). It should be noted that these coma scores are not specific for malaria and other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis) should be excluded. Therefore, each severe malaria case will be reviewed by GSK medical staff according to standard procedure for signal detection. In addition, a panel of experts will perform case ascertainment. The same procedures will be followed as for meningitis and AESI. Two selected experts will independently review all cerebral malaria cases and severe malaria cases with an uncertain diagnosis and outcome after review by the GSK safety physician. These last cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external experts' review. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section [9.2.6.6](#)).

Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

9.2.7.5. Management of AESI, other AE leading to hospitalisation, meningitis cases, malaria, abscess at injection site and foot positional deformations

Children showing defined signs and symptoms during a follow-up visit will be referred to a health care facility for further assessment if in need of investigation and care.

Children diagnosed with an AESI, meningitis or cerebral malaria will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

Case management will be performed as in EPI-MAL-002. This section might be adapted according to experiences gained during EPI-MAL-002.

9.2.7.6. Package for standard of care

Any child participating in active surveillance presenting at primary health care level should have access to basic care that can be dispensed at this level, including:

- Consultation, essential medicines, RDT and any laboratory test available, if needed for diagnosis.
- Treatment for common diseases including malaria.

At the hospital level, any child enrolled in the study should have access to care and treatment as available, including:

- Admission and emergency care, diagnostic testing including laboratory and radiological examinations, treatment and care until discharge.
- For protocol-defined AESI and meningitis: diagnostic testing according to the algorithms (see medical Job Aid) and treatment required until the end of the study.

9.2.7.7. Capacity building

Capacity building from the sites **that conducted** EPI-MAL-002 **which** also participated in EPI-MAL-003 **was** utilized to strengthen early case finding and diagnosis of the events of interest. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building **was** provided before **the** start of EPI-MAL-003 and throughout the study.

- Training

The Agence de Médecine Préventive [AMP] will provide intensive training for the study staff, community health workers and health care professionals working at all health care facilities in the study area on diagnosis of AESI, and meningitis, and on

pharmacovigilance. Appropriate training packages and educational material will be developed. The community health workers involved in active surveillance will be trained to recognize clinical symptoms, using simplified visual aids (non-medical Job Aid). Health care professionals will be trained using medical Job Aid, developed to facilitate diagnosis using decision-making algorithms.

In addition, all sites will have access to online continued medical education, training packages (including training on AESI, meningitis, HIV and hemoglobinopathies) and a telemedicine system established by the Réseau en Afrique Francophone pour la Télémédecine [RAFT, Geneva]. The latter will allow the investigators to discuss cases with their colleagues and with medical experts.

In EPI-MAL-002, health care (including EPI staff) and study staff **were** trained in pharmacovigilance procedures. This training will also be provided to any new health care and study staff hired during the course of that study or for study EPI-MAL-003 using the same materials.

- Laboratory support

GSK will support the first line laboratory testing. First, an external laboratory, CLS, is contracted to assess laboratory quality system and as needed, will provide technical assistance in quality systems as well as laboratory training and support/coaching. Second, the principal investigator or designee of each study site/cluster is requested to ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents such as lumbar puncture kits or malaria RDT for diagnosis of meningitis and malaria, respectively.

CLS will perform PCR and serology testing on CSF and serum samples in order to complement the diagnosis done by the first line laboratory.

9.2.8. Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Active safety follow-up through home visits may be replaced by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.
- For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact.
- The study conclusion home visit may be replaced by a telephone call or other means of virtual contact.
- A retrospective data collection of medical events based on medical records may be implemented at any of the health care facilities.

Note: Certain restrictions might make it impossible for parents/LARs to provide written consent for changes in study procedures during special circumstances. Parents/LARs of subjects already enrolled will provide consent verbally.

9.3. Variables

Safety and effectiveness/impact endpoints are aligned in EPI-MAL-002 and EPI-MAL-003.

9.3.1. Co-primary endpoints

In children included in active or enhanced hospitalisation surveillance:

- Occurrence of AESI (see Section 9.2.6.1 for definition).
- Occurrence of aetiology-confirmed meningitis (see Section 9.2.6.4 for case definition).

9.3.2. Secondary endpoints

9.3.2.1. Safety endpoints

In children included in active or enhanced hospitalisation surveillance*:

- Occurrence of probable meningitis (final classification) (see Section 9.2.6.4 for case definition).
- Occurrence of clinically suspected meningitis (final classification) (see Section 9.2.6.4 for case definition).
- Occurrence of meningitis cases identified at site level (first line laboratory) (see Section 9.2.6.4 for case definition).
- Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- Occurrence of hospitalisation (including those attributed to an AESI, meningitis or malaria)*.
- Occurrence of febrile convulsions during **the 3-day period (Days 0-3) and** 7-day period (Days 0-6) following each dose of RTS,S/AS01_E (see Section 9.2.6.5 for case definition)*.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation (see Section 9.2.6.10 for case definitions)*.
- Occurrence of other AE leading to hospitalisation (see section 9.2.6.3 and section 9.2.6.9 for definitions)*.

****Occurrence of hospitalisation, other AE leading to hospitalisation, febrile convulsions and quality indicators will only be conducted for the Interim Analysis and not for the Final Analysis.***

9.3.2.2. Effectiveness and impact endpoints

In children included in active surveillance:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
 - Any malaria (including *P. falciparum* malaria) (see Section 9.2.6.6 for case definitions);
 - Severe malaria (including *P. falciparum* malaria) (see Section 9.2.6.6 for case definitions);
 - Cerebral malaria (see Section 9.2.6.6 for case definitions).
- Occurrence of anaemia at hospital entry among hospitalised children (see Section 9.2.6.7 for case definition).
- Occurrence of hospitalisation*
 - All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria (see Section 9.2.6.8 for case definition).
- Occurrence of death
 - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death) (see Section 9.2.6.9 for case definition).

****Occurrence of all-cause hospitalisation will only be conducted for the Interim Analysis and not for the Final Analysis.***

9.3.3. Patient characteristics and potential confounding variables**9.3.3.1. Recorded in EPI-MAL-002 and EPI-MAL-003**

For all enrolled study participants, socio-demographic characteristics, data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated) will be recorded in the eCRF. Information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals will be recorded. Data on vaccination, more specifically dates and doses of RTS,S/AS01_E and EPI vaccine administration, as well as data on medical history including co-morbidities (e.g. chronic diseases, such as known HIV infection), or diagnosed congenital diseases, such as known hemoglobinopathies, will also be collected. In case of hospitalisation, type of health care facility will be collected.

For children enrolled in enhanced hospitalisation surveillance or hospitalised children in active surveillance, additional information on co-morbidities will be captured such as

malnutrition, chronic disease or diagnosed congenital disease, known HIV infection, known hemoglobinopathies.

Of note, the vaccine history will be ascertained for all enrolled study participants through the following channels: individual vaccination cards, vaccination registers at the health care facilities and vaccination data collected during study area census rounds. If any of the sources described here above confirm vaccination, it will be assumed that vaccination has taken place for the analysis.

9.3.3.2. Recorded in EPI-MAL-005

Malaria transmission intensity (MTI) data will be collected through EPI-MAL-005 (see Section 9.4.4 for more detail). Rainfall and humidity, where available, will be collected at the study area level. Bednet use, seasonal malaria chemoprevention and other malaria control measures will also be collected at the study site population and individual levels (which will be summarized at centre level).

The *P. falciparum* parasite prevalence will be measured as a way to characterise the MTI. The *P. falciparum* parasite prevalence will be computed as the proportion of study participants infected with *P. falciparum* parasitaemia divided by the total number of study participants tested, and will be estimated through annual cross sectional surveys (study start, every 12 months, and study end) during malaria peak transmission, in study participants at least 6 months and less than 10 years of age at the time of survey. These estimates will be calculated for each year and for each site separately.

Considering that the main reservoir of malaria is in the population between 5-20 years old (based on data collected in study EPI-MAL-001 parallel to the pivotal efficacy Phase III trial) and that MTI will be assessed directly following the introduction of the vaccine, it is assumed that there will be negligible herd immunity effect as a small proportion of the study participants will be vaccinated.

Moreover, the parasite prevalence will also be estimated in two different subgroups of the total cohort of the EPI-MAL-005. These two subgroups will consider only vaccine eligible study participants and only vaccine ineligible study participants, respectively. The vaccine ineligible study participants are defined as those study participants that on the basis of age would be ineligible for RTS,S/AS01_E vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the recommendation for RTS,S/AS01_E vaccination in the country.

Therefore, the year- and centre- specific MTIs computed on this vaccine ineligible subgroup (control group) will be included as covariates in the model of the study EPI-MAL-003 to assess annual fluctuations and/or changes due to other malaria control intervention. Note that if there is any herd effect, then the vaccine effect estimated in the EPI-MAL-003 adjusted for annual fluctuation would be an underestimation of the true vaccine effect.

9.4. Data sources

9.4.1. HDSS (or equivalent surveillance system) databases

Each site maintains a demographic database which is updated on a regular basis to include births, deaths, immigrations and emigrations. Data regarding vaccinations may also be included in the study site database. This information is obtained through census rounds (at least once a year) and constantly updated in between the rounds with the help of key-informants living in the community. Cause of deaths is established by trained fieldworkers using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home. From this database, the listing of children at the beginning of the study provided the study site with a basis for recruitment of children <18 months old for active surveillance and for the total number of children < 5 years of age recorded at least once a year during the study duration. During the study, further newborns may *have been* identified by one of several possible mechanisms (depending on the site): by subsequent HDSS or equivalent surveillance system updates, by existing community-based informers who report new births/deaths/other events to the study sites between censuses, at the time of first EPI vaccination (e.g. BCG vaccination or first DTP/HepB/Hib vaccination), or at birth (if born at a health care facility).

If a site is not part of the INDEPTH network, the INDEPTH procedures for demographic census and for verbal autopsy might be implemented to ensure consistency across study sites.

9.4.2. Active surveillance and enhanced hospitalisation surveillance

Note: the enrolment to active surveillance was completed on 06 April 2021; the below instructions for screening and enrolment of study participants are no longer applicable.

Study participants enrolled in active surveillance will have data collected during home visits, outpatient visits and hospitalisations at all health care facilities, while study participants enrolled in enhanced hospitalisation surveillance will have data collected during hospitalisation only (see also study procedures in Section 9.2.7).

The first level of screening will be done at the community level during follow-up visits by study community health workers who will be trained to recognise signs and symptoms of AESI and meningitis. Any study participants presenting with specific signs or symptoms, as described by the Job Aid tool, will be referred to the health care facility (usually primary health care facility) where the public health care staff will perform clinical assessment according to routine practice. If a suspected AESI, meningitis or severe malaria case including cerebral malaria is detected at the primary health care facility level, the study participant will be referred to a higher level health care facility (hospital) to confirm the diagnosis based on the highest level of diagnostic certainty available (see Annex 5). If another event is detected at the primary health care facility level, the study participant might be referred to a higher level health care facility according to the routine practice. In the case of a seriously sick child, this child will be referred directly to the hospital by the community health worker.

Training on AESI and meningitis diagnosis, HIV and hemoglobinopathies will be provided and support will be available from specialised health care professionals to confirm diagnosis (see Section 9.2.7.7).

The surveillance system will also be implemented in the study area at each health care level. Health care workers will record all outpatient visits (referral and non-referral) of study participants enrolled in the active surveillance up to the end of the active follow-up on a register allowing for the collection of basic data (e.g. date of visit, clinical diagnoses and rapid testing confirmation, referral or treatment). In case appropriate registers are not available in the facilities, study registers will be developed. At enrolment, study participants participating in active surveillance will be given study specific stickers with the study participant's study number. The stickers can be used on the health care facility's registers if no other system is in place to indicate a study participant's visit and facilitate identification of data from enrolled study participants from the facility's register. The recorded data will be collected retrospectively on a regular basis and encoded in the eCRF.

Every day study staff will perform a round at hospitals and other health care facilities (with hospitalisation facility) to see all newly hospitalised children that could be eligible for the study. Parents/LARs of eligible children not yet enrolled into the study should be asked if they would agree to their child's participation and signed or witnessed and thumbprinted informed consent shall be obtained.

The monthly total number of children < 5 years of age requiring hospitalisation (see Section 9.2.6.8) will be recorded in the logbook monthly for the study duration, for the purpose of the aggregated data analysis.

All enrolled hospitalised children will have their diagnosis recorded with main symptoms and results from routinely performed confirmatory tests. In the case of AESI and meningitis, additional information should be recorded according to clinical and laboratory standard of diagnosis (see Annex 5). Study staff will complete the eCRF containing all relevant information for each enrolled study participant, to include an International Classification of Diseases (ICD) code allocated by a physician. All enrolled hospitalised study participants diagnosed with suspected AESI or meningitis will have a sample of approximately 5 mL of whole blood taken; in the case of neurological AESI or meningitis requiring a CSF sample according to routine practice, where possible, an additional aliquot will be reserved. Admitted study participants are expected to receive care by hospital staff following National guidance. As part of good medical practice, the clinical staff will ensure that sick study participants admitted to hospital will receive adequate care provided by health care facilities (see Section 9.2.7.6).

AESI, other AE leading to hospitalisation meningitis, or malaria will be recorded in the eCRF. Data entry is described in Section 9.6.

The investigator will assess the maximum intensity (mild, moderate, severe) that occurred over the duration of the event for all AESI, other AE leading to hospitalisation or meningitis reported during the study. The assessment will be based on the investigator's clinical judgement.

9.4.3. Baseline study EPI-MAL-002

The study EPI-MAL-002 **was** designed to estimate baseline incidence rates of AESI, other AE leading to hospitalisations, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality prior to introduction of RTS,S/AS01_E. It also served as the platform for capacity building for EPI-MAL-003, with the overall goal to increase the sensitivity and specificity of capturing rare safety events post vaccination.

9.4.4. Malaria transmission intensity study EPI-MAL-005

Annual fluctuations in malaria incidence occur as a result of changes in transmission intensity, which may be caused by changes in environmental factors such as rainfall or changes in usage of other malaria control interventions (use of bednets for example). Therefore, by taking into account these variations in MTI and malaria control intervention coverage, more accurate estimations of the vaccine impact on malaria disease diagnosed by RDT and/or microscopy during EPI-MAL-003 will be possible. Those estimations will be used as covariates in the models, as described in Sections 9.7.7.2 and 9.7.7.3.

EPI-MAL-005 started in Q4 2014, is **being conducted** to run in parallel with EPI-MAL-002 and EPI-MAL-003, in similar if not identical settings, and will assess the following parameters: prevalence of *P. falciparum* parasitaemia, use of malaria control interventions at community level, changes in environmental factors such as rainfall, changes in health care seeking behaviour, within-site geographical heterogeneity in MTI and individual malaria prevention measures and risk factors for malaria. Compliance with DTP-based, measles and RTS,S/AS01_E vaccines will also be collected.

It may happen that study participants enrolled in EPI-MAL-003 are also enrolled in EPI-MAL-005. Cases of malaria detected only during the annual home visits planned for EPI-MAL-005 will not be included in the analysis of EPI-MAL-003. However, if the cases of malaria are detected during an EPI-MAL-005 home visit that coincides with a home visit scheduled in EPI-MAL-003, the events will be captured in EPI-MAL-003.

9.5. Study size

The study **targeted** enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children **were** estimated to be enrolled in active surveillance, assuming that the distribution according to the administration of RTS,S/AS01_E in the exposed clusters **would** be the following:

- 10% without any dose, corresponding to 2,250 unvaccinated children (in the exposed clusters);
- 10% with an incomplete primary schedule (i.e. 1 or 2 doses), corresponding to 2,250 partially vaccinated children;

- 80% with the full primary schedule (i.e. 3 doses), corresponding to 18,000 vaccinated children. Among those children, two scenarios **were** considered with regards to the uptake of the 4th dose of RTS,S/AS01_E: either 50% (i.e. 9,000 children), or 75% (i.e. 13,500 children).

Note that the size of each exposed/unexposed cluster **was** assumed to be around 4,000 children, leading to a total of less than 20 clusters (12 clusters **were** planned). As no reference values of the Intra-Cluster Correlation (ICC) for AESI, meningitis or malaria are currently available in the literature, simulations have been performed in order to estimate over dispersion in the Poisson regression model. Based on these estimations, an over dispersion of 2 is assumed for the cluster design comparison estimations.

Based on these assumptions, power estimations are presented for the main objectives in the following sections.

9.5.1. Sample size for co-primary objectives

The study size for the co-primary objectives is done for the exposed clusters in order to give precision of the incidence of the endpoints where the vaccination will take place.

Among children enrolled in the active surveillance, 20,250 children are assumed to be vaccinated (at least partially).

The co-primary objectives will estimate the incidence of AESI, and meningitis. The precision of the estimate is related to the incidence and the period at-risk of these events following any dose, with a censoring of the follow-up time when the study participant receives the next dose. For some of the AESI the incidence could be very rare (around 1/100,000 person-years [PY]) and the period at-risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis.

[Table 6](#) provides an estimation of the 95% CIs based on:

- A sample of 20,250 children (2,250 partially vaccinated, and 18,000 vaccinated),
- Different numbers of detected events (for the less frequent events),
- Different risk periods following dose administration (with censoring to one month for the two first doses),
- A follow-up corresponding to the risk period after dose 4,
- A schedule with 50% of the vaccinated children receiving the 4th dose of RTS,S/AS01_E, or with 75% receiving the 4th dose of RTS,S/AS01_E (4 doses).

For example, the 95% CI around the observed incidence of 15.5 per 100,000 PY (1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], with 50% of the study participants receiving the 4th dose of RTS,S/AS01_E) will be [0.4, 86.1]. Other assumptions are displayed in [Table 6](#) (rounded to 20,250 study participants).

Table 6 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events following dose administration based on 20,250 study participants, different numbers of detected events, different risk periods and two scenarios for the 4th dose uptake of RTS,S/AS01_E

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
50% of the children with primary schedule received a 4th dose (in vaccinated clusters)					
1	2 weeks	2552.88	39.2	1.0	218.2
1	6 weeks	6468.75	15.5	0.4	86.1
1	3 months	10406.25	9.6	0.2	53.5
1	6 months	17718.75	5.6	0.1	31.4
1	12 months	32343.75	3.1	0.1	17.2
3	2 weeks	2552.88	117.5	24.2	343.4
3	6 weeks	6468.75	46.4	9.6	135.5
3	3 months	10406.25	28.8	5.9	84.3
3	6 months	17718.75	16.9	3.5	49.5
3	12 months	32343.75	9.3	1.9	27.1
5	2 weeks	2552.88	195.9	63.6	457.1
5	6 weeks	6468.75	77.3	25.1	180.4
5	3 months	10406.25	48.0	15.6	112.1
5	6 months	17718.75	28.2	9.2	65.9
5	12 months	32343.75	15.5	5.0	36.1
75% of the children with primary schedule received a 4th dose (in vaccinated clusters)					
1	2 weeks	2725.96	36.7	0.9	204.4
1	6 weeks	6987.98	14.3	0.4	79.7
1	3 months	11531.25	8.7	0.2	48.3
1	6 months	19968.75	5.0	0.1	27.9
1	12 months	36843.75	2.7	0.1	15.1
3	2 weeks	2725.96	110.1	22.7	321.6
3	6 weeks	6987.98	42.9	8.9	125.5
3	3 months	11531.25	26.0	5.4	76.0
3	6 months	19968.75	15.0	3.1	43.9
3	12 months	36843.75	8.1	1.7	23.8
5	2 weeks	2725.96	183.4	59.6	428.0
5	6 weeks	6987.98	71.6	23.2	167.0
5	3 months	11531.25	43.4	14.1	101.2
5	6 months	19968.75	25.0	8.1	58.4
5	12 months	36843.75	13.6	4.4	31.7

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990]

A sample size of 20,250 study participants was used for this table.

The follow-up per study participant is computed assuming previously mentioned distribution of the administration of RTS,S/AS01_E, with one-month of interval between the first three doses, which limits the follow-up of dose 1 and dose 2 when the risk period is higher than 1 month.

In addition, these incidences will be estimated, using the data collected for both active and enhanced hospitalisation surveillances, for all children less than 5 years of age during the study. Table 7 provides an estimation of the 95% CIs for the surveillances for all children less than 5 years of age based on:

- A birth cohort of 11,500 children (corresponding to the assumed birth cohort either of the exposed clusters or the unexposed clusters);

- A follow-up of 2 years (as expected to be in the EPI-MAL-002), and 5.2 years (see Section 9.2.5 for the details of study period approximated to be 62 months);
- Different numbers of detected events (for the less frequent events and chosen to estimate similar incidences with two assumed follow-ups).

For example, the 95% CI around the observed incidence of 21.7 per 100,000 PY (25 events detected) will be [14.1, 32.1] for a follow-up of 2 years and respectively the 95% CI around the observed incidence of 23.9 per 100,000 PY (71 events detected) will be [18.7, 30.1] for a follow-up 5.2 years. Other assumptions are displayed in Table 7.

Table 7 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events among all children less than 5 years of age based on 11,500 birth cohort, and different numbers of detected events

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in all children < 5 years during a follow-up of 2 years					
1	2 years	115000	0.9	0.0	4.8
5	2 years	115000	4.3	1.4	10.1
25	2 years	115000	21.7	14.1	32.1
50	2 years	115000	43.5	32.3	57.3
Events in all children < 5 years during a follow-up of 5.2 years					
2	5.2 years	297083	0.7	0.1	2.4
14	5.2 years	297083	4.7	2.6	7.9
71	5.2 years	297083	23.9	18.7	30.1
141	5.2 years	297083	47.5	40.0	56.0

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990]

9.5.2. Sample size for meningitis monitoring

The study size for the monitoring of meningitis cases is only for the exposed clusters as the monitoring will use the background incidence estimated from the EPI-MAL-002 study.

The potential risk of meningitis observed in MALARIA-055 will be further monitored using MaxSPRT method [Kulldorff, 2011].

Table 8 below provides the average accrued number of cases needed to reject H_0 (i.e. no increase in the risk of meningitis after introduction of the RTS,S/AS01_E vaccine) for different upper limits T (see Section 9.7.9.2) and for different true RRs when $\alpha = 0.05$.

Table 8 **Average length of surveillance* and power for the Poisson-based MaxSPRT [Kulldorff, 2011] for different true relative risks when alpha = 0.05**

True RR	Average number of cases to reject H ₀					Power (%)				
	1.5	2	3	5	8	1.5	2	3	5	8
T = 8	4.80	6.70	6.89	4.29	3.05	24.60%	60.16%	97.00%	100.00%	100.00%
T = 10	6.08	8.29	7.43	4.37	3.10	28.16%	68.78%	99.06%	100.00%	100.00%
T = 12	7.48	9.66	7.67	4.43	3.14	31.60%	75.60%	99.66%	100.00%	100.00%

T is the expected number of meningitis cases under the null hypothesis; RR is the true relative risk

* The average length of surveillance is defined not in terms of set time period, but the time to record a certain number of meningitis cases.

With T = 10 (estimated as the cumulative number of meningitis cases based on EPI-MAL-002 background incidence, EPI-MAL-003 cohort size and period of follow-up of 1 year following dose 3), a true RR = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters. Note that the total follow-up at the end of the study will be longer which increases the power.

9.5.3. Sample size to estimate the risk associated with the vaccination

9.5.3.1. Before-after design

The RR (for AESI, meningitis and cerebral malaria) by comparing the partially or fully vaccinated children of the EPI-MAL-003 exposed clusters versus the children of the EPI-MAL-002 (same age group and same country [site]) that would be detected with 80% power and two-sided alpha = 5% (without multiplicity adjustment and without adjustment for covariates) is given in [Table 9](#) for different values of the baseline incidences (in PY), and the RR for mortality overall and by gender is given in [Table 10](#).

Table 9 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	10827.6	64.2	19.2	3.9
6 weeks	329.8	13.7	6.5	2.4
3 months	91.9	7.8	4.3	2.0
6 months	31.4	4.8	3.1	1.7
12 months	12.8	3.2	2.3	1.5
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	9721.6	61.2	18.6	3.8
6 weeks	302.2	13.1	6.3	2.3
3 months	84.1	7.5	4.2	1.9
6 months	29.0	4.6	3.0	1.7
12 months	12.0	3.1	2.3	1.5

* This incidence corresponds to the assumption considered for meningitis

** This incidence corresponds to the assumptions considered for cerebral malaria

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]

Period at-risk	Baseline incidence 1000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	2.63	3.87
6 weeks	1.85	2.36
3 months	1.62	1.97
6 months	1.45	1.68
12 months	1.32	1.47
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	2.60	3.80
6 weeks	1.83	2.33
3 months	1.60	1.93
6 months	1.43	1.66
12 months	1.30	1.45

9.5.3.2. Cluster design

In the same way, the RR (for AESI, meningitis and cerebral malaria) by comparing the partially or fully vaccinated children of the EPI-MAL-003 exposed clusters versus the

children from the EPI-MAL-003 unexposed clusters that would be detected with 80% power, an over dispersion (coefficient of 2) and two-sided alpha = 5% (without multiplicity adjustment and without adjustment for covariates) is given in [Table 11](#) for different values of the baseline incidences (in PY), and the RR for mortality overall and by gender is given in [Table 12](#).

Table 11 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	10479.2	63.4	19.1	3.9
6 weeks	325.5	13.7	6.5	2.4
3 months	91.4	7.8	4.4	2.0
6 months	31.4	4.9	3.1	1.7
12 months	12.9	3.3	2.3	1.5
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	9141.4	59.6	18.3	3.8
6 weeks	295.0	13.1	6.3	2.3
3 months	82.5	7.4	4.2	1.9
6 months	28.6	4.6	3.0	1.7
12 months	12.0	3.1	2.3	1.5

* This incidence corresponds to the assumption considered for meningitis

** This incidence corresponds to the assumptions considered for cerebral malaria

Table 12 Detectable relative risk for mortality overall and by gender with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]

Period at-risk	Baseline incidence 13000/100000 PY - 80% power	
	Overall	Per gender
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	2.65	3.88
6 weeks	1.86	2.37
3 months	1.63	1.98
6 months	1.45	1.69
12 months	1.32	1.48
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	2.60	3.80
6 weeks	1.83	2.33
3 months	1.61	1.94
6 months	1.44	1.66
12 months	1.31	1.46

9.5.4. Sample size for the effectiveness and impact on severe malaria

For the objective to estimate the effectiveness and impact of the RTS,S/AS01_E vaccine on episodes of severe malaria (including *P. falciparum* malaria) diagnosed by RDT and/or microscopy, the following baseline assumptions were used for the sample size calculations:

- Alpha: 5%

- Baseline incidence rate of severe malaria: 0.03 episode per PY for moderate endemicity; 0.05/PY for high endemicity. Over all study sites (the two levels of endemicity are covered by the sites selected), the incidence of 0.03 episode per PY is considered to take the conservative approach. The study EPI-MAL-005 will provide us with the endemicity at the time of the enrolment.
- 22,500 children in the exposed clusters with assumptions around the distribution according the administration of RTS,S/AS01_E as detailed at the beginning of Section 9.5.
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01_E.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters.
- An over dispersion (coefficient of 2).

Effectiveness (direct effect) and impact (indirect, total and overall effects) will be measured, meaning that reference and comparison groups will not include the same cohort of children depending on the analyses.

The effect which can be detected with 80% of power using the Poisson regression method [PASS, 2005], considering the study site as a covariate to adjust for the various endemicity (assumed to include a correlation equal to 0.20) has been estimated for the total and direct effects.

9.5.4.1. Effectiveness (direct effect)

The direct effect is based on the following groups:

- Reference group: Unvaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 unvaccinated children from the exposed clusters);
- Comparison group: Vaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 vaccinated children from the exposed clusters).

Table 13 presents the direct effect which could be detected with 80% of power, going from 23% to 33% for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

Table 13 Detectable direct effect for severe malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

	Severe Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	31%	33%	38%
D3-> D4+1Y (50%)	0.03		22%	24%	27%
D3-> D4+1Y (75%)	0.03		21%	23%	26%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.4.2. Impact using the before-after design

The total effect for the before-after design is based on the following groups:

- Reference group: Unvaccinated children from the “Before” active surveillance (i.e. EPI-MAL-002), same age group and same country (site);
- Comparison group: Vaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 exposed clusters).

Of note, sample size for impact of vaccination is estimated for the total effect, but analysis will be done also for indirect and overall effects.

Table 14 presents the total effect which could be detected with 80% of power, going from 16% to 23% for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

Table 14 Detectable total effect for severe malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]

	Severe Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	21%	23%	26%
D3-> D4+1Y (50%)	0.03		16%	18%	21%
D3-> D4+1Y (75%)	0.03		15%	16%	18%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.4.3. Impact using the cluster design

The total effect for the cluster design is based on the following groups:

- Reference group: Unvaccinated children from the unexposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 unexposed clusters);
- Comparison group: Vaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 vaccinated children from the exposed clusters).

Table 15 presents the total effect for the cluster design which could be detected with 80% of power, going from 16% to 23% for a correlation equal to 0.20, and depending on the scenario.

Table 15 Detectable total effect for severe malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

	Severe Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	21%	23%	26%
D3-> D4+1Y (50%)	0.03		17%	19%	21%
D3-> D4+1Y (75%)	0.03		15%	16%	19%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.5. Sample size for the effectiveness and impact on cerebral malaria

The following baseline assumptions were used for the sample size calculations in order to estimate the RR of the RTS,S/AS01_E vaccine on cerebral malaria:

- Alpha: 5%;
- Baseline incidence rate of cerebral malaria: 0.005 episode per PY;
- 22,500 children in the exposed clusters;
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01_E.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters.

- An over dispersion (coefficient of 2).

As done for severe malaria in Section 9.5.4, direct effect and indirect, total and overall effects will be measured and Poisson regression method [PASS, 2005] was used to estimate the RR which can be detected with 80% of power for the total and the direct effects.

9.5.5.1. Effectiveness (direct effect)

Table 16 presents the direct effect which could be detected with 80% of power, going from 1.88 to 2.66 for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

Table 16 Detectable direct effect in terms of relative risk for cerebral malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

	Cerebral Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	2.40	2.66	3.10
D3-> D4+1Y (50%)	0.005		1.79	1.92	2.12
D3-> D4+1Y (75%)	0.005		1.76	1.88	2.07

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.5.2. Impact using the before-after design

Table 17 presents the total effect which could be detected with 80% of power, going from 1.51 to 1.82 for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

Table 17 Detectable total effect in terms of relative risk for cerebral malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]

	Cerebral Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	1.71	1.82	1.99
D3-> D4+1Y (50%)	0.005		1.51	1.58	1.70
D3-> D4+1Y (75%)	0.005		1.45	1.51	1.60

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.5.3. Impact using the cluster design

Table 18 presents the total effect in terms of RR which could be detected with 80% of power, going from 1.52 to 1.82 for a correlation equal to 0.20, and depending on the scenario.

Table 18 Detectable total effect in terms of relative risk for cerebral malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

	Cerebral Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	1.72	1.82	2.00
D3-> D4+1Y (50%)	0.005		1.53	1.60	1.72
D3-> D4+1Y (75%)	0.005		1.45	1.52	1.61

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.6. Sample size for the effectiveness and impact on mortality rate, overall and per gender

For the objective to estimate the effectiveness and impact of the RTS,S/AS01_E vaccine on mortality rate, overall and per gender, the following baseline assumptions were used for the sample size calculations:

- Alpha: 5%;
- Reference mortality rate: 1/100PY

*In real-life setting under 5 years mortality in SSA is estimated to be 5% (World Bank).

- 22,500 children in the exposed clusters for overall estimation and half for gender-specific estimation;
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01_E.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters for overall estimation and half for gender-specific estimation;
- An over dispersion (coefficient of 2).

As done for severe malaria in Section 9.5.4, direct effect and indirect, total and overall effects will be measured and Poisson regression method. [PASS, 2005] was used to estimate the mortality rate ratio which can be detected with 80% of power for the total and the direct effects.

9.5.6.1. Effectiveness (direct effect)

Table 19 presents the direct effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going 1.56 to 2.00 for overall and from 1.88 to 2.66 per gender, and depending on the scenario.

Table 19 Detectable direct effect in terms of mortality rate ratio, overall and per gender with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.01	1.86	2.00	2.23	2.40	2.66	3.10
D3-> D4+1Y (50%)	0.01	1.51	1.59	1.70	1.79	1.92	2.12
D3-> D4+1Y (75%)	0.01	1.49	1.56	1.68	1.76	1.88	2.07

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.6.2. Impact using the before-after design

Table 20 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from 1.34 to 1.53 for overall and from 1.51 to 1.82 per gender, and depending on the scenario.

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.01	1.47	1.53	1.63	1.71	1.82	1.99
D3-> D4+1Y (50%)	0.01	1.34	1.39	1.46	1.51	1.58	1.70
D3-> D4+1Y (75%)	0.01	1.30	1.34	1.40	1.45	1.51	1.60

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.5.6.3. Impact using the cluster design

Table 21 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from 1.35 to 1.54 for overall and from 1.52 to 1.82 per gender, and depending on the scenario.

Table 21 Detectable total effect in terms of mortality rate ratio, overall and per gender in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.01	1.47	1.54	1.64	1.72	1.82	2.00
D3-> D4+1Y (50%)	0.01	1.35	1.40	1.48	1.53	1.60	1.72
D3-> D4+1Y (75%)	0.01	1.31	1.35	1.41	1.45	1.52	1.61

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01_E vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01_E

9.6. Data management

A validated defined electronic data collection tool will be used as the method for data collection.

In all cases, study participant initials will not be collected nor transmitted to GSK. Study participant data necessary for analysis and reporting will be entered/ transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designate. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator **can download** the data generated at his/her investigational site **directly from the electronic data collection tool**.

9.7. Data analysis

All analyses will be detailed in a Statistical Analysis Plan (SAP).

Descriptive statistics will be computed by cluster status (exposed or unexposed), vaccination status, age group, gender, study site and overall, as well as by type of surveillance.

Moreover, descriptive analysis of safety endpoints will be computed for specific sub-populations such as children with hemoglobinopathy and HIV-positive children.

All comparisons, except for the meningitis cases monitoring (Section 9.7.6.2.2), will be performed separately for each of the designs described in Section 9.5 (i.e. before-after design and cluster design). As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters from the same countries (sites) and same age group (**Interim Analysis only**). The cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters (**Interim Analysis and Final Analysis**).

9.7.1. Study population

The eligible population is defined in Section 9.2.2.

The enrolled set will include all children enrolled in the study (i.e. either from the exposed or the unexposed clusters), through active and enhanced hospitalisation surveillance, and will include a mix of children vaccinated with RTS,S/AS01_E and unvaccinated children (refer to Sections 9.2.3 and 9.2.4 for inclusion and exclusion criteria). All the information for these study participants will be collected in the eCRF (after receiving signed or witnessed and thumbprinted informed consent).

The Analysis set will include all evaluable study participants (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study). A detailed, comprehensive list of reasons for elimination from the Analysis set will be established at the time of data cleaning.

All analyses will be conducted on the Analysis set, unless otherwise detailed. The analyses will be done also on the enrolled set only if there are more than 5% of eliminated study participants; except for the demography where all the tables will be performed for both sets.

A detailed, comprehensive list of reasons for elimination from analyses will be established at the time of data cleaning.

Children from the exposed clusters receiving at least one dose of RTS,S/AS01_E will be defined as the vaccinated study participants and will be identified either through active or enhanced hospitalisation surveillance.

The unvaccinated study participants either from the exposed or the unexposed clusters will include all children not vaccinated with RTS,S/AS01_E and will be identified through active or enhanced hospitalisation surveillance.

In a same way, specific sub-populations such as children with hemoglobinopathy and HIV-positive children will be defined in order to run descriptive analyses for safety endpoints.

9.7.2. Study participant disposition

For the enrolled set and Analysis set, study participant disposition will be summarised, by study sites and overall, by computing for both exposed and unexposed clusters for

children from the active surveillance and for children from the enhanced hospitalisation surveillance:

- Number of enrolled children;
- Number (%) of non-eligible children regarding inclusion and exclusion criteria (see Section 9.2.3 and 9.2.4);
- Number of children in Analysis set;
- Main results:
 - Number of subjects with at least one AESI and number of AESI;
 - Number of subjects with at least one meningitis case and number of meningitis cases;
 - Number of subjects with at least one episode of any malaria and number of malaria cases.

9.7.3. Demographics and characteristics at study entry

Demographics (age at study entry, gender, site, country) will be summarised for the enrolled set and the Analysis set separately from the exposed and the unexposed clusters, for the vaccinated and unvaccinated children enrolled in the active and enhanced hospitalisation surveillance using descriptive statistics.

Frequency tables will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

The subjects from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-003 unexposed clusters Analysis set will be compared for their demographic characteristics.

In the same way, the subjects from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-002 Analysis set will be compared (*Interim Analysis only*).

9.7.4. Exposure description

For all study participants from the exposed clusters, the vaccine history will be summarized. As detailed in Section 9.3.3.1, vaccine history will be collected from different sources (i.e. individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system). If any of the sources confirm RTS,S/AS01_E vaccination, it will be assumed that vaccination has taken place. Based on this information, the RTS,S/AS01_E vaccine coverage in the exposed clusters may be estimated.

In addition, the number of RTS,S/AS01_E doses received will be described for the vaccinated children. The age at each dose receipt and the time between doses will also be described using descriptive statistics.

The vaccination status will be described by type of surveillance, study site, and gender.

Exposure to other vaccines (Yes/No) during the study period will be summarised in frequency tables (n, %) for both exposed and unexposed clusters for the RTS,S/AS01_E vaccinated and unvaccinated children.

The exposure to other vaccines will be compared between the baseline cohort (EPI-MAL-002) and the EPI-MAL-003 exposed clusters (***Interim Analysis only***) as well as between the EPI-MAL-003 unexposed clusters and the EPI-MAL-003 exposed clusters (***Interim Analysis and Final Analysis***).

9.7.5. Analysis for co-primary objectives

9.7.5.1. Analysis population

The population will include the study participants from the active surveillance of the exposed clusters of the EPI-MAL-003 study.

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance. The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.

9.7.5.2. Statistical approach

9.7.5.2.1. Incidence rate of AESI

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance.

Incidence following immunisation

The incidence rate of each AESI and other AE leading to hospitalisation will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable. The at-risk period will follow any dose, with a censoring of study participants when they receive the following dose. The minimum at-risk period for the analyses is 2 weeks. All AESI expected to occur between 0 day and 13 days following dose administration (see [Table 3](#)) will be analysed with an at-risk period of 2 weeks. The at-risk period of 6 weeks will be used for AESI expecting to occur between 14 days and 6 weeks. Finally, at-risk periods of 3 months, and 6 months will be for the AESI expected to occur between 6 weeks and 3 months, and between 3 months and 6 months, respectively.

The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first RTS,S/AS01_E vaccination for the vaccinated study participants and virtual vaccination corresponding to the week before

first visit for the unvaccinated study participants) and the end of the at-risk period or the earliest of the followings:

- Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis);
- Date of end of study period;
- Date when child reaches 5 years;
- Date of last contact (lost-to follow-up, defined as two unsuccessful attempts to visit the child at home within the month of the scheduled visit);
- Date of death.

Note that a child may come back into the study after a certain period of lost-to-follow-up. In such case, the person-time will only consider the duration when the child was present on site (e.g. from reference date to migration date, then from immigration date to the end).

Each AESI will be grouped as follows after case ascertainment for both confirmed and non-confirmed cases (see Section 9.2.7.4):

- Nerves and central nervous system: ADEM, encephalitis, Guillain-Barre Syndrome, HHE, generalised convulsive seizure;
- Hepato-, gastrointestinal and renal system: intussusception, hepatic failure or renal insufficiency;
- Skin and mucous membrane, bone and joints system: juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease;
- Systemic diseases and haematology: diabetes mellitus type I, thrombocytopenia, anaphylaxis.

Meningitis will not be grouped with other AESI and will be considered as a single endpoint (see case definition in Section 9.2.6.4).

Incidence rates of these composite endpoints will be calculated as described for individual AESI in case of multiple cases in a study participant, only the first event **after each dose** will be considered in this analysis.

9.7.5.2.2. Incidence rate of aetiology-confirmed meningitis

Incidence rate (and 95% CI) of aetiology-confirmed meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for an AESI.

Of note, the at-risk period of 12 months will be used for meningitis. This assumption is based on meningitis cases reported in MALARIA-055. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.

9.7.6. Analysis for secondary safety objectives

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance. The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.

9.7.6.1. Analysis population

The analyses of secondary endpoints will be conducted and adjusted by the exposure status. The same population as for the co-primary objectives (see Section 9.7.5.1) will be used.

Study participants from the active surveillance of the EPI-MAL-002 study will be used for comparison purposes with the exposed clusters of EPI-MAL-003 study in a before-after design (***Interim Analysis only***). Subjects from the 5-17 months age group of the EPI-MAL-002 study will be included.

Moreover, study participants from the active surveillance of the unexposed clusters of the EPI-MAL-003 study will be used for comparison with the exposed clusters of the EPI-MAL-003 study in a cluster design.

9.7.6.2. Meningitis cases

9.7.6.2.1. Incidence rate of aetiology-confirmed, probable and/or clinically suspected meningitis

The incidence rate (and 95% CI) of probable meningitis, the incidence rate (and 95% CI) of aetiology-confirmed and/or probable meningitis, and the incidence rate (and 95% CI) of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for aetiology-confirmed meningitis (described in Section 9.7.5.2.2).

9.7.6.2.2. Meningitis cases monitoring

For all suspected meningitis at the site level (based on first line laboratory results), a monthly listing report will be checked by the monitoring and GSK safety teams, and every 6 months (could be adapted based on the findings resulting from EPI-MAL-002) the number of cases of meningitis as well as the cumulative number of cases will be tabulated in the progress report. The description of the cases will be done according to the first line laboratory classification (see Section 9.2.7.4.1).

Among vaccinated subjects from both exposed and unexposed clusters, the maximum likelihood and the log-likelihood ratios will be estimated each month if new cases are detected by means of MaxSPRT method [Kulldorff, 2011] on all suspected meningitis occurring within the at-risk period at the site level. The upper limit T (needed in

MaxSPRT method, [Kulldorff, 2011]) will be re-estimated based on the findings resulting at the end of EPI-MAL-002. If the log-likelihood ratio reaches a critical value (see Section 9.7.9.2) during the study, the comparison between vaccinated and unvaccinated study participants (see Section 9.7.6.7) will be done after having received the complete assessment of suspected cases (using the second line laboratory classification). For interim analysis and at the end of the study, if the threshold is not reached, the comparisons between vaccinated and unvaccinated study participants using the before-after design (**Interim Analysis only**) and the cluster design (**Interim Analysis and Final Analysis**) will be done anyway.

If the signal is confirmed, further investigation will be performed with additional focus on the subset of children diagnosed with meningitis (see also Section 9.2.7.4.1).

9.7.6.3. Incidence rate of cerebral malaria

Incidence rate (and 95% CI) of cerebral malaria will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

9.7.6.4. Mortality rate

Mortality rate and 95% CI (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), both overall and by gender, will be estimated with the same approach as for an AESI as described in Section 9.7.5.2 using the entire follow-up as at-risk period. As also explained in this section, different mortality risk periods might be considered as sensitivity analyses based on the distribution of the Time to Death after vaccination.

9.7.6.5. Cause of hospitalisation due to AESI, meningitis or malaria and death in children < 5 years vaccinated with RTS,S/AS01_E and unvaccinated children < 5 years

Descriptive analysis of the causes of hospitalisation (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) will consist in computing the number of cases, person-time and incidence (with 95% CI).

Note: these analyses will only be conducted for the Interim Analysis and not for the Final Analysis.

Descriptive analysis of the causes of death (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) will be done by gender, RTS,S/AS01_E vaccination status, study site and overall.

9.7.6.6. Other AE leading to hospitalisation

Incidence rate (and 95% CI) of other AE leading to hospitalisation will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

All other AE leading to hospitalisation will be coded using MedDRA and presented by SOC and PT.

Note: these analyses will only be conducted for the Interim Analysis and not for the Final Analysis.

9.7.6.7. Comparison of vaccinated and unvaccinated populations

Comparisons will be performed using the before-after design, the cluster design and comparing vaccinated and unvaccinated subjects within the exposed clusters. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons concludes on an observed imbalance in mortality in girls, the following sensitivity analyses might be conducted:

- Additional comparisons by subgroups:
Characteristics at the first scheduled visit will be compared between boys and girls. This may allow defining subgroups based on which additional comparison may be conducted.
- Analysis according to the last vaccine administered or co-administered vaccines.
- Analyses of the cause of death:
Depending on the distribution of the causes of death (see Section 9.7.6.5), analyses of the occurrence of death will be conducted including/excluding specific causes of death overall and by gender. At least, sensitivity analyses including and excluding death associated with malaria and, including and excluding deaths associated with accidents and poisonings will be done overall and by gender.

9.7.6.7.1. Before-after comparison

Before-after comparison using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

Further analyses of AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) (see Section 9.7.5.2) will consist of a comparison of its incidence rate before (i.e. unvaccinated EPI-MAL-002 from active surveillance) and after (vaccinated EPIMAL003 from active surveillance) introduction of RTS,S/AS01_E vaccine by means of a Poisson regression model with the study site as an adjusted factor. The effect of the exposure status will be assessed based on the incidence rate ratio and its 95% CI. The incidence rate following immunisation will use the at-risk period as defined in Section 9.7.5.2.1. In addition, those comparisons will be done for each group of AESI.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the

RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the before cohort (EPI-MAL-002)

- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the before cohort (EPI-MAL-002).

No adjustment on alpha will be performed.

The Poisson regression model will include the number of cases in each cohort as the dependent variable, the exposure status (vaccinated: EPI-MAL-003 [X=1] versus baseline: EPI-MAL-002 [X=0]) as a binary independent variable, the study site as a covariate, and the log-transformed total PY as an offset. Adjustment on study site will reflect the different endemicity and implementation between countries.

The details are given in Section 9.7.9.1.

Of note, multivariable models will be conducted for a specific AESI, MedDRA SOC and PT of other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) if a signal is detected (i.e. the null hypothesis is rejected).

The analyses described above in the present section will also be conducted for each group of AESI, and for aetiology-confirmed meningitis, probable meningitis, aetiology-confirmed and/or probable meningitis, and aetiology-confirmed, probable and/or clinically suspected meningitis.

The attributable risk in the vaccinated study participants will be derived for AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) as (Risk Ratio-1)/Risk Ratio [Cole, 1971].

Finally, a model with study site considered as random effect will be performed as sensitive analysis for the analysis of AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) (Section 9.7.9.1.2).

9.7.6.7.2. Cluster design comparison

Analyses of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis or cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of the exposed and the unexposed clusters from EPI-MAL-003 by means of a random-effect Poisson regression model with the clusters as random effect.

9.7.6.7.3. Exposed clusters comparison

For the exposed clusters only, analyses of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis and cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of vaccinated study participants from

the exposed clusters of EPI-MAL-003 and unvaccinated study participants from the exposed clusters of EPI-MAL-003 by means of a Poisson regression model with the study site as an adjusted factor.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation (***Interim Analysis only***), meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation (***Interim Analysis only***), meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

9.7.6.8. Febrile convulsion

The frequency (with 95% CI) of febrile convulsion within **3 and 7** ~~and 30~~ days post vaccination will be reported in all study participants from the exposed clusters (***Interim Analysis only***).

9.7.6.9. Surveillance indicator analysis

The analysis done on AESI will also be conducted on the incidence of foot positional deformations as a birth defect (negative control) and abscess at the injection site (positive control) (***Interim Analysis only***).

The incidence rate of the negative control should not increase after the vaccination, while an increase of the incidence rate of the positive control after vaccination is expected.

9.7.7. Analysis for secondary effectiveness and impact objectives

The analyses of effectiveness and impact will be performed only on children enrolled in the active surveillance for both exposed and unexposed clusters.

9.7.7.1. Analysis population

Two main analyses on effectiveness and impact endpoints will be performed:

- one year after the 3rd dose of RTS,S/AS01_E vaccine evaluated from 3rd dose, and for children who have received the 3 doses before 12 months of age,
- one year after the 4th dose of RTS,S/AS01_E evaluated from 3rd dose, and for children who have received the 3 doses before 12 months of age and the 4th dose of RTS,S/AS01_E before 30 months of age.

Additional analyses will be performed on effectiveness and impact endpoints at:

- two years after the 3rd dose of RTS,S/AS01_E vaccine evaluated from 3rd dose, and for children who did not receive the 4th dose of RTS,S/AS01_E,

- two years after the 4th dose of RTS,S/AS01_E for children who received it, evaluated from the 1st dose of vaccine,
- two years after the 4th dose of RTS,S/AS01_E for children who received it, evaluated from the 3rd dose of vaccine.

Comparisons will be performed using the direct effect design, the before-after design (**Interim Analysis only**) and the cluster design. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

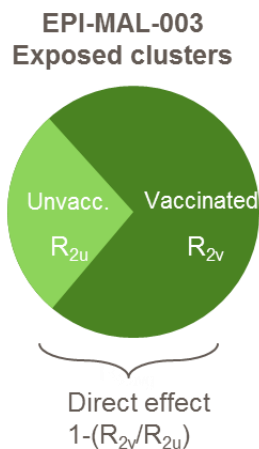
For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons will conclude on an observed imbalance in mortality in girls, additional comparisons might be performed on subgroups. Those subgroups will be defined based on the observed difference between boys and girls in the characteristics at first visit (see also Section 9.7.6.7). In addition, an analysis according to last vaccine administered and/or co-administered will also be done.

9.7.7.1.1. Effectiveness (direct effect)

For any malaria, severe malaria and cerebral malaria, vaccine effectiveness (direct effect) will be estimated on adjusted models as explained in Figure 3 [Halloran, 1997] below.

In the same way, for occurrence of anaemia and mortality rate, direct effect will be estimated.

Figure 3 Diagram on effectiveness (adapted from Halloran and Longini [Halloran, 1997])



R_{2v} = risk of endpoint after vaccine introduction among vaccinated study participants
R_{2u} = risk of endpoint after vaccine introduction among unvaccinated study participants

The direct effect will be computed on the exposed clusters of EPI-MAL-003 and is defined as the comparison between unvaccinated study participants and vaccinated study participants (from active surveillance).

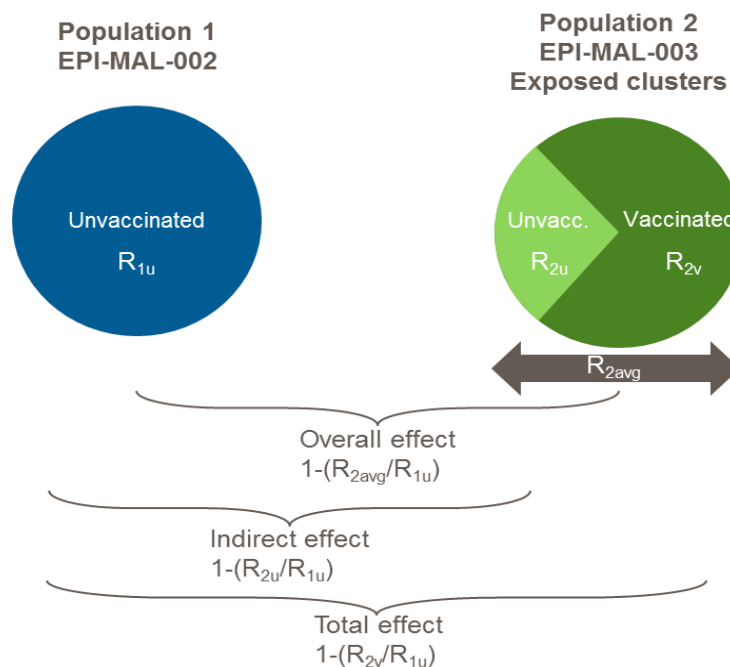
9.7.7.1.2. Impact using the before-after design

Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

For any malaria, severe malaria and cerebral malaria, impact of vaccination (indirect, total and overall effects) will be estimated on adjusted models as explained in [Figure 4](#) [[Halloran, 1997](#)] below.

In the same way, for occurrence of anaemia and mortality rate, indirect, total and overall effects will be estimated.

Figure 4 Diagram on impact presenting the different vaccine effects for the before-after design (adapted from Halloran and Longini [[Halloran, 1997](#)])



R_{1u} = risk of endpoint before vaccine introduction among unvaccinated study participants

R_{2v} = risk of endpoint after vaccine introduction among vaccinated study participants

R_{2u} = risk of endpoint after vaccine introduction among unvaccinated study participants

R_{2avg} = risk of endpoint after vaccine introduction in the overall population (vaccinated and unvaccinated study participants)

The population will depend on the type of effect and is therefore detailed according to these different types:

- Indirect effect for before-after design:

The indirect effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 ('before') and unvaccinated study participants from EPI-MAL-003 (exposed clusters of 'after') (from active surveillance).

- Total effect for before-after design:

The total effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 ('before') and vaccinated study participants from EPI-MAL-003 (exposed clusters of 'after') (from active surveillance).

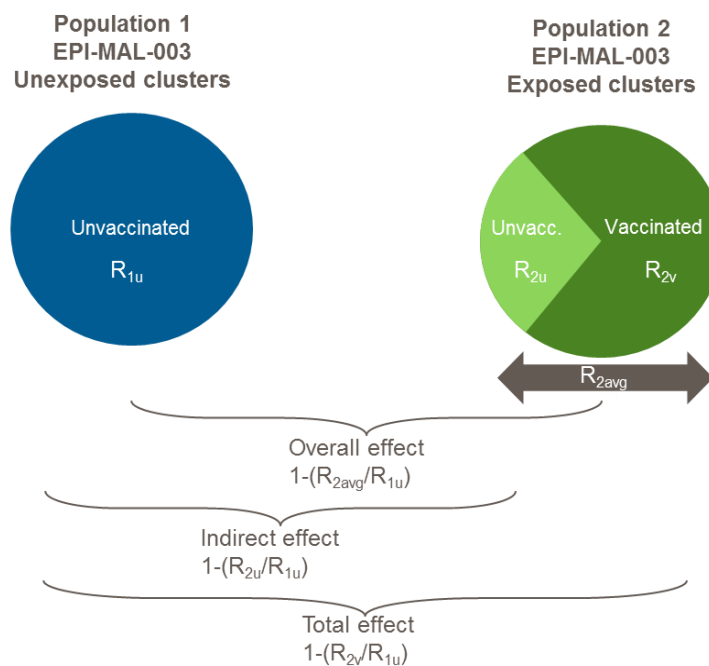
- Overall effect for before-after design:

The overall effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 ('before') and vaccinated and unvaccinated study participants from EPI-MAL-003 (exposed clusters of 'after') (from active surveillance).

9.7.7.1.3. Impact using the cluster design

For the same endpoints, impact of vaccination will be estimated as part of the cluster design on adjusted models as explained in [Figure 5 \[Halloran, 1997\]](#) below.

Figure 5 Diagram on impact presenting the different vaccine effects for the cluster design (adapted from Halloran and Longini [[Halloran, 1997](#)])



R_{1u} = risk of endpoint in the unexposed clusters

R_{2v} = risk of endpoint in the exposed clusters among vaccinated study participants

R_{2u} = risk of endpoint in the exposed clusters among unvaccinated study participants

R_{2avg} = risk of endpoint after vaccine introduction in the overall population (vaccinated and unvaccinated study participants)

The types of effect for the cluster design are detailed below:

- Indirect effect for the cluster design:
The indirect effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).
- Total effect for the cluster design:
The total effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).
- Overall effect for the cluster design:
The overall effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

9.7.7.2. Comparison of incidence rate of effectiveness or impact endpoints

Incidence rates for each event will be calculated by dividing the number of cases by person-time as defined in [Table 22](#).

For analyses using detailed information from the eCRF, children whose parents do not consent for them to take part in the active surveillance group will not be included in the denominator.

As part of the before-after design, these incidence rates will be compared by means of Poisson regression models (the dependent variable will be the number of events), using the exposure status as a binary independent variable in the model and the study site as a covariate. The details are given in [Section 9.7.9.1](#).

As done for safety endpoints, for cluster-design comparison random-effect Poisson regression model will be used.

Table 22 Incidence rate and prevalence calculations for effectiveness and impact objectives (children enrolled in active surveillance)

Endpoints	Numerator	Denominator
Any malaria	# cases of any malaria Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Any <i>P. falciparum</i> malaria	# cases of any malaria due to <i>P. falciparum</i> Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Severe malaria	# cases of severe malaria Source: Hospitalisations	Person-years contribution of enrolled children
Severe <i>P. falciparum</i> malaria	# cases of severe malaria due to <i>P. falciparum</i> Source: Hospitalisations	Person-years contribution of enrolled children

Endpoints	Numerator	Denominator
Cerebral malaria	# cases of cerebral malaria Source: Hospitalisations	Person-years contribution of enrolled children
Anaemia in hospitalised children	# cases of anaemia Source: Hospitalisations	Number of enrolled children
Death – all cause	# deaths (due to any cause) Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS (or equivalent surveillance system) register	Person-years contribution of enrolled children
Malaria attributed deaths	# cases of deaths with malaria listed as a contributing cause Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS (or equivalent surveillance system) register	Person-years contribution of enrolled children
Hospitalisation due to AESI (<i>Interim Analysis only</i>), meningitis, malaria	# of children hospitalised for AESI,... during study period Source: Hospitalisations	Person-years contribution of enrolled children
Malaria attributed hospitalisation	# of children hospitalised during study period where malaria is listed as the primary diagnosis Source: Hospitalisations	Person-years contribution of enrolled children

Note: For cerebral malaria, incidence following immunisation will be derived (see Section 9.7.5.2.1)

9.7.7.3. Comparison of time to event of effectiveness or impact endpoints

9.7.7.3.1. Effectiveness

The models will include exposure status and the study site as covariate. Hazard ratio will be derived with its Wald's 95% CI. The model will include the exposure status as:

- Vaccinated study participants versus unvaccinated study participants both from the EPI-MAL-003 exposed clusters.

9.7.7.3.2. Impact using the before-after design

Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

For the before-after design, the models will include different exposure status and the study site as covariate. Hazard ratio will be derived with its Wald's 95% CI. Further models will include the exposure status as:

- Unvaccinated study participants from EPI-MAL-002 versus unvaccinated study participants from the EPI-MAL-003 exposed clusters;
- Unvaccinated study participants from EPI-MAL-002 versus vaccinated study participants from the EPI-MAL-003 exposed clusters;
- Unvaccinated study participants from EPI-MAL-002 versus unvaccinated and vaccinated study participants from the EPI-MAL-003 exposed clusters.

9.7.7.3.3. Impact using the cluster design

For the cluster design, models will include the exposure status as:

- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus unvaccinated study participants from the EPIMAL-003 exposed clusters;
- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus vaccinated study participants from the EPIMAL-003 exposed clusters;
- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus unvaccinated and vaccinated study participants from the EPI-MAL-003 exposed clusters.

Univariate and multivariable Cox models will also be performed using same strategy for covariates selection.

In the design, as the different events from a same cluster are treated as independent observations in the Cox model, robust variance estimates adjusted for the correlation within clusters will be obtained using the robust estimation method derived as an extension of the information sandwich estimator [[Lin](#), 1989; [Zeger](#), 1986].

9.7.8. Statistical considerations

All the statistical calculations will be done in SAS 9.2 or higher.

Unless specified otherwise, all the statistical tests will be two-sided at alpha level of 0.05.

9.7.8.1. Handling of missing data

A worst case allocation will be done for suspected events (i.e. suspected AESI, suspected malaria) for which confirmation of the outcome is not available.

9.7.8.2. Descriptive statistics

Frequency tables including number of cases and percentages will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

9.7.9. Statistical models**9.7.9.1. Poisson regression model****9.7.9.1.1. Fixed effect model**

Poisson regression will be conducted using the SAS GENMOD procedure. The dependent variable is the number of events (Y). The main model (Model 1) will include the exposure status (vaccinated [$X=1$] versus unvaccinated [$X=0$]) as a binary

independent variable, the study site [Z] as a fixed effect, and the log-transformed total person-time (PY) of each vaccinated and unvaccinated cohort as an offset.

Main model: $\ln(Y) = \beta_0 + \beta_1 X + \beta_2 Z + \ln(PY)$

The coefficients β_1 and β_2 are the coefficients associated to exposure effect and study sites, respectively. The risk ratio (vaccinated/unvaccinated) will be derived as the exponential of the coefficient associated with the exposure status and its 95% Wald CI.

The SAS code is:

```
PROC GENMOD data=<filename> ;
  CLASS X Z;
  MODEL Y= X Z / OFFSET=Ln_PY DIST=poisson LINK=log ;
RUN;
```

For each model, the following assumptions will be checked in order to interpret the results obtained from the Poisson regression: the outcome variable follows a Poisson distribution and does not have an excessive number of zeros. The deviance will measure the adequacy of the model. If the scaled deviance is closed to one, the regression model is adequate. Otherwise, the validity of the model is questionable. In particular, value greater than 1 indicates over dispersion.

In case of over dispersion, corrective measures will include the introduction of a dispersion parameter with respect to the Poisson model. This will be done by adding the option DSCALE and examining the fit statistics. If over dispersion is still a problem, another alternative approach such as a negative binomial distribution model will be considered.

This last method will be detailed in the further SAP. Of note, the same procedure PROC GENMOD will be adapted by specifying option DIST=negbin in the model statement:

```
PROC GENMOD data=<filename> ;
  CLASS X Z;
  MODEL Y= X Z / OFFSET=Ln_PY DIST=negbin LINK=log ;
RUN;
```

9.7.9.1.2. Mixed regression

Mixed-Poisson model will be used including clusters as random-effect. Those models will be conducted using the SAS GLIMMIX procedure.

The method will also be detailed in the SAP.

9.7.9.2. Maximised sequential probability ratio tests (MaxSPRT)

The Sequential Probability Ratio Test (SPRT) is a method adapted to safety surveillance first proposed by Spiegelhalter et al [[Spiegelhalter, 2003](#)].

One strength of SPRT is the fact that repeated measurement error adjustments are taken into account in the SPRT process. The Type I and Type II error levels also apply to the entire process (not to each specific month), hence multiplicity testing is handled.

However, SPRT is sensitive to the choice of RR required in the alternative hypothesis.

MaxSPRT, based on a composite alternative hypothesis, works well across a range of RRs [Kulldorff, 2011].

MaxSPRT will be based on:

- Null hypothesis (H0): there is no increase in the risk of meningitis after introduction of the vaccine.
- Alternative hypothesis (H1): there is a RR-fold increase of the risk of meningitis after introduction of the vaccine where $RR > 1$.

Let C_t be the random variable representing the number of meningitis cases within D days after vaccination given in the period $[0, t]$ (Month t, TBC) and let c_t be the corresponding number of meningitis.

Under the null hypothesis, C_t follows a Poisson distribution with mean μ_t .

For the Poisson model, the MaxSPRT likelihood ratio test statistic is

$$LR_t = e^{\mu_t - C_t} (C_t / \mu_t)^{C_t}$$

when $c_t \geq \mu_t$ and $LR_t = 1$ otherwise

The log-likelihood ratio is

$$LLR_t = (\mu_t - c_t) + c_t \ln(c_t / \mu_t)$$

when $c_t \geq \mu_t$ and $LLR_t = 0$ otherwise

Upper limit

The MaxSPRT method uses a critical value for the different MaxSPRT based log-likelihood ratios. This critical value is defined by the alpha level and by an upper limit which is the expected number of accrued events under the null hypothesis.

Kulldorff et al [Kulldorff, 2011] provide tables based on exact calculations with critical values for different upper limits.

The null hypothesis is then rejected when the MaxSPRT based log-likelihood ratio reaches the critical value. The MaxSPRT analysis will be done based on all suspected meningitis at the site level. If the null hypothesis is rejected at one moment, the comparison between vaccinated and unvaccinated study participants will be done (see Section 9.7.6.7), after having received the complete assessment of the meningitis cases (second line laboratory classification). Of note, for interim analysis and at the end of the study, if the threshold is not reached, the comparisons between vaccinated and

unvaccinated study participants using the before-after design and the cluster design will be done anyway (see Section 9.7.6.2.2).

9.7.10. Conduct of analysis

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the **SAP** / final study report.

9.7.11. Sequence of analyses

Descriptive progress reports (including listings and statistical tables for description of AESI, other AE leading to hospitalisation, meningitis and malaria, including severe malaria and cerebral malaria) will be produced every 6 months after study start.

9.7.12. Statistical considerations for interim analyses

An interim analysis will be performed one year after the last study participant received the last dose of RTS,S/AS01_E vaccine primary schedule (i.e. 3rd dose). This interim analysis will be done with clean data* on safety endpoints, and effectiveness and impact endpoints (considering one year after the third dose of RTS,S/AS01_E vaccine evaluated from third dose, and for children who have received the 3 doses before 12 months of age, see Section 9.7.7.1).

Of note, further details will be provided in the SAP.

* Some data may change after the interim analysis as access to the eCRF will still be granted to sites and investigators throughout the follow-up period, until study conclusion.

Final analysis will be carried out on clean data collected up to study conclusion. ***The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.***

Moreover, if a safety signal is detected before that timepoint, the GSK safety physician in collaboration with the study site principal investigator and RAFT could request that the external panel of experts conduct a causality assessment. The external panel of experts may ask for ad-hoc interim analyses to conduct this assessment.

9.7.13. Statistical analyses during special circumstances

Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.

9.8. Quality control

To comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) or other applicable guidelines, administrative obligations relating to data

collection, monitoring, archiving data, audits, confidentiality, ownership and publications must be met.

9.8.1. Monitoring by GSK Biologicals site monitors or delegates

Monitoring visits by a GSK Site Monitor or delegate are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP or other applicable guidelines and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), verifying that the site staff and facilities continue to be adequate to conduct the study).

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of study participants are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV GSK understands verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor will freeze the screen, after she/he estimates that data are authentic, accurate and complete.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

9.8.2. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or

inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

9.8.3. Audits

To ensure compliance with GCP or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

9.9. Limitations of the research methods

Following the SAGE/MPAC recommendations, this protocol takes into account a follow-up of enrolled children to the age of 5 years, with events collected for each study participant in the active surveillance over 44 months. This post-implementation safety study will enrol children in the age range 5-17 months at first dose.

Some uncertainties remain regarding recommendations for use of RTS,S/AS01_E in SSA and what will be the vaccine uptake at the start of the vaccine programme implementation, for both the primary series and for the 4th dose of RTS,S/AS01_E. Contents of the protocol might be adapted depending on NRA approval and MoH guidelines in each of the participating countries.

To better take into account the potential scenarios and to perform the study most close to routine medical practice, a cohort design that allows the prospective collection of standardised information seems to be the most suitable approach. Collecting data at a

large population level (population size estimated at 45,000 study participants – 22,500 in exposed and 22,500 in unexposed clusters) is challenging from an operational perspective in SSA countries. Where possible, to base the studies on existing HDSS or equivalent surveillance system offers the opportunity to benefit from existing research and health care structures, in a population that is already part of a demographic and health indicators survey, and thus likely to be willing to participate in additional research related to malaria and the implementation of the RTS,S/AS01_E as a new malaria control intervention. This approach will facilitate the early collection of data on both the safety and effects on malaria of the RTS,S/AS01_E vaccine. Pre-malaria vaccine implementation of the surveillance efforts will allow the collection of data in a well-characterised population and better understanding of fluctuations over time in the community of AE (including AESI and meningitis) and malaria disease.

This study targeted enrolling at least 20,250 vaccinated children for evaluation of the safety of RTS,S/AS01_E (in total, 22,500 children **were** estimated to be enrolled in active surveillance in the exposed clusters, assuming that 80% of study participants in the exposed clusters **would** receive at least three doses of RTS,S/AS01_E, 10% **would** receive one or two doses and 10% **would** not have any dose even though they are assigned to the exposed clusters cohort).

GSK acknowledges that this sample may be limited for detection of very rare diseases for evaluation of safety of RTS,S/AS01_E. To address safety research with very rare outcomes, most epidemiological studies are based on existing disease-specific registries or large healthcare databases such as insurance claim databases, which do not exist in SSA at the time being. Thus, the limitation in the ability to detect increases in rare events is partly related to the fact that the vaccine will be implemented only in SSA. The enhanced hospitalisation surveillance should help to identify additional cases of AESI, other AE leading to hospitalisation, meningitis, and any severe malaria occurring in children living in the study area but not enrolled in the active surveillance.

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified. Training of physicians and field staff **started** during the pre-implementation study (EPI-MAL-002). For the study sites of EPI-MAL-003 where the EPI-MAL-002 was not conducted, training **was** provided before **the** start of EPI-MAL-003. All efforts will be made to ensure an optimal standardised way of collecting data across the different sites. Progress reports every 6 months will help in monitoring the participation rate, the vaccination coverage and the trends in event detection.

Detecting the occurrence of AESI and meningitis cases following immunisation with RTS,S/AS01_E after its introduction in vaccination programmes are the primary objectives of this study. AESI and meningitis cases require specific diagnostic methods and such data may not be routinely collected in the study settings, potentially leading to under-reporting. Therefore, specific training and monitoring of the field teams (community health workers, health care facilities staff, physicians and hospital staff) will be provided. The reinforcement of the pharmacovigilance practices and clinical and laboratory data collection most close to routine medical practice is a key component of both studies, and of both the exposed and unexposed clusters in the EPI-MAL-003 study. All procedures will be performed in line with the current national guideline

recommendations in each of the participating countries. On one hand, improvement in surveillance over time may increase sensitivity in detecting those events during EPI-MAL-003 better than in the early phase of EPI-MAL-002 and this potential bias to the before-after comparison will be taken into account when analysing data collected over time. Surveillance quality indicators will be utilised to help detect trends in changes in surveillance capacity. On the other hand, the sensitivity in detecting these events during EPI-MAL-003 might be different between the exposed and the unexposed clusters, for example due to different health care structures, different accesses to care, or different routine case ascertainment procedures. To balance for characteristics which themselves could influence the frequency of the outcome measures, clusters will be stratified by the capacity of hospitals and health facilities within the clusters, by malaria transmission (measured during the baseline period as community parasite prevalence) and by geographic location. Surveillance quality indicators will also be used to help detect differences between the clusters.

Longitudinal detection of events such as meningitis might also be difficult to interpret because of the changing meningitis disease epidemiology. The study **includes** some countries of the “meningitis belt”, which is affected yearly by bacterial meningitis epidemics (mostly meningococcal meningitis). This zone comprises 22 countries from Senegal in the West to Ethiopia in the East. ***From 1928 to 2018, 2,628,283 cases including 151,808 deaths were reported to WHO-AFRO in the 53 African countries during the meningitis epidemics period, with a mean case-fatality rate of 5.77% [Mazamay, 2021]. The highest case numbers were reported in 1996 (184,487 cases). The mean incidence of meningitis cases in Africa from 1928 to 2018 was 216 per 100,000 inhabitants (SD ± 14.8). Epidemic meningococcal group A disease outbreaks have recorded incidence rates up to 100 per 100,000 [Soeters, 2019].*** Despite successful introduction of a meningococcal A conjugate vaccine in the African meningitis belt since 2010 [Novak, 2012], meningococcal meningitis outbreaks **was a possibility** in some study sites during the EPI-MAL-002 and EPI-MAL-003 study periods, due to other *Neisseria meningitidis* serogroups, or if the study site is in a region/country which has not yet introduced the vaccine. Therefore, the interpretation of differences in meningitis incidence rates should take into account the epidemiological context of each site. As for AESI, all efforts will be made to standardize meningitis diagnosis and reach an optimal proportion of laboratory confirmed cases to establish the aetiology. The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts (blinded to RTS,S vaccination status as much as possible). In addition, other evidence such as data generated by the meningitis surveillance in place in those countries, or the monitoring of meningitis in the older non-vaccine eligible children will be taken into account for the analysis of the events.

Because surveillance will be conducted in study areas covering mainly rural areas, children who are severely ill might die before being transported to hospital. In EPI-MAL-002 and EPI-MAL-003, in the event of death, the cause of death **is** systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital. However, ascertaining the cause of death remains a concern considering the limitation of the verbal autopsy

methods in the field, **and** is why all-cause mortality is an important endpoint to consider in this study.

*If a site is not part of the INDEPTH, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

All efforts **were/are being** made to standardize data collection during EPI-MAL-002 and EPI-MAL-003, both in exposed and unexposed clusters. However, due to the long duration of both studies, changes in diagnostic procedures, implementation of malaria control measures such as seasonal malaria chemoprevention [WHO, 2012(a)], and changes in treatment measures will have to be considered during the analyses of the safety and effectiveness/impact data. Potential confounders **were/will** be collected at individual level during EPI-MAL-002 and EPI-MAL-003 and at community level during EPI-MAL-005. Some study participants might also leave the study area during the study period but this is regularly documented through demographic census (scheduled at least once a year during the study periods).

In addition to the 22,500 children in the unexposed clusters, this study **targeted** enrolling at least 2,250 unvaccinated children in the exposed clusters for evaluation of effectiveness and impact of RTS,S/AS01_E. Estimates for direct effect based on the population size were computed using the most conservative assumptions. The vaccine uptake in the exposed clusters may be very high and the number of unvaccinated children in EPI-MAL-003 may be too low to reliably estimate the direct vaccine effect. In this instance, the unvaccinated comparison group may have to be derived from EPI-MAL-002 (estimations of the overall and total vaccine effects in the before-after design) or from the EPI-MAL-003 unexposed clusters (estimations of the overall and total vaccine effects in the cluster design). The addition of an unvaccinated cohort in EPI-MAL-003 (either from the exposed or the unexposed clusters) should address most concerns with regards to biases potentially introduced in the ‘before’ (EPI-MAL-002) and ‘after’ (EPI-MAL-003 exposed clusters) impact approach. It should provide an estimate of effectiveness (direct effect); together with data gathered during EPI-MAL-002 or in EPI-MAL-003 unexposed clusters, the indirect, total and overall effects may be estimated through two different approaches (Section 9.7.7). Potential differences between vaccinated and unvaccinated groups cannot be excluded, for example, unvaccinated children may have different background risk of malaria or health care seeking behaviours. To be able to compare the groups, parents/ LARs **were** invited to enrol their child into the active surveillance when children **presented** for administration of DTP/HepB/Hib vaccine, regardless of whether they subsequently decided to vaccinate their child with RTS,S/AS01_E or not. In addition, the same follow-up will be conducted (same study period, same timing for the inclusion visit and same number of home visits) and the same data collection will be prospectively implemented. However, the objective is to be able to collect data to estimate both the direct effect and the vaccine impact (indirect, total and overall effects). Considering the low proportion of vaccinated study participants in the population at the beginning of the vaccination programme implementation where EPI-MAL-003 **is being conducted**, there is some likelihood that an indirect effect (also named herd effect) will not be estimable in this study.

To embed the various measures of vaccine effect within the post-implementation safety study EPI-MAL-003 has several advantages: (1) Effectiveness/impact data will be obtained at early stages because those countries will be the early adopters of the vaccine, (2) there will be benefit from the comprehensive infrastructure initially put in place for the safety component and from the large vaccinated population. This will also allow vaccine effects to be estimated at Year one and Year two after the last dose, thus avoiding having to develop new infrastructures in different locations. In addition, ethical concerns are minimal as withholding or delaying vaccination is avoided.

The co-primary objectives will provide estimates of the incidence of AESI and of aetiology-confirmed meningitis. The secondary objectives will provide estimates of the incidence of other meningitis case definitions, assess the potential association between RTS,S/AS01_E vaccination and the occurrence of the different endpoints, and estimate the vaccine effectiveness and impact of vaccination with RTS,S/AS01_E on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.

In the framework of the secondary objectives, the comparisons will be done considering the before-after design (comparing occurrence of events in subjects from EPI-MAL-002 with subjects from the exposed clusters of EPI-MAL-003; **Interim Analysis only**), and considering the cluster design (comparing occurrence of events in subjects from the unexposed clusters of EPI-MAL-003 with subjects from the exposed clusters of EPI-MAL-003; **Interim Analysis and Final Analysis**). Both comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

Integrating the Phase IV in the MVIP and adding a concurrent unvaccinated cohort (unexposed clusters) to EPI-MAL-003 have some impact on study designs but also allow strengthening the post-approval plan of RTS,S/AS01_E. The latter now considers two comparisons (before-after and cluster design comparisons) allowing adjustment for both temporal and geographical variability in terms of, **for example**, malaria transmission, disease incidence, access to care, **and** use of other malaria control measures. On one hand, temporal bias might occur due to **factors such as** seasonality and year to year variations, or due to variation in control measures, **amongst others**. On the other hand, geographical bias might occur due to, **for example**, differences in health care infrastructure/facilities between sites, due to the epidemiology of several diseases, especially of infectious disease, or due to variation in controls measures. Therefore, the two comparisons are considered complementary and should provide more robust results.

It is important to note that a fixed number of clusters are included in the cluster design comparison (currently 6 exposed clusters and 6 unexposed clusters of around 4,000 subjects each are planned) which does not allow for robust intra-cluster adjustment. As concluded in [Hemming, 2011], designing a cluster trial with a fixed number of clusters might mean that the study will not be feasible, irrespective of how many individuals are included within each cluster. Also, cluster trials with fewer than five clusters per arm are, in general, inadvisable, since parametric tests may be unreliable with such small numbers [Puffer, 2005]. In addition, the clusters that are/will be allocated to the Phase IV studies have not been randomized to allow before-after comparison (EPI-MAL-002 sites that will

provide baseline incidences of the endpoints of interest **were to become** clusters implementing RTS,S/AS01_E vaccine). Moreover, unexposed EPI-MAL-003 clusters will be conveniently selected by the MoH based on the following characteristics: malaria transmission, geographic location, access to care and population size. These characteristics will be captured through the yearly cross-sectional survey in the EPI-MAL-005 study to adjust the comparison. In order to minimize the impact of those major limitations on the interpretability of the study results, GSK Biologicals has put measures in place to maximize cluster comparability and to assess consistency of the results using different study designs. However, if the intra-cluster correlation coefficient is high (intra-cluster correlation coefficient $> k / n$ where k is the number of clusters, and n is the average number of subjects per cluster [Hemming, 2011]), then the results should be interpreted with caution.

Finally, since the Phase IV is fully integrated in the **MVIP**, contamination between exposed and unexposed clusters (also called cross-contamination) is a potential risk that should be considered. It is possible that children living in unexposed clusters will seek for vaccination in neighbouring exposed clusters. Such “contamination” may tend to underestimate vaccine impact. As per WHO-led evaluation protocol of the pilot implementation programme, the level of contamination will be reduced by selecting clusters which are as geographically large as possible, making it more difficult for people to seek vaccinations outside their own cluster. Moreover, as detailed in Section 9.3.3.1, in the framework of EPI-MAL-003, vaccine history will be collected at individual level from different sources (i.e. individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system) in order to fully describe vaccine coverage in both exposed and unexposed clusters.

A SAP will complement the protocol to detail the way the data will be handled for each analysis. Contents of the protocol might be adapted based on NRA approval and MoH guidelines at country level. The interpretation of the results will take into account the limitations described above.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the ICH Guideline for GCP, Guidelines for Good Pharmacovigilance Practices (GPP) [ISPE, 2015], other applicable guidelines, all applicable study participant privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK obtained **favourable** opinion/approval to conduct the study prior to a site initiating the study in any country, according to local requirements, or **was to** document that neither a favourable opinion nor an approval to conduct the study **was** needed.

Conduct of the study includes, but is not limited to, the following:

- IRB/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Study participants' parent(s)/LAR(s) informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK Biologicals will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed and thumbprinted informed consent must be obtained from each study participant's parent(s)/LAR(s) or the impartial witness, as appropriate, prior to participation in the study.

GSK Biologicals prepared a model ICF which **embodies** the applicable ICH GCP or other applicable guidelines, and GSK Biologicals required elements. While it is strongly recommended that this model ICF be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Safety definitions

11.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

11.1.2. Definition of a serious adverse event

A SAE is any adverse event that:

- a. Results in death.
- b. Is life-threatening.

NB: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the study participants was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- c. Requires hospitalisation or prolongation of existing hospitalisation.

NB: In general, hospitalisation signifies that the study participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the adverse event should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE.

- d. Results in disability/incapacity,

NB: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

For the details of what qualifies for reporting to GSK for this study please refer to Section [11.3](#).

11.2. Detecting and recording adverse events

11.2.1. Time period for detecting and recording adverse events

All relevant AEs will be collected and recorded from the time the parent(s)/LAR(s) of the study participant consent for their child/ward to participate in the study until study conclusion (i.e. study end or the child reaches 5 years of age, whichever occurs first).

11.3. Recording of adverse events via eCRF

Any AE, which is serious (refer to Section 11.1.2) and which, in the opinion of the investigator, is suspected to be related to the protocol required blood draw for any suspected AESI or meningitis case, will be recorded in the Expedited Adverse Event screen in the eCRF, which will subsequently be uploaded into GSK's safety database for potential expedited reporting to health authorities.

For some other specific events (see list below), which are captured in various screens in the eCRF (e.g. meningitis screen, malaria screen), minimal data also need to be recorded for the event in the Expedited Adverse Event screen of the eCRF:

- Any case of suspected AESI in a child who received at least one dose of RTS,S/AS01_E;
- Any case of suspected meningitis in a child who received at least one dose of RTS,S/AS01_E;
- Any case of severe malaria, including cerebral malaria, in a child who received at least one dose of RTS,S/AS01_E;
- Any case with a fatal outcome in a child who received at least one dose of RTS,S/AS01_E;
- Any other AE (i.e. other than those listed above) which is identified during a hospitalization in a child who received at least one dose of RTS,S/AS01_E AND which, in the opinion of the investigator, is related to RTS,S/AS01_E;

In addition to the minimal data recorded in the Expedited Adverse Event report screen of the eCRF for these events, data from other screens in the eCRF will also be uploaded into GSK's safety database for providing more complete information on the case for potential expedited reporting to health authorities.

NOTE: These events all need to be entered in the EXPEDITED ADVERSE EVENT report screen of the eCRF within 24 hours of the investigator becoming aware of the event.

11.3.1. Evaluation of adverse events

11.3.1.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all AEs recorded in the Expedited Adverse Event screen of the eCRF.

The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such a SAE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

11.3.1.2. Assessment of causality

The investigator will provide an assessment of causality for all AEs recorded in the Expedited Adverse Event screen of the eCRF.

The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, other concomitant therapy and other risk factors will be considered and investigated. The investigator will also consult the Product Information (Summary of Product Characteristics) to determine his/her assessment.

There may be situations when an AE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the AE to GSK Biologicals. The investigator may change his/ her opinion of causality in light of follow-up information and update the information previously recorded in the eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Note: for all AEs recorded in the Expedited Adverse Event screen of the eCRF, apart from those events considered as related to the study procedure involving a blood draw for suspected cases AESI or meningitis, the investigator will be asked to provide an assessment of causality between the event and RTS,S/AS01_E.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the event may have been caused by the RTS,S/AS01_E vaccine?

- YES : There is a reasonable possibility that the RTS,S/AS01_E vaccine contributed to the event.
- NO : There is no reasonable possibility that the RTS,S/AS01_E vaccine contributed to the event. There are other, more likely causes and administration of the RTS,S/AS01_E vaccine is not suspected to have contributed to the event.

Possible contributing factors include:

- Medical history
- Medication(s)
- Protocol required blood draw for a suspected AESI or meningitis case
- Other procedure not required by the protocol
- Erroneous administration
- Other cause (specify).

11.3.1.3. Assessment of outcomes

The investigator will provide an outcome for all AEs recorded in the Expedited Adverse Event screen of the eCRF using the following options:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae.
- Fatal.

11.4. Reporting of adverse events not via eCRF

The following events need to be reported but not within the framework of the study.

- Any AE which, in the opinion of the investigator, is suspected to be related to a GSK licensed product other than RTS,S/AS01_E must be reported, within 24 hours of awareness, directly to GSK Safety for entry in GSK's safety database, and potential expedited reporting to relevant National Health authorities. See Sponsor Information Sheet for contact details for reporting these types of events ([Annex 4](#)).
- Any AE which, in the opinion of the investigator, is suspected to be related to a non-GSK licensed product should be reported, to the relevant National Health authority following national reporting procedures for adverse drug reactions.
- Any AE which, in the opinion of the investigator is suspected to be related to RTS,S/AS01_E and which is not collected per study protocol, must be reported to relevant National Health authorities following the local pharmacovigilance legislation.

11.4.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must complete, then date and sign a paper Expedited Adverse Event Report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department using the following contact details (again within 24 hours of awareness).

Back-up Study Contact for Reporting AEs
24/24 hour and 7/7 day availability: Email: ogm28723@gsk.com GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +32 2 656 8009

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is back working again, the investigator (or designee) must complete the Expedited Adverse Event report in the eCRF. The final valid information for regulatory reporting will be the information reported through the electronic reporting system.

11.4.2. Updating of adverse event information after removal of write access to the study participant's eCRF

If additional AE information is received after removal of the write access to the study participant's eCRF, new or updated information should be recorded on the appropriate paper report (see Section [11.4.1](#)), with all changes signed and dated by the investigator. The updated report should be faxed to GSK Biologicals Clinical Safety and Pharmacovigilance department using the contact details provided in Section [11.4.1](#).

11.4.3. Regulatory reporting requirements for adverse events

GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under epidemiological investigation. Prompt notification of AEs by the investigator to the Study Contact for Reporting AEs is essential so that legal obligations and ethical responsibilities towards the safety of other study participants are met.

11.5. Follow-up of adverse events

- For AESIs, meningitis or cerebral malaria, children, will be followed up after hospital discharge up to study conclusion in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge (see Section [9.2.7.5](#)).
- For all events, including AESIs, meningitis and cerebral malaria, the investigator will follow-up the study participant until the event has resolved, subsided, stabilised,

disappeared, or until is otherwise explained, or the study participant is lost to follow-up. Follow-up to characterize an SAE is described in Sections 9.1.1 and 9.2.7.

Note: enrolment to EHS and data collection will stop following Ethics Committee approval of Protocol Amendment 3; for subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge.

GSK Biologicals may request that the investigator performs or arranges for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE. The investigator is obliged to assist. If a study participant dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

To comply with Guidelines for GPP or other applicable guidelines administrative obligations relating to data collection, archiving data, audits, confidentiality and publications must be fulfilled.

Study information from this protocol will be posted on public registers (e.g. GSK Clinical Study Register, clinicaltrials.gov, Pan African Clinical Trials Registry) and the European Union Post-Authorisation Studies (EU PAS) register before the start of the study, as applicable.

Progress reports will be written and submitted every six months. An interim analysis will be performed one year after the last study participant received the last dose of RTS,S/AS01_E vaccine primary schedule (i.e. 3rd dose). This interim analysis will be done with clean data* on safety endpoints, and effectiveness and impact endpoints.

* Some data may change after the interim analysis as access to the eCRF will still be granted to sites and investigators throughout the follow-up period, until study conclusion.

A final report will be written and submitted.

For the three studies (EPI-MAL-002, EPI-MAL-003, EPI-MAL-005) a Safety Post Approval Program Partnership Committee has been created and will ensure preparation and review of manuscripts resulting from the studies. This Committee is composed of local principal investigators with GSK representation. This Committee acts as the main governance body for the studies. (Charter is available upon request.)

A manuscript will be submitted to a peer reviewed journal for publication within the policy defined timelines. In addition, study information will be posted to the GSK Clinical Study Register.

13. REFERENCES

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Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. Biometrics. 1986;42:121-130.

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	List of stand-alone documents
2.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Glossary of terms
3.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Trademarks
4.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Sponsor Information
5.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Case definitions for protocol-defined AESI and surveillance indicators
6.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Study specific guidance document
7.	115056 (EPI-MALARIA-003 VS AME)	24 Oct 2024	Amendment to the protocol
8.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Protocol Amendment 3 sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	Protocol Amendment 3 investigator agreement
10.	115056 (EPI-MAL-003 VS AME)	24 Oct 2024	ENCePP Checklist for study protocols

Annex 2 Glossary of terms

Active surveillance:	Screening for AESI and other diseases during study follow-up visits at the community level.
Adverse event of special interest (AESI):	A predefined list of adverse events that are potentially associated with RTS,S/AS01 _E , that have historically been associated with vaccines other than RTS,S/AS01 _E , or may hypothetically be associated with RTS,S/AS01 _E due to the fact that this vaccine has components which are new compared to current widely used vaccines.
Adverse event:	Any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Cohort event monitoring:	A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time [The Uppsala Monitoring Centre , 2011].
Cohort study:	A form of epidemiological study where study participants in a study population are classified according to their exposure status/disease and followed over time (prospective/retrospective) to ascertain the outcome(s).
DTP/HepB/Hib	This refers to Diphtheria, Tetanus, and Pertussis (DTP), or DTP-Hepatitis B (DTP-HepB tetravalent) or DTP-HepB-Haemophilus influenza type b (Hib) (DTP-HepB-Hib pentavalent) vaccines.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enhanced hospitalisation surveillance:	Case detection during hospitalisation through monitoring of medical records and registries.
Epidemiology study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all study participants at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Exposed clusters	Study sites where the RTS,S/AS01 _E vaccine will be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Hospitalisation:	Study participants requiring overnight stay in a health care facility.
Interventional human subject research:	Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.
National EPI:	Routine vaccination programmes, administered by the national EPI system in place, usually given at 6, 10 and 14 weeks of age (e.g. DTP/HepB/Hib vaccines. NOTE: in some countries the EPI schedule may differ by a few weeks).
Pharmacovigilance:	Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs) [WHO , 2012(b)].
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.

Serious adverse event:	A serious adverse event (SAE) is any untoward medical occurrence that: a. results in death; b. is life-threatening; c. requires hospitalisation or prolongation of existing hospitalisation; d. results in disability/incapacity; Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.
Site monitor:	An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.
Study participant number:	A unique number identifying a study participant, assigned to each study participant consenting to participate in the study.
Study participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Unexposed clusters	Study sites where the RTS,S/AS01 _E vaccine will not be implemented in the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Vaccine ineligible	Vaccine ineligible is defined as those study participants that on the basis of age would be ineligible for RTS,S/AS01 _E vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the label for RTS,S/AS01 _E vaccination in the country.

Annex 3 Trademarks

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the abstract), the names of the vaccines will be written without the superscript symbol TM or ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Mosquirix TM	<i>Plasmodium falciparum</i> and hepatitis B vaccine (recombinant, adjuvanted)
Rotarix®	Live attenuated human rotavirus vaccine
Pediarix®	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus combined vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
RotaTaq® (Merck & CO., Inc.)	Live, oral, pentavalent rotavirus vaccine

Annex 4 Sponsor Information

1. Sponsor:

GlaxoSmithKline Biologicals

Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study:

Refer to the local study contact information document.

3. Sponsor Study Monitor:

Refer to the local study contact information document.

4. Study Contact for Reporting of a Serious Adverse Event (SAE):

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section [11](#) Management and reporting of adverse events /adverse reactions.

Annex 5 Case definitions for protocol-defined AESI and Surveillance Indicators

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Nerves and Central Nervous System		
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)	LEVEL 1 - Diffuse or multifocal demyelination revealed on histopathological sampling OR Focal or multifocal impairment of the central nervous system <i>with</i> ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, most often focal) - Sensory abnormalities - Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). - Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus AND - On MRI: diffuse or multi-focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences AND - Monophasic character of the illness (absence of relapse within a minimum of 3 months of symptomatic nadir) LEVEL 2 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	Focal or multifocal impairment of the central nervous system <i>with ≥ 1 of the following signs:</i> • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry) • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus AND • On MRI: Diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences AND • Follow up insufficient to confirm a monophasic nature of the illness (absence of relapse within a minimum of three months after the clinical nadir). LEVEL 3 • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND Focal or multifocal impairment of the central nervous system <i>with ≥ 1 of the following signs:</i> • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus. Exclusion criteria for all levels of diagnostic certitude • Authentication of an acute infection or of a differential diagnosis is compatible with the clinical picture • Relapse of the illness at any moment after a minimum period of three months of clinical improvement after the nadir of clinical symptoms. • MRI images or histopathology in the clinical diagnosis is compatible with the case definition with the diagnosis of ADEM. In Summary ADEM can be confirmed if: • The clinical diagnosis is compatible with the case definition. • All differentials diagnoses have been excluded • The CSF exam supports the diagnosis of ADEM. NB: Plan for diagnostic confirmation by a neurologist (and MRI if possible). Generally the illness completely resolves in a few months. The diagnosis must be confirmed by a clinical examination performed 3 months after the nadir of the clinical symptoms.	
ENCEPHALITIS	LEVEL 1 • Demonstration of acute inflammation of the central nervous system parenchyma (+/- the meninges) on histopathology	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	LEVEL 2 - Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND <i>One or more of the following signs:</i> - Absent or diminished reflexes to external stimuli (such as a loud noise or painful stimuli) - Absent or markedly diminished eye contact - Inadequate or absent response to an external stimuli - Seizures with loss of consciousness OR Focal or multifocal impairment of the central nervous system <i>with</i> ≥ 1 of the following signs: - Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) - Cranial nerve abnormality/abnormalities - Visual field defect/defects - Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) - Motor weakness (diffuse or focal, more often focal) - Sensory abnormalities - Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) - Cerebellar dysfunction, such as ataxia, dysmetria, cerebellar nystagmus AND <i>Two or more of the following signs:</i> - Fever ($\geq 37.5^{\circ}\text{C}$) - CSF: Pleocytosis >15 leukocytes/ mm^3 in a child 2 months of age or younger	presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AEI	Diagnosis/Level of Diagnostic Certainty	References
	— >5 leukocytes/ mm³ in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis. LEVEL 3 • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) AND <i>One or more of the following signs:</i> • Absent or diminished response to external stimuli (such as a loud noise, painful stimuli) • Absent or markedly diminished eye contact • Inconsistent or absent response to an external stimuli • Seizures with associated loss of consciousness OR Focal or multifocal impairment of the central nervous system <i>with ≥ 1 of the following signs:</i> • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) • Cerebellar impairment, such as ataxia, dysmetria, cerebellar nystagmus AND <i>One of the following signs:</i>	

Body system/ AEsI	Diagnosis/Level of Diagnostic Certainty	References
	• Fever ($\geq 37.5^{\circ}\text{C}$) • CSF: Pleocytosis – >15 leukocytes/ mm^3 in a child 2 months of age or younger – >5 leukocytes/ mm^3 in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis Evaluation Criteria • Exclude the presence of all diseases (cancer, toxic-metabolic encephalopathy, vascular problems, trauma, meningitis etc.) In Summary The diagnosis of encephalitis is confirmed if: • The clinical diagnosis is compatible with the case definition. AND • The CSF analysis is compatible with an encephalitis picture. AND • The differential diagnoses (especially meningitis) have been excluded.	
GUILLAIN-BARRÉ SYNDROME	LEVEL 1 • Bilateral weakness (symmetric) with flaccid extremities (usually of all 4 limbs) AND • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND • Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase AND • Electromyography: Electrophysiological signs the clinical diagnosis is compatible	Sejvar JJ, Kohl KS, Gidudu J, et al. The Brighton Collaboration Guillain-Barré Syndrome Working Group. Guillain-Barré Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine. 2011; 29(3): 599–612.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	with the case definition with GBS AND - Albuminocytologic dissociation: hyperproteinorachia (elevation of CSF protein) and normal CSF white cell count [< 50 cells/μl] AND - Absence of plausible differential diagnosis (to explain the motor weakness) LEVEL 2 - Bilateral AND flaccid weakness of the extremities AND - Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND - Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND - CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value) OR - If CSF not collected or results not available, electrophysiologic studies consistent with GBS AND - Absence of identified alternative diagnosis for weakness LEVEL 3 - Bilateral AND flaccid weakness of the extremities AND - Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities AND - Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND - Absence of plausible differential diagnosis (to explain the motor weakness) In Summary The diagnosis of Guillain-Barre Syndrome can be confirmed if: - The clinical diagnosis is compatible with the case definition - The poliovirus is not isolated from the stool - The CSF examination is compatible with GBS: Hyperproteinorachia (elevation of CSF protein), absence of pleocytosis. - There is diagnostic confirmation by a neurologist.	
GENERALIZED CONVULSIVE SEIZURE	LEVEL 1 - Witnessed sudden loss of consciousness AND - Generalized tonic, clonic, tonic-clonic or atonic motor manifestations LEVEL 2 - Reported sudden loss of consciousness AND - Generalized tonic, clonic, tonic-clonic or atonic motor manifestations LEVEL 3 - Reported sudden loss of consciousness AND - Other generalized motor manifestations In Summary The diagnosis of generalized seizure can be confirmed if: - The clinical diagnosis is compatible with the case definition. - The history of present illness evokes seizure activity - The etiological work up is negative: (i.e. acute intoxication,	Bonhoeffer J, Menkes J, Gold MS, et al; The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22:557-562.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	trauma, severe malaria etc. have all been excluded). (Amended 15 October 2020)	
HYPOTONIC HYPORESPONSIVE EPISODE (HHE)	LEVEL 1 - Hypotonia (muscular weakness) AND - Reduction or absence of response to sensory or verbal stimuli AND - Pallor or cyanosis LEVEL 2 - Indeterminate muscle tone AND - Reduction or absence of response to sensory or verbal stimuli AND - Pallor or cyanosis OR - Hypotonia (muscular weakness) AND - Reduction or absence of response to sensory or verbal stimuli AND - Indeterminate skin color LEVEL 3 - Normal muscle tone AND - Reduction or absence of response to sensory or verbal stimuli AND - Pallor or cyanosis OR - Hypotonia (muscular weakness) AND - Indeterminate response to sensory or verbal stimuli AND - Palor or cyanosis.	Bonhoeffer J, et al. Brighton Collaboration HHE Working Group. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004; 22(5-6): 563–568.
Hepato-Gastrointestinal and Renal System		
HEPATIC FAILURE	Major criteria Total serum bilirubin ≥ 1.5 times the upper limit of normal (ULN) OR	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and

Body system/ AEI	Diagnosis/Level of Diagnostic Certainty	References
	- Elevation of the serum transaminases (ALT, AST ≥ 3 times the upper limit of normal (ULN)) AND - Coagulopathy unresponsive to vitamin K (prothrombin time (PT) ≥ 15 seconds or INR ≥ 1.5). In Summary The diagnosis of hepatic insufficiency can be confirmed if: - The diagnosis can be considered if the major criteria are present and confirmed on at least two blood draws. - The etiologies of the most frequent causes of jaundice and alterations of liver function tests and, the non-hepatic encephalopathies are excluded: viral hepatitis, malaria, sickle cell anemia, exposure to toxins and medicines. NB: In case of fortuitous discovery of a perturbation in the hepatic panel without clinical manifestations, it is recommended to do a follow up hepatic panel.	presentation of immunization safety data. Vaccine. 2012;30(33): 5038–5058.
INTUSSUSCEPTION	I) Definition of criteria DIAGNOSTIC CRITERIA - Surgical criteria - Demonstration of intussusception during exploratory surgery - Imaging criteria - Demonstration of intussusception via non-barium or aircontrast enema; - Demonstration via ultrasound of an intra-abdominal mass with specific characteristics – target (or doughnut) sign on transverse images and pseudokidney or sandwich sign on longitudinal images – the reduction of these signs by hydrostatic enema is also confirmed by ultrasound. Major criteria	Bines JE, Kohl K, Forster J, et al and the Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:569–574.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	- Symptoms and signs of intestinal obstruction: - History of vomiting bile AND - Clinical examination shows acute abdominal distention and abnormal or absent bowel sounds OR - Radiological examination (plain abdominal X-ray) shows air-fluid levels and loops of distended small bowel. - Signs of intussusception, ≥ 1 following signs: - Abdominal mass - Rectal mass - Rectal prolapse - Plain abdominal X-ray shows a soft tissue mass - Abdominal ultrasound shows a soft tissue mass - Abdominal CT shows a soft tissue mass - Evidence of vascular compromise or venous congestion: - Anal bleeding OR "Currant jelly stools" OR - Blood detected during rectal examination Minor criteria - Predisposing factors: aged < 1 year, male - Abdominal pain - Lethargy - Pallor - Hypovolemic shock - Plain abdominal X-ray showing an abnormal and unspecific distribution of air in the intestines. II) Diagnostic certainty levels LEVEL 1 - Surgical criteria:	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	The demonstration of invagination of the intestine at surgery; AND/OR - Radiologic criteria: The demonstration of invagination of the intestine by either air or liquid contrast enema; OR The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on postreduction ultrasound; AND/OR - Autopsy criteria: The demonstration of invagination of the intestine. LEVEL 2 - Clinical criteria: Two major criteria or One major criterion and three minor criteria. LEVEL 3 - Clinical criteria: Four or more minor criteria.	
RENAL INSUFFICIENCY	Major criteria Creatinine ≥ 1.5 times the upper limit of normal (ULN) or 1.5 times the patient's initial value. Minor criteria Urine production $<0.5\text{ml/kg/hour}$ In Summary Renal insufficiency can be confirmed if: - The major criteria is present and confirmed (at least two blood draws) - The etiological diagnosis has been carried out.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038–5058.
Skin and Mucous Membranes & Bones and Joints		
HENOCH SCHÖNLEIN PURPURA	I) Definition of criteria MAJOR CRITERIA - Purpura (mandatory criterion) Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia - Abdominal pain Diffuse abdominal colicky pain with acute onset assessed by	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	history and physical examination. May include intussusception and gastrointestinal bleeding - Histopathology Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit - Arthritis or arthralgias Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. - Renal involvement Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or $\geq 2+$ on dipstick. MINOR CRITERIA - Other diagnoses unlikely (exclude meningitis) II) Diagnostic certainty levels LEVEL 1 - Purpura or petechiae (mandatory) with lower limb predominance AND ≥ 1 following criteria - Abdominal pain - Histopathology - Arthritis or arthralgias - Renal involvement AND - Absence of thrombocytopenia LEVEL 2 - Purpura or petechiae (mandatory) with lower limb predominance AND - Absence of thrombocytopenia.	
JUVENILE CHRONIC ARTHRITIS	Juvenile Chronic Arthritis is defined by an evolution of symptoms of at least	Medical websites resources: e.g. http://www.arthritis.co.za/jra.htm ;

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	three months. The clinical examination often reveals a child with growth retardation. The different clinical forms are the following: 1. Pauciarticular form (the most common form between 1 and 3 years of age). Clinically this presents with: • Involvement of four or less joints • Symmetric involvement of the small joints • Tenosynovitis of the flexor tendons and erosive nodules (frequent) • Rheumatoid factor seronegativity These signs can be associated with: • A positive anti-nuclear antibody (among 40 to 75% of children) • Uveitis 2. Polyarticular form • Affects 5 or more joints • Rheumatoid factor IgM can be positive or negative • Hips, cervical spine, hands and feet are the joints the most often affected, followed by the knees, wrists and ankles. • Among the patients seronegative for the rheumatoid factor, an association of fever, hepatosplenomegaly and symmetrical arthritis has been described. 3. Systemic form • Accompanied by a fever up to 39.5°C during at least two weeks • A typical rash on the trunk and thighs can be seen • Frequent involvement of the wrists, knees, ankles as well as the temporomandibular joint, and the hands. • The illness typically lasts between 2 and 5 years before complete resolution In Summary The diagnosis of Juvenile Chronic Arthritis (JCA) can be confirmed if:	http://emedicine.medscape.com/article/1007276-overview; http://www.med.univ-rennes1.fr/etud/pediatric/arthritis_cique.hthronm

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References	
	- The clinical diagnosis responds to the case definition - The biological panel shows signs of chronic inflammation - The most frequent differential diagnoses are excluded - If necessary, the diagnosis should be confirmed by a specialist. The symptoms must last at least 3 months before concluding JCA. A confirmation of the diagnosis requires a follow up visit 3 months after the beginning of the illness.		
STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)	Symptoms start by a feeling of malaise, fever, headache, cough and conjunctivitis. Then the macular eruption appears, rapidly transforming into confluent bullae over one to three days. Nails and eyebrows can be lost due to epidermal involvement. The diagnosis of Stevens-Johnson syndrome becomes evident with the appearance of cutaneous lesions, the rapid and expansive progression of symptoms, which include two mucosal sites.		
	Diagnosi s	Lesion morpholo gy	Body surface area detachme nt
	SJS	Maculae, bullae, atypical target lesions	≤10%
	SJS-TEN overlap	Maculae, bullae, atypical target lesions	10-30%
	TEN with spots	Maculae, bullae, atypical target lesions	≥30%
	In Summary The diagnosis of STEVENS-JOHNSON SYNDROME (SJS) can be confirmed if: The clinical diagnosis responds to the case definition		

Body system/ AEI	Diagnosis/Level of Diagnostic Certainty	References
	- The etiological research indicates exposure to a triggering element (medication, immunization, toxin, febrile state, virus) - In case of doubt, consultation of a specialist is necessary.	
KAWASAKI DISEASE	I) DEFINITION OF CRITERIA Major criteria - Fever ≥ 5 days - Clinical criteria: Signs of mucocutaneous inflammation: - Polymorphic exanthem - Non-exudative bilateral conjunctivitis - Involvement of the lips and oral cavity: erythema, cracked lips, "strawberry red" tongue, diffuse inflammation of the oral and pharyngeal mucosa - Involvement of the hands and feet: erythema of the palms and/or soles, oedema of the hands and/or the feet. Hand and/or foot periungual peeling skin (week 2-3 of disease course) - Usually unilateral neck lymphadenopathy (≥ 1.5 cm) Minor criteria - Erythrocyte sedimentation rate ≥ 40 mm/h or CRP ≥ 3 mg/dL - Echocardiogram showing coronary artery or heart involvement II) Diagnostic certainty levels LEVEL 1 - Fever ≥ 5 days AND ≥ 4 clinical criteria: AND - Other diagnoses unlikely after clinical examination and laboratory tests LEVEL 2 - Fever ≥ 5 days	Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND < 4 clinical criteria: AND - Erythrocyte sedimentation rate $\geq$ 40 mm/h OR CRP $\geq$ 3 mg/dL AND - Other diagnoses unlikely after clinical examination and laboratory tests LEVEL 3 - Fever $\geq$ 5 days AND < 4 clinical criteria: AND - Normal erythrocyte sedimentation rate OR normal CRP AND - Coronary artery or heart involvement AND - Other diagnoses unlikely after clinical examination and laboratory tests.	
Cardiovascular system and blood disorders		
ANAPHYLAXIS	For all levels of diagnostic certainty - Sudden onset AND - Rapid progression of signs and symptoms AND - Involving multiple ($\geq$ 2) organ systems, as follows: LEVEL 1 $\geq$1 major dermatological criterion AND $\geq$1 major cardiovascular AND/OR $\geq$1 major respiratory criterion LEVEL 2 $\geq$1 major cardiovascular AND $\geq$1 major respiratory criterion OR $\geq$1 major cardiovascular OR respiratory criterion AND $\geq$1 minor criterion involving $\geq$1 different system (other than	Rüggeberg JU, Gold MS, Bayas JM et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-5684.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	cardiovascular or respiratory systems) OR • ≥ 1 major dermatologic AND ≥ 1 minor cardiovascular AND/OR minor respiratory criterion LEVEL 3 • ≥ 1 minor cardiovascular OR respiratory criterion AND • ≥ 1 minor criterion from each of ≥ 2 different systems/categories In Summary The diagnosis can be confirmed if: • The clinical diagnosis is compatible with the case definition (at least 2 major signs/criteria) • Symptom onset occurred after a short period of time (a few minutes to hours) after exposure to a food item, an insect sting, a vaccination, or contact with a product allergen (such as peanuts) • If the child reports a known allergy, one major sign/criteria following exposure to a known allergen is sufficient for a diagnosis of anaphylaxis.	
DIABETES MELLITUS TYPE 1	• Serum fasting glucose $\geq 7\text{mmol/L}$ ($> 126\text{ mg/dL}$) OR • Postprandial serum glucose $\geq 11.1\text{mmol/L}$ ($\geq 200\text{ mg/dL}$) 2 hours after ingesting 1.75 g/kg (max. 75g) of glucose (oral glucose tolerance test) OR • A1C Hemoglobin $\geq 6.5\%$ AND Hyperglycemia AND • No other cause of hyperglycemia In Summary The diagnosis of type 1 diabetes mellitus can be confirmed when a confirmed hyperglycemia responds to the case definition.	WHO Definition and Diagnosis of diabetes mellitus and intermediate hyperglycaemia, 2006 and http://www.nlm.nih.gov/medlineplus/encyclopedia.html
THROMBOCYTOPE NIA	LEVEL 1	Wise RP, Bonhoeffer J, Beeler J, et al. Brighton Collaboration Thrombocytopenia Working

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	- Platelet concentration < to 150 x 10⁶/mL AND - Confirmation par blood smear OR - Clinical signs of spontaneous bleeding (i.e. non traumatic)* LEVEL 2 - Platelet concentration < to 150 x 10⁶/mL. <i>*Spontaneous bleeding (i.e. non traumatic), includes purpura (i.e. petechiae, purpura sensu stricto, ecchymoses) exudative hemorrhage, hematomas, hematemesis, occult bleeding par rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding, conjunctival bleeding, intracranial bleeding.</i> In Summary The diagnosis of thrombocytopenia can be confirmed if: - It corresponds to the level 1 of diagnostic certainty case definition - An etiological investigation was carried out.	Group. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5717–5724.
Surveillance indicators		
INJECTION SITE ABSCESS Abscess of infectious aetiology	LEVEL 1 - Spontaneous or surgical drainage of the mass contents AND - Microbiologic confirmation (Gram stain, culture or other exam) of the presence of bacteria with or without altered polynuclear neutrophils in the aspirated/drained fluid. LEVEL 2 In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. - Spontaneous or surgical drainage of the purulent fluid from the mass contents	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31): 5821–5838.

Body system/ AEI	Diagnosis/Level of Diagnostic Certainty	References
	OR - Mass collection diagnosed by an imaging technique or the mass is fluctuant. AND - Signs of localized inflammation including at least one of the following aspects: erythema, pain on light palpation, and warmth to the touch at the injection site. AND - Resolution of symptoms after antibiotic therapy	
INJECTION SITE ABSCCESS Sterile abscess	LEVEL 1 - Spontaneous or surgical drainage of the mass contents AND - Drainage liquid obtained before the beginning of antibiotic therapy and no infectious pathogen found on examination (Gram stain, culture or other examination) LEVEL 2 In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. - Non purulent fluid is spontaneous or surgically drained from the mass OR - A collection of material, such as fluid, is diagnosed by imagery or, there is fluctuance on palpation. AND - Absence of signs of local inflammation: erythema, pain on light palpation, warmth to the touch at the injection site OR - No improvement following a course of an antibiotic treatment. In Summary	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31): 5821–5838.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	An injection site abscess is confirmed by a clinical diagnosis responding to the case definition.	
FOOT POSITIONAL DEFORMATIONS	Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot OR Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg OR Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.	

Annex 6 Study specific guidance document**SCREENING TOOL FOR ASSESSING SERIOUS DELAYS IN DEVELOPMENTAL MILESTONES AND/OR PHYSICAL DISABILITIES IN CHILDREN FROM 3 MONTHS TO 36 MONTHS OF AGE**

If the caregiver responds negatively to 2 or more questions, the child should be referred to a medical consultation for further investigations according to routine medical practice. All questions are to be responded by YES or NO.

A. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 3-4 MONTHS

A1	Does your baby smile to familiar people?
A2	Has your baby begin to make sounds?
A3	Does your baby follow moving people or objects with eyes?
A4	Does your baby hold his head unsupported?
A5	Does your baby bring his hands to his mouth?

B. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 5-9 MONTHS

B1	Does your baby grasp objects with both hands?
B2	Can your baby sit with support?
B3	Does your baby respond to sounds by making sounds?
B4	Does your baby know familiar faces and know if someone is a stranger?

C. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 10-15 MONTHS

C1	Does your baby sit without support?
C2	Does your baby crawl on hands and knees?
C3	Does your baby take steps holding on to furniture, walls, etc?
C4	Does your baby try to imitate words and sounds and respond to simple requests?
C5	Does your baby show fear in some situations?

D. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 16-21 MONTHS

D1	Does your child point to things?
D2	Does your child say several single words?
D3	Does your child walk without any help?
D4	Does your child use 4-10 different words?

E. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 22-28 MONTHS

E1	Does your child copy others, especially adults and older children?
E2	Does your child say short sentences?
E3	Does your child follow simple instructions?
E4	Does your child run?

E5	Does your child scribble or draw?
E6	Does your child enjoy simple stories or songs?

F. SCREENING QUESTIONS FOR CAREGIVER OF CHILDREN AGED 29-36 MONTHS

F1	Does your child walk, run, climb, and kick a ball easily?
F2	Does your child talk using 2 to 3 short sentences?
F3	Can your child say his name or age?
F4	Does your child understand what "two" means?
F5	Does your child feed himself?

Annex 7 Amendment to the protocol

GLAXOSMITHKLINE BIOLOGICALS VACCINE VALUE & HEALTH SCIENCE (VVHS) Protocol Amendment 1	
eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Amendment number:	Amendment 1
Amendment date:	24 April 2019
Co-ordinating author:	PPD, Lead Scientific Writer (GSK Biologicals)
Rationale/background for changes: Considering the RTS,S/AS01_E vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site. • Protocol Amendment 1 has been put in place because the EPI-MAL-002 study will no longer be conducted in Malawi meaning that the EPI-MAL-003 sample size of the before/after comparison has been updated. • The reference to EPI-MAL-002 study conduct in Malawi was removed and clarifications provided in other sections.	

Amended text has been included in bold italics and deleted text in strikethrough in the following sections:

- 1 **Section 1** – EU PAS Register No included
- 2 **Section 1 - Countries of study:** Sites in sub-Saharan Africa (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system ~~census and vaccine registries.~~

Sites in sub-Saharan Africa (SSA) countries have been ~~or will be~~ selected -----

In order to align with the MVIP, the study sites for the GlaxoSmithKline (GSK) Phase IV studies have been, ~~or will be,~~ selected from the 3 countries where the RTS,S/AS01_E vaccine will be implemented. Sites from ***Ghana and Kenya*** ~~these 3 countries~~ that were

part of study EPI-MAL-002 should become study sites in study EPI-MAL-003 which will be exposed clusters.

- 3 **Section 1 - Authors:** PPD, Clinical and Epidemiology Scientist (Keyrus Biopharma for GSK Biologicals), PPD, Statistician (4Clinics for GSK Biologicals), PPD, Epidemiology Lead – Malaria (GSK Biologicals), PPD, Project Delivery Lead (GSK Biologicals), PPD, Clinical Laboratory Sciences Study Manager (Business & Decision for GSK Biologicals), PPD, Senior Study Delivery Lead (GSK Biologicals), PPD, Africa Senior Local Delivery Lead (GSK Biologicals), PPD, Local Delivery Lead (GSK Biologicals), PPD. To be confirmed, Local Medical Leads (GSK Biologicals).
- 4 **Section 1-Countries of study:** Sites in sub-Saharan Africa (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system census and of vaccine registries.
- 5 **Responsible Parties:** PPD (DVM, MSc, PhD; Senior Epidemiology Lead - Malaria) and PPD (PhDMD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.
- 6 **Section 2 Opinion Holder:** © 2017-2019 GSK group of companies or its licensor.
- 7 **Section 4 Abstract- Rationale and background:** RTS,S/AS01E will be is the first vaccine to be implemented for the prevention of malaria and it is will be the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01E vaccine will be implemented. Sites from **Ghana and Kenya** these 3 countries that were part of study EPI-MAL-002 **are exposed clusters in EPI-MAL-003** should become study sites in EPI-MAL-003 which will be exposed clusters. The first vaccine introduction is foreseen in 2018 2019.

8 **Section 4 Abstract- Population, including the setting and study population:**

~~Some sites have already been identified to conduct the~~ **All** EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005 studies **sites have been identified** from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system census and of vaccine registries.

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01E in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria have ~~started~~ **enrolled** for EPI-MAL-002

In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01E vaccine will be

implemented. Sites from **Ghana and Kenya** that were part of study EPI-MAL-002 **are exposed clusters in EPI-MAL-003** ~~should become study sites in EPI-MAL-003 which will be exposed clusters.~~

~~In case one or more of the sites conducting EPI-MAL-002 cannot participate in EPI-MAL-003, a replacement strategy has been elaborated. It could consist of extending the recruitment period (depending on vaccine implementation strategy).~~

9 Section 4 Abstract- Data sources:

- Total number of children < 5 years of age (**according to year and gender**) recorded at the beginning of the study, at least once a year during the study duration and at the end of the study;
- Other demographic data (cause and date of deaths, migrations), **if available**;
- Information related to vaccination, **if available**.

10 Section 5 Amendments and Updates:

Amendment 1 Final:24 April 2019.

The rationale for protocol amendment 1, is provided in Annex 7. None.

11 Section 6 Milestones: This programme **initially planned will to** make the RTS,S/AS01_E vaccine available in selected areas, starting in 2018

Start of data collection	Q2 2018* Q1 2019
End of data collection	Q4 2024 Q3 2024**
Study progress reports	1 progress report every 6 months
Interim epoch analysis	Q4 2024 Q3 2022*** and ad-hoc (if triggered by a safety signal)
Registration in the EU PAS register	To be determined
Statistical analysis completed	Q3 2024 Q3 2025
Final report of study results	Q4 2024 Q4 2025

* Tentative; dependent on implementation of vaccine use by Ministry of Health

Tentative date; depending on recruitment timelines **and implementation of vaccination by the Ministries of Health

*** Tentative date, depending on recruitment timelines and implementation **of vaccination by the Ministries of Health**

12 Section 7.1 Background: RTS,S/AS01_E ~~will be~~ **is** the first vaccine to be implemented for the prevention of malaria and it ~~will be~~ **is** the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

If the RTS,S/AS01_E vaccine is implemented at the expected target of **2019 2018**, EPI-MAL-002 and EPI-MAL-003 may partly be run concomitantly in the same study sites.

Sites selection has been/~~will be~~ done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO

13 Section 7.4 Summary of the study rationale: The first vaccine introduction is foreseen in **2019 2018**, if approved and recommended by local health authorities.

As much as possible, sites have been selected for EPI-MAL-002 and EPI-MAL-005 based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system ~~census and vaccine registries~~.

- 14 **Section 9.1 Study design: Catch-up group:** Children *identified at 1st RTS,S/AS01_E dose administration (schedule will depend on pilot implementation programme and national regulation)* who *either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start*. ~~identified at 1st RTS,S/AS01_E dose administration (schedule will depend on pilot implementation programme and national regulation).~~ This at group will include only RTS,S/AS01_E vaccinated children (from exposed clusters). Indeed, the objective of this catch-up is to include all the children who will receive the RTS,S/AS01_E vaccine and who could not be recruited at *the* time of DTP/HepB/Hib administration *because the study had not yet started*.

All ~~enrolled~~ children *enrolled in the active surveillance* will be followed-up through home visits (Figure 1, see also Section 9.2.7.1). Children receiving at least one dose of RTS,S/AS01_E will be defined as the vaccinated study participants. For these children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01_E vaccine, up to 2 years after the last dose. For children *not vaccinated with RTS,S/AS01_E in the exposed clusters whose parents/LARs elect not to have them vaccinated with RTS,S/AS01_E (unvaccinated children) and children in the unexposed clusters*, visits will be scheduled at equal points in time. *Note that, in practice, it is possible to find RTS,S/AS01_E vaccinated children in an unexposed cluster (e.g., parents/LARs from an unexposed cluster can decide to have their child vaccinated in another cluster where the vaccine is available) or RTS,S/AS01_E unvaccinated children in an exposed cluster (e.g. parents/LARs from an exposed cluster can decide not to have their child vaccinated).*

Figure 1 footnote: The catch-up group of the active surveillance will include a group of *children identified at 1st RTS,S/AS01_E dose administration (schedule will depend on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start*. This group includes RTS,S/AS01_E vaccinated children from exposed clusters.

~~children who received at least one dose of DTP/HepB/Hib, whose age corresponds to the age after 3rd DTP/HepB/Hib dose and identified at the 1st dose of RTS,S/AS01_E vaccine.~~

- 15 **Section 9.1.1 Rationale for the study design:** In addition, as the vaccine will be implemented using a cluster design (sites in Kenya and Ghana ~~Malawi~~ where the EPI-MAL-002 ~~was~~ *is* running should become part of the intervention areas, and new sites ~~will be have been~~ selected to be part of the comparison areas of the EPI-MAL-003), a concurrent unvaccinated cohort may be added as a comparator.

Selected study sites are expected to have a HDSS or equivalent surveillance system in place. If a site does not have *a HDSS* ~~an equivalent surveillance system~~ in place, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

- 16 **Section 9.2.1 Study population:** Note: If a site is not part of the INDEPTH network ~~or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01_E vaccine is planned to be implemented according to MVIP, ~~were/will be~~ added to the already defined study sites for EPI-MAL-002 as described below.

In order to align with the MVIP, the study sites for the GSK's baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) have been, ~~or will be~~, selected as follows:

- Sites have been, ~~or will be~~, selected from the 3 countries where the RTS,S/AS01_E vaccine will be implemented ***in the framework of the MVIP***. ~~The only exception is for Burkina Faso sites that started EPI-MAL-002 have early terminated the study activities on 06 June 2018 (with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI). Burkina Faso sites will not be included in EPI-MAL-003 because the MVIP will not take place in the country.~~ ***as they have already started EPI-MAL-002. They will continue participating in EPI-MAL-002 until study end; however they will not be included in EPI-MAL-003 because the MVIP will not take place in the country. Their data will therefore not be included neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies, nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study (e.g. background incidence of meningitis for study sample size and the exposure to other vaccines). Considering the RTS,S/AS01_E vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site.***
- As per WHO guidance, study sites from Ghana and Kenya ~~and Malawi~~ included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters. ~~Two new sites located in Malawi are planned to be included in EPI-MAL-002.~~

Exposed and unexposed clusters will be comparable in terms of malaria transmission, health facilities level, geographical region and population size.

- As per WHO guidance, study sites from Ghana and Kenya ~~Malawi~~ included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.

- Selection of the ~~unexposed~~ **remaining** study sites/clusters that will be included in the EPI-MAL-003 study is **completed ongoing** and is fully embedded in the MVIP.
 - In summary: currently, a total of 35 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa] ~~2 in Burkina Faso [Sapone, Nouna]~~) are enrolling study participants in the EPI-MAL-002 study. ~~Two sites in Malawi have fulfilled the criteria of the study feasibility assessment and are planned to initiate the EPI-MAL-002 study in Q1-Q2-2018.~~ With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 **sites** should become exposed study sites/clusters in EPI-MAL-003. Selection of the **remaining** ~~unexposed~~ study sites/clusters that will be included in the EPI-MAL-003 study is **completed ongoing** and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.
 - ~~A replacement strategy has also been elaborated in case one or more of the sites conducting EPI-MAL-002 cannot participate in EPIMAL003. It could consist of extending the recruitment period (depending on vaccine implementation strategy).~~
- 17 **Section 9.2.2 Eligible population:** In addition, parents/ LARs will be invited to enrol their child into the active surveillance when children ***are presenting for 1st administration of RTS,S/AS01_E vaccine and who either received all DTP/HepB/Hib doses before study start or who received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start, are presenting for 1st administration of RTS,S/AS01_E vaccine (catch-up group).***
- For enhanced hospitalisation surveillance,** parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are under the age of 5 years and who can be linked to the HDSS or equivalent surveillance system ~~census~~, will be approached to enrol their child into this study
- 18 **Section 9.2.3 Inclusion criteria:** For enrolment in the active surveillance – Catch-up group: children must be aged < 18 months, received at least one dose of DTP/HepB/Hib vaccine, whose age corresponds to the age after the 3rd dose of DTP/HepB/Hib vaccine, ~~(= identified at 1st RTS,S/AS01_E dose administration who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start)~~ and identified at 1st RTS,S/AS01_E dose administration (This group will include children from exposed clusters only)
- 19 **Section 9.2.6.9 Death:** * If a site is not part of the INDEPTH network, ~~or does not have an equivalent surveillance system in place,~~ the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.
- 20 **Section 9.2.7.1.1 Enrolment and follow-up:** Parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine (V0) (any visit for DTP/HepB/Hib vaccine) ***or 1st RTS,S/AS01_E dose during the catch-up group enrolment period (Section 9.2.3).***

- 21 **Section 9.2.7.1.2 Surveillance of AESI, other AE leading to hospitalisation or death, meningitis and malaria during follow-up:** If a site is not part of the INDEPTH network, ~~or does not have an equivalent surveillance system in place,~~ the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites

An alert system by mobile phone will be developed in the early stages of EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate suspected AESI, meningitis or ~~severe~~ **cerebral** malaria episodes to study staff in near real time.

- 22 **Section 9.2.7.1.4. Outline of study procedures Table 4 footnote 1:**

Completion of Enrolment visit procedures should be achieved within a maximum of 10 days after the administration of DTP/HepB/Hib vaccine for the DTP group or at Visit 1 for the catch-up group.

Table 4 footnote 6: If a site is not part of the INDEPTH network, ~~or does not have an equivalent surveillance system in place,~~ the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites

- 23 **Section 9.2.7.3.2. Laboratory assays:** ~~GSK~~**The Principal Investigator or designee of each study site/cluster** will ensure ***monitoring of the availability of*** ~~that all~~ consumables and reagents ~~for are available to perform first-line routine~~ ***practice testing for of all diseases under investigation study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents according to good medical practice and routine practice.***

- 24 **Section 9.2.7.4.1. Meningitis cases:** If needed, ***in case of stock out,*** GSK will ***assess the need of*** supplementing reagents and consumables ~~to ensure that all diagnostic procedures can be conducted according to protocol.~~

Job Aids for medical staff and training on standardised diagnosis are put in place ***as*** in EPI-MAL-002 to improve the sensitivity and specificity of the case diagnosis for all meningitis.

- 25 **Final meningitis case ascertainment:** The experts will be blinded with regards to ***RTS,S*** vaccine exposure ***as much as possible.***

They will also be provided with all the data available in the eCRF (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records).

- 26 **Section 9.2.7.4.2 AESI:** The experts will be blinded with regards to ***RTS,S*** vaccine exposure ***as much as possible.*** They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.1).

- 27 **Section 9.2.7.4.3. Other AE leading to hospitalisation or death:** They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (*excluding RTS,S*) and any other relevant information identified in patient medical records) and classify the cases.
- 28 **Section 9.2.7.4.4. Malaria:** They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (*excluding RTS,S*) and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.6.)
- 29 **Section 9.2.7.7. Capacity building: Laboratory support:** *GSK will support the first line laboratory testing. First, an external laboratory, CLS, is contracted to assess laboratory quality system and as needed, will provide technical assistance in quality systems as well as laboratory training and support/coaching. Second, the principal investigator or designee of each study site/cluster is requested to ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents such as* ~~GSK will ensure that all first line laboratory diagnostic procedures can be conducted according to routine practice by complementing reagents and consumables where needed. Specifically, if necessary, lumbar puncture kits and or malaria RDT will be provided to the sites to facilitate adherence to the routine procedures required for diagnosis of meningitis and malaria, respectively. In addition, an external laboratory, CLS, is contracted to provide Quality Assessment & Control and training for laboratory technicians.~~

Use of time sensitive event device: In addition to data systems traditionally utilised in post approval safety studies, an alert system using mobile phones has been developed **as** in EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate time-sensitive events to study staff. The alert system will be implemented in order to closely monitor AESI, meningitis cases, and ~~severe~~ **cerebral** malaria and to ensure that all the procedures and tests specified in the protocol are done for a proper diagnosis of the diseases while maintaining the safety of the patients.

In addition, GSK will also be made aware of AESI, meningitis cases, and ~~severe malaria cases including cerebral malaria cases~~ (GSK will not receive any patient's personally identifiable information via that system).

- 30 **Section 9.3.3.2. Recorded in EPI-MAL-005:** Bednet use, seasonal malaria chemoprevention and other malaria control measures will also be collected at the ~~HDSS or equivalent surveillance system~~ **study site** population and individual levels (which will be summarized at centre level).
- 31 **Section 9.4.1. HDSS (or equivalent surveillance system) databases (or equivalent surveillance systems):** ~~Each HDSS or equivalent surveillance system site maintains a demographic database which is updated on a regular basis to include births, deaths, immigrations and emigrations. Data regarding vaccinations~~ **may** is also included in the study site database.

If a site is not part of the INDEPTH network or does not have an equivalent surveillance system in place, the INDEPTH procedures for demographic census and for verbal autopsy might be implemented to ensure consistency across study sites.

32 **Section 9.4.2. Active surveillance and enhanced hospitalisation surveillance:** The surveillance system will also be implemented in the study area at each health care level within the HDSS or equivalent surveillance system catchment area.

33 **Section 9.5.3.1. Before-after design:**

Table 9 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the before-after design based on a Poisson regression method [PASS, 20052012]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	10827.64665.0	64.244.0	19.214.7	3.93.4
6 weeks	329.8498.2	13.710.8	6.55.4	2.42.2
3 months	91.961.4	7.86.4	4.33.8	2.01.8
6 months	31.422.7	4.84.1	3.12.8	1.71.6
12 months	12.810.4	3.22.9	2.32.4	1.51.4
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E				
2 weeks	9721.64453.2	61.243.4	18.614.4	3.83.4
6 weeks	302.2189.0	13.110.6	6.35.4	2.32.1
3 months	84.156.8	7.56.2	4.23.7	1.91.8
6 months	29.021.6	4.64.0	3.02.7	1.71.6
12 months	12.09.7	3.12.8	2.32.4	1.51.4

* This incidence corresponds to the assumption considered for meningitis

** This incidence corresponds to the assumptions considered for cerebral malaria

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, 20052012]

Period at-risk	Baseline incidence 3000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	1.771.66	2.22.04
6 weeks	1.41.38	1.71.57
3 months	1.31.28	1.51.42
6 months	1.21.21	1.41.31
12 months	1.171.15	1.251.22
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	1.81.66	2.22.03
6 weeks	1.41.37	1.61.56
3 months	1.31.28	1.51.41
6 months	1.21.21	1.31.30
12 months	1.171.15	1.241.21

34 Section 9.5.4.2. Impact using the before-after design:

Table 14 Detectable total effect for severe malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 20052012]

	Severe Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	~~21%18%~~	~~23%20%~~	~~26%23%~~
D3-> D4+1Y (50%)	0.03		~~16%14%~~	~~18%16%~~	~~21%18%~~
D3-> D4+1Y (75%)	0.03		~~15%13%~~	~~16%14%~~	~~18%16%~~

35 Section 9.5.5.2. Impact using the before-after design:

Table 17 Detectable total effect in terms of relative risk for cerebral malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005 2012]

	Cerebral Malaria	Power	80%		
			Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	~~1,711.62~~	~~1,821.72~~	~~1,991.86~~
D3-> D4+1Y (50%)	0.005		~~1,511.43~~	~~1,581.49~~	~~1,701.58~~
D3-> D4+1Y (75%)	0.005		~~1,451.38~~	~~1,511.44~~	~~1,601.52~~

36 Section 9.5.6.2. Impact using the before-after design:

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 20052012]

	Mortality	Correlation of covariates					
		Overall			Per gender		
		0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.03	~~1.251.22~~	~~1.281.25~~	~~1.331.29~~	~~1.371.33~~	~~1.421.37~~	~~1.501.44~~
D3-> D4+1Y (50%)	0.03	~~1.191.16~~	~~1.211.18~~	~~1.251.21~~	~~1.271.23~~	~~1.311.26~~	~~1.361.31~~
D3-> D4+1Y (75%)	0.03	~~1.161.14~~	~~1.191.16~~	~~1.221.19~~	~~1.241.21~~	~~1.271.23~~	~~1.321.28~~

37 **Sections 9.7.1., 9.7.2 and 9.7.3** “Total cohort” replaced by “enrolled set”,
“According-to-protocol (ATP) cohort” replaced by “Analysis set” and “cohort”
replaced by “set” where applicable.

38 Section 9.7.6.2.2. Meningitis cases monitoring: *In the exposed clusters, Among vaccinated subjects from both exposed and unexposed clusters, the maximum likelihood and the log-likelihood ratios will be estimated each month if new cases*

are detected by means of MaxSPRT method [Kulldorf, 2011] on all suspected meningitis occurring within the at-risk period at the site level.

- 39 **Section 9.9. Limitations of the research methods:** ~~Candidate countries with moderate/high transmission of malaria and where the pilot implementation is likely to take place have already been identified for participation to EPI-MAL-003. Other settings in SSA with moderate to high transmission of malaria, from the 3 countries where the RTS,S/AS01_E vaccine will be implemented (see Section 9.2.1), might be added to the already defined study sites, and/or recruitment in the sites already defined might be increased to reach the target number of study participants, ensuring alignment with countries identified by WHO for the staged pilot implementation.~~

For the study sites of EPI-MAL-003 ~~which are unexposed clusters and where the EPI-MAL-002 was not conducted~~, training will be provided before start of EPI-MAL-003.

The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts (blinded to **RTS,S** vaccination status **as much as possible**).

*If a site is not part of the INDEPTH, ~~or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

- 40 **Section 13 References: PASS 2012: Poisson Regression Power Analysis (Signorini D). 'Sample size for Poisson regression', Biometrika. 1991;78(2): 446-450.**

- 41 **Annex 1 List of stand-alone documents:**

No.	Document Reference No	Date	Title
7.	115056 (EPI-MALARIA-003 VS AME)	24 April 2019	<i>Amendment to the protocol</i>
8.	115056 (EPI-MAL-003 VS AME)	24 April 2019	Protocol Amendment 1 sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	24 April 2019	Protocol Amendment 1 investigator agreement
10.	115056 (EPI-MAL-003 VS AME)	24 April 2019	ENCePP Checklist for study protocols

GLAXOSMITHKLINE BIOLOGICALS VACCINE VALUE & HEALTH SCIENCE (VVHS) Protocol Amendment 2	
eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Amendment number:	2
Amendment date:	15 October 2020
Co-ordinating author:	PPD Lead Scientific Writer (GSK)
Rationale/background for changes: - GSK decided to focus the co-primary study objectives to events classified as identified risk (febrile convulsion) or potential risk (meningitis, cerebral malaria) as per <i>Mosquirix</i> RMP. As a consequence, the study objective ‘other AEs leading to hospitalisation’ is now considered as a secondary objective. - As the term “Other AEs leading to hospitalisation or death” intended to refer to all the hospitalisations due to other AEs (including the fatal ones) and does not include fatalities that did not occur in the hospital, “or death” has been removed in order to avoid any confusion. - The EHS eligibility criteria has been revised to include only subjects who are at least 6 weeks and < 5 years of age to allow collection of medical events for a targeted population (avoiding the collection of events related to perinatal period, except foot positional deformation as birth defect). The MVIP is considering implementing the malaria vaccine in unexposed clusters as from 2023. This decision will directly impact the temporal (before/after) and concurrent (exposed versus unexposed clusters) comparisons. Based on this, GSK decided to stop the EHS recruitment as from 01 January 2023 in sites that were not involved in the EPI-MAL-002 study and study conclusion will be conducted in a timely manner for already enrolled subjects in those sites (EHS will stop in all sites in Malawi, Siaya and Nyando sites in Kenya and unexposed sites in Ghana). Measures that may be applicable during special circumstances (e.g., COVID-19 pandemic) in order to protect participant’s welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity have been outlined. The mobile phone alert system that was planned to be implemented will no longer be implemented and wording about it in the protocol has been deleted. There was an inaccuracy in the baseline incidence of mortality used in the sample size computations for the risk and for the effectiveness and impact on mortality overall and per gender. The baseline incidence has been corrected to 1,000/100,000 person-years according to World Bank estimates.	

Amended text has been included in bold italics and deleted text in ~~strikethrough~~ in the following sections:

1. **Section 1 - Research question and objectives:** Co-primary objectives: To estimate the incidence of adverse events of special interest (AESI), ~~and of other adverse events (AE) leading to hospitalisation or death,~~ in children vaccinated with RTS,S/AS01E.
2. **Section 1 – Authors:** PPD [REDACTED] Epidemiology Lead – Malaria (GSK Biologicals), PPD [REDACTED], **Epidemiology Lead - Malaria** Clinical and Epidemiology Scientist (GSK Biologicals), PPD [REDACTED], **Oversight Data Manager**, PPD [REDACTED], PPD [REDACTED] / **(ICON for GSK Biologicals)**, Mobile Phone Alert System: Parexel (represented by PPD [REDACTED], Senior Project Manager)
3. **Section 2 – OPINION HOLDER:** © 2017-~~2019~~ GSK group of companies or its licensor.
4. **Section 3 - RESPONSIBLE PARTIES:** PPD [REDACTED] (~~DVM, MSc, PhD; Senior Epidemiology Lead – Malaria~~) and PPD [REDACTED] (**PhD; Epidemiology Lead – Malaria**) / PPD [REDACTED] (MD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.
5. **Section 4 – ABSTRACT: Rationale and background:** The first vaccine introduction ***started in April*** is ~~foreseen in 2019 in Malawi and Ghana.~~

other adverse events (AE) leading to hospitalisation ~~or death,~~

The three studies ~~will be~~ **are** conducted in similar if not identical settings and with the same methodology for identification and characterisation of the events of interest

6. **Section 4 – Research question and objectives: Co-primary objectives:** To estimate the incidence of AESI, ~~and of other AE leading to hospitalisation or death,~~ in children vaccinated with RTS,S/AS01E.

Secondary Objectives – Safety:

- To estimate the incidence of other AEs leading to hospitalisation.
- To describe risk factors for AESI, ~~other AE leading to hospitalisation or death,~~ meningitis, and malaria.
- To describe the causes of hospitalisation (including AESI, ~~other AE,~~ meningitis and malaria).
- To assess the potential association between vaccination and AESI, ~~and other AE leading to hospitalisation or death~~ by comparing the incidence of these events in children vaccinated with RTS,S/AS01E with the incidence of these events in children not vaccinated with RTS,S/AS01E.
- ***To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01E with the incidence of these events in children not vaccinated with RTS,S/AS01E.***

Effectiveness and impact: the incidence of ~~all-cause hospitalisations and~~ hospitalisations attributed to malaria (including *P. falciparum*).

7. **Section 4 – ABSTRACT: Study design:** The diseases under surveillance for safety include AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and severe malaria including cerebral malaria.

Unexposed clusters: Study sites where the RTS,S/AS01_E vaccine will not be implemented *at the beginning of* ~~in~~ the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.

8. **Section 4 – ABSTRACT: Variables: Co-primary endpoints:**

- ~~Occurrence of other AE leading to hospitalisation or death~~

Secondary endpoints:

Safety endpoints

- Occurrence of hospitalisation (including those attributed to an AESI, ~~other AE~~, meningitis or malaria), or death.
- ***Occurrence of other AE leading to hospitalisation***

9. **Section 4-ABSTRACT: Data sources**

- Data relevant to the diagnosis of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and malaria (including cerebral malaria)
- Baseline incidence rates of AESI, other AE leading to hospitalisation or ~~death~~.....

10. **Section 4 - ABSTRACT: Study size**

- With the before-after design, and depending on the follow-up, the total effect for severe malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, ranges from ~~14~~ 16% to ~~20~~ 23%, and the direct effect, from 23% to 33%.
- With the before-after design, and depending on the follow-up, the total effect for cerebral malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, expressed as RR ranges from ~~1.51-1.44~~ to **1.82** ~~1.87~~, and the direct effect, from ~~-1.55 1.88~~ to **1.88** ~~2.66~~.

11. **Section 4 – ABSTRACT: Data analysis**

Analysis of co-primary objectives: The incidence rate of each AESI, ~~and other AE leading to hospitalisation or death~~ will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable.

12. **Section 5 – AMENDMENTS AND UPDATES:**

Amendment 2 Final: 15 October 2020

The rationales for protocol amendment 1 & **protocol amendment 2, is are** provided in Annex 7.

13. **Section 6 – MILESTONES:** This programme initially planned to make the RTS,S/AS01_E vaccine available in selected areas, starting in 2018 [WHO, 2017], **but the RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries in 2019.**

~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of 20,250 RTS,S/AS01_E recipients. Similarly,~~

Milestone	Planned date
End of data collection	~~Q3 Q1 2024~~ 2025*
Study progress reports	1 progress report every 6 months
Interim epoch analysis	~~Q3 Q2 2022~~ 2023** and ad-hoc (if triggered by a safety signal)
Registration in the EU PAS register	~~EUPAS28541~~ To be determined
NCT Number	NCT03855995
Statistical analysis completed	~~Q3 Q4~~ 2025*
Final report of study results	~~Q4 Q1~~ 20252026*

*Tentative date; depending on recruitment timelines and implementation of vaccination by the Ministries of Health

**Tentative date, depending on recruitment timelines and implementation of vaccination by the Ministries of Health

14. **Section 7.1 –Background:** GSK Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01_E, for routine immunisation of children living in malaria-endemic countries of SSA. RTS,S/AS01_E is the first vaccine to be implemented for the prevention of malaria and it **is** the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

The pre-implementation (i.e. before vaccine implementation) surveillance study EPI MAL 002, will measure the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation ~~or death~~, meningitis and malaria morbidity and mortality

~~If~~The RTS,S/AS01_E vaccine ~~was~~ **is** implemented in selected areas/clusters of 3 SSA countries (Ghana, Kenya and Malawi) in 2019. ~~at the expected target of,~~ As the vaccine becomes available in the study sites that are exposed clusters, EPI-MAL-003 will be initiated. EPI-MAL-002 and EPI-MAL-003 ~~may are~~ partly be run concomitantly in the same study sites.

The three studies ~~will be~~ **are** conducted in similar if not identical settings. Sites selection has been done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO [WHO, 2017] (refer also to Section 9.2.1), in order to ensure synergy between the latter and those three studies.

~~In~~ **From** each pilot country, about 256,000 children ~~will be~~ **are expected to be** included into the pilot implementation programme (about 128,000 children in the RTS,S/AS01_E clusters [exposed clusters] and about 128,000 in the comparison arm [unexposed clusters]).

Table 2 footnote: C3C group: children and infants to receive 3 doses of a control vaccine on a 0-1-2-month schedule + a dose of a control vaccine at study Month 20. **Note that it is only for the 5-17 months age category.**

- Low fatality rate overall in study MALARIA-055 compared to what could be expected: 1 to 2% in each group, while in real-life setting mortality under 5 *years old* in SSA is estimated to be 3% (WHO) to 5% (World bank);

15. Section 7.3 – Efficacy results of the clinical development of RTS,S/AS01_E:

In three trial sites (Korogwe, Tanzania; Nanoro, Burkina Faso and Kombewa, Kenya) of the MALARIA-055 study, children were followed for 3 additional years to further document the long-term incidence of severe malaria in RTS,S/AS01_E and control groups (study MALARIA-076). Secondary objectives included evaluation of the incidence of clinical malaria, parasite prevalence, and serious adverse events of special interest.

The incidence of severe malaria was very low in each of the three study sites and was consistent with the epidemiology of the disease in high transmission areas – showing a decreased incidence of severe malaria with increasing age during childhood. There was no indication of rebound of severe malaria during the three additional years of follow-up in children who received either 3, or 4 doses of RTS,S/AS01_E.

In Nanoro (Burkina Faso), the site with highly seasonal malaria transmission, an increased susceptibility to uncomplicated malaria was observed. This increase did however not outweighing the initial benefit offered by the RTS,S/AS01_E vaccine, and most importantly did not appear to result in an increase of severe malaria cases.

In all three sites vaccine efficacy estimates against clinical malaria and the impact in terms of clinical cases averted remained positive over the six- to seven-year period, starting from the first vaccine dose in study MALARIA-055 until the end of follow-up in study MALARIA -076

Overall vaccine efficacy over the 7-year follow-up period was:

- against clinical malaria: 4 doses: 24% (95% CI: 16, 31); 3 doses: 19% (95% CI: 11, 27)

- against severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32) [Tinto, 2019].

- 16. Section 7.4 – Summary of study rationale:** The first vaccine introduction *occurred* in 2019 *after* approval ~~ed~~ and recommendation ~~ed~~ by local health authorities. *The RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries and plan to expand the RTS,S/AS01_E vaccination programme to the unexposed areas/clusters from 2023 is under discussion.* ~~is foreseen,~~

or which may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines), other AE leading to hospitalisation ~~or death~~, and meningitis (potential risk) among a minimum of 20,250 vaccinated study participants from exposed clusters.

The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation), of approximately 30,000 children in several sites in SSA countries (with at least 20,000 children enrolled where the RTS,S/AS01_E vaccine will be implemented), will

measure the baseline incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and malaria morbidity and mortality.

EPI-MAL-003 ~~will be~~ **is** conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005

17. **Section 8.1 – Co-primary objectives:** To estimate the incidence of AESI, ~~and of other AE leading to hospitalisation or death~~, in children vaccinated with RTS,S/AS01E.

18. **Section 8.2.1 - Safety:** *To estimate the incidence of other AE leading to hospitalisation*

- To describe risk factors for AESI, other AE leading to hospitalization ~~or death~~, meningitis, and malaria.

To assess the potential association between vaccination and AESI, ~~and other AE leading to hospitalisation or death~~ by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E

To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E.

19. **Section 9.1 – Study design:** The design will include active surveillance (*corresponds to a prospective cohort monitoring*) and enhanced hospitalisation surveillance (Figure 1) in both exposed and unexposed clusters (see Annex 2 for definitions).

Catch-up group: Children identified at 1st RTS,S/AS01_E dose administration (schedule ~~will~~ depends on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start.

Enhanced hospitalisation surveillance: All children *who are at least 6 weeks and <5 years of age* ~~under the age of~~, within the study areas in both exposed and unexposed clusters, not already enrolled in the active surveillance (because parents/LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance **at the time of hospitalisation**, are eligible for enrolment in enhanced hospitalisation surveillance ~~throughout the whole study period~~ (Figure 1, see also Section 9.2.7.2). A home visit will be conducted at study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Since the MoHs of the countries participating in the MVIP according to the SAGE/MAPC recommendation plan to expand the RTS,S/AS01_E vaccine implementation to the unexposed clusters from 2023, clusters that were initially unexposed will become exposed with regards to RTS,S/AS01_E vaccination. This change in vaccine implementation directly impacts the current study plan. Therefore, the enrolment of subjects in the enhanced hospitalisation surveillance

will be stopped in clusters that were not involved in the EPI-MAL-002 study (i.e. all clusters in Malawi; unexposed clusters in Ghana and 1 exposed and 2 unexposed clusters in Kenya) as from 01 January 2023. Subjects already enrolled in EHS will continue to be followed until study conclusion., in order to capture information on their subsequent hospitalisations. Study conclusion will be conducted in a timely manner from 01 January 2023.

As initially planned, the enrolment of subjects in EHS will be pursued until the end of study in clusters involved in the EPI-MAL-002 study because this will provide relevant information for the before/after comparison.

Figure 1 footnote:

The catch-up group of the active surveillance will include a group of children identified at 1st RTS,S/AS01E dose administration (schedule will depends on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group includes RTS,S/AS01E vaccinated children from exposed clusters.

For active surveillance, continuous monitoring of hospitalisations will be done throughout the whole study period. For EHS, the continuous monitoring of hospitalisations will be done throughout the whole study period for clusters involved in EPI-MAL-002 study. For the other clusters not involved in EPI-MAL-002 study, enrolment into EHS will be stopped and study conclusion will be conducted in a timely manner from 01 January 2023.

The diseases under surveillance for safety include AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and severe malaria including cerebral malaria.

20. **Section 9.1.1 - Rational for study design:** Study EPI-MAL-003 ~~will be~~ *is* conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005 studies. The pre implementation study EPI MAL 002 (i.e. before vaccine implementation) measures the baseline incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated.

Active surveillance: If a SAE (**AESI or meningitis or severe malaria including cerebral malaria**) is detected in the child, he or she will be followed for an additional 12 months to further characterise the event.

Enhanced hospitalisation surveillance

other AE leading to hospitalisation ~~or death~~

~~Throughout the whole study period,~~ All hospitalised children **who are at least 6 weeks and <5 years of age** ~~under the age of~~ within the study areas who are not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance, are eligible for enrolment in enhanced hospitalisation surveillance, to allow for data collection regarding that hospital visit and any subsequent ~~hospital visits~~ **hospitalisations** until study conclusion.

21. **Section 9.2.1- Study population:** The cohort is considered dynamic, as **infants** ~~newborns~~ and immigrants are included in the cohort and the birth or in-migration date is recorded. Similarly, deaths and outmigrations- are recorded.

- In summary: currently, a total of 3 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa]) ~~are **have enrolling**~~ **enrolled** study participants in the EPI-MAL-002 study. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 sites ~~should~~ **have** become exposed study sites/clusters in EPI-MAL-003. Selection of the remaining study sites/clusters that will be included in the EPI-MAL-003 study is completed and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.

Taking into account a global birth cohort of 23,000 children **at the time of EPI-MAL-002 study preparation**, and the refusal rate of parents for their children to join the study, an expected number of at least 45,000 children, including 22,500 children in the exposed clusters (with minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children) and 22,500 children in the unexposed clusters will be part of the active surveillance of the study. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. ~~In the participating sites, the vaccine coverage is not expected to be low. However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure that the target of minimum 20,250 RTS,S/AS01_E recipients is reached. Similarly,~~

22. **Section 9.2.2 – Eligible population: For enhanced hospitalisation surveillance**, parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are **at least 6 weeks and** <5 years **of age** ~~under the age of~~ and who can be linked to the HDSS or equivalent surveillance system, will be approached to enrol their child into this study:
 - If a child, who is first identified during hospitalization by study staff, fulfills the eligibility criteria for enrolment in active surveillance (within the recruitment period), enrolment in active surveillance will be proposed. If the parents/LARs decline enrolment in active surveillance **and if the child fulfills the eligibility criteria for enrolment in enhanced hospitalisation surveillance**, enrolment in enhanced hospitalisation surveillance will be proposed.
23. **Section 9.2.3 – Inclusion criteria:** For enrolment in the enhanced hospitalisation surveillance: children must be aged **at least 6 weeks and** <5 years **at the time of hospitalisation** ~~and hospitalised~~ at any time during the study. (This group will include children from exposed and unexposed clusters.)
24. **Section 9.2.5 – Study period:** Taking into account a global birth cohort of 23,000 children **at the time of EPI-MAL-002 study preparation** (11,500 children in the exposed clusters, and 11,500 children in the.....)

~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of minimum 20,250 RTS,S/AS01_E recipients. Similarly,~~

(Children reporting a SAE **due to study procedure might** ~~will~~ have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months).

25. Section 9.2.6 – Case definitions

Hepato-Gastrointestinal and Renal System				
Intussusception	Average rate 1 case per 3,300; yearly variations 1:2,500 to 1:5,000 (<1 yr old, Panama) [Sáez-Llorens, 2004]; <5/100,000 PY (<9 wks), 62/100,000 PY (26-29 wks), 26/100,000 PY (52 wks) (US) [Tate, 2008]; 8.1/100,000 PY (<1 yr Australia) [Justice, 2005]	Overall estimate of risk of IS during the 7 days after vaccination with Rotarix 6.8 (95% CI: 2.4, 19.0) and with RotaTeq 9.9 (95% CI: 3.7, 26.4) after dose 1. within 7 days is estimated at 5.4 (95% CI: 3.9-7.4) after 1st dose Rotarix and 5.5 (95% CI: 3.3-9.3) after 1st dose RotaTeq. Small increase after dose 2 for both vaccines [Carlin, 2013; Rosillon, 2015]	1 to 7 days after 1st and 2nd doses of Rotarix and RotaTeq vaccines	BC

26. Section 9.2.6.3: Collection of hospitalisations for an AE other than AESI or meningitis or any malaria or severe malaria (including cerebral malaria) will be stopped as of 01 January 2023 in subjects previously enrolled in EHS, in sites not involved in EPI-MAL-002 study. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria) will continue to be collected as part of continuous monitoring for subjects enrolled in AS in all sites or EHS in sites involved in EPI-MAL-002 study.

27. Section 9.2.6.9: Deaths, including malaria attributed deaths with an uncertain diagnosis and outcome after review by the GSK safety physician, will be reviewed by the expert panel to confirm the primary/secondary cause of death (see Section 9.2.7.4.3).

28. Section 9.2.7.1.1 – Enrolment and follow-up: Surveillance of AESI, other AE leading to hospitalisation or death, meningitis and malaria will be performed as described below.

29. Section 9.2.7.1.2 - Surveillance of AESI, other AE leading to hospitalisation or death, meningitis and malaria during follow-up.

The surveillance of AESI, other AE leading to hospitalisation or death, meningitis and measures of malaria burden will be done at different levels in line with the surveillance strategy implemented for the EPI-MAL-002 study.

- Reporting by primary health care facilities and hospitals**

SAE **due to study procedure might** have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months.

An alert system by mobile phone will be developed in the early stages of EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate suspected AESI, meningitis or cerebral malaria episodes to study staff in near real time. The study staff, as designated by the principal investigator, will provide necessary guidance for appropriate case management. Mobile phone reporting logs will be cross-checked with hospital discharge logs and primary health care facility registries for process improvement.

To maximise the possibility of capturing an AESI, ~~other AE leading to hospitalisation or death~~, meningitis, or malaria, an active search will be performed by the study staff through hospital rounds and by regular (at least 3 times a week) review of patient records at primary health care facilities.

The eCRFs for the reporting of AESI, ~~other AE leading to hospitalisation or death~~, meningitis, or malaria will allow timely reporting of the first signs and symptoms detected by the community health workers and health care staff and completion of diagnostic information, as more results from examination in hospitals with specialised care become available. Clinicians in charge of the patients may seek consultation with RAFT study physicians for case confirmation. Data entry is described in Section 9.6.

The maximum intensity (mild, moderate, severe) of each AESI, ~~other AE leading to hospitalisation or death~~, and meningitis recorded in the eCRFs will be assigned to categories.

30. Section 9.2.7.1.3: Surveillance of other AE leading to hospitalisation during follow-up

The surveillance of other AE leading to hospitalisation will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.

31. Section 9.2.7.1.4: Surveillance for death

The surveillance of death will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2

32. Section 9.2.7.1.6 - Table 4: List of study procedures for participants in active surveillance

Visit days	1W (5-10 D) after 1 st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2 nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3 rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3 rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4 th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4 th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4 th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first (±2 W)
Record any detected signs and symptoms including AESI, other AE, leading to hospitalisation or death, meningitis, malaria, abscess at injection site, foot positional deformations	•	•	•	•	•	•	•	•	•	

33. Section 9.2.7.2.13. Record cases of suspected AESI, other AE leading to hospitalisation or death, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations

34. Section 9.2.7.2.15 – Study conclusion

Note: For subjects enrolled in EHS, data collection of other AE leading to hospitalisation will be stopped as from 1st January 2023 in sites not participating in EPI-MAL-002. For those subjects, a study conclusion visit will be conducted in a timely manner from 01 January 2023. For subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge.

35. Section 9.2.7.2.16 – Outline of study procedures: Table 5 List of study procedure to be conducted in the event of hospitalization

Type of contact	Hospitalisation visit	Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) (±2 W)
Record any cases of death and cause of death	•	•

* For subjects enrolled in EHS in sites not participating in EPI-MAL-002, a study conclusion visit will be conducted in a timely manner from 01 January 2023.

36. Section 9.2.7.4.3. Other AE leading to hospitalisation or Death

Other AE leading to hospitalisation or Death with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts. These cases will be flagged in the eCRF during the manual cleaning

by the GSK safety physician, for external expert review. Two selected experts will independently review ***and confirm the possible cause of death*** the cases. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases ***according to the cause of death***.

37. **Section 9.2.7.4.4 Other AE leading to hospitalization**

Other AE leading to hospitalisation or with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts as described in Section 9.2.7.4.3.

38. **Section 9.2.7.5. Management of AESI, other AE leading to hospitalisation or death, meningitis cases, malaria, abscess at injection site and foot positional deformations**

39. **Section 9.2.7.7 Capacity building**

• **~~Use of time sensitive event device~~**

~~In addition to data systems traditionally utilised in post approval safety studies, an alert system using mobile phones has been developed as in EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate time sensitive events to study staff. The alert system will be implemented in order to closely monitor AESI, meningitis cases, and cerebral malaria and to ensure that all the procedures and tests specified in the protocol are done for a proper diagnosis of the diseases while maintaining the safety of the patients. Mobile phone reporting logs will be cross-checked with hospital discharge logs and primary health care facility registries for process improvement.~~

~~In addition, GSK will also be made aware of AESI, meningitis cases, and cerebral malaria cases (GSK will not receive any patient's personally identifiable information via that system). The system should act as an alert system between the health care facilities and the principal investigator, but is not intended to replace the reporting through eCRF (as defined in Section 11).~~

40. **Section 9.2.8 Study procedures during special circumstances**

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Active safety follow-up through home visits may be replaced by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.***
- ***For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact .***

- *The study conclusion home visit maybe replaced by a telephone call or other means of virtual contact.*
- *A retrospective data collection of medical events based on medical records may be implemented at any of the health care facilities.*

Note: Certain restrictions might make it impossible for parents/LARs to provide written consent for changes in study procedures during special circumstances. Parents/LARs of subjects already enrolled will provide consent verbally.

41. Section 9.3.1 - Co-primary endpoints:

- ~~Occurrence of other AE leading to hospitalisation or death (see Sections 9.2.6.3 and 9.2.6.9 for definitions).~~

42. Section 9.3.2.1 - Safety endpoints:

- Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis or malaria) or death.
- *Occurrence of other AE leading to hospitalisation (see section 9.2.6.3 and section 9.2.6.9 for definitions).*

43. Section 9.4.2 – Active surveillance and enhanced hospitalisation surveillance

- e. AESI, other AE leading to hospitalisation ~~or death~~, meningitis, or malaria will be recorded in the eCRF. Data entry is described in Section 9.6

The investigator will assess the maximum intensity (mild, moderate, severe) that occurred over the duration of the event for all AESI, other AE leading to hospitalisation ~~or death~~, or meningitis reported during the study. The assessment will be based on the investigator's clinical judgement.

44. Section 9.4.3 – Baseline study EPI_MAL-002

The study EPI-MAL-002 is designed to estimate baseline incidence rates of AESI, other AE leading to hospitalisations ~~or death~~, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality prior to introduction of RTS,S/AS01E.

45. **Section 9.5.1 – Sample size for co-primary objectives:** For example, the 95% CI around the observed incidence of 21.7 (23.9) per 100,000 PY (25 events detected) will be [14.1, 32.1] (~~[18.7, 30.1]~~) for a follow-up of 2 years (~~respectively 5.2 years~~) **and respectively the 95% CI around the observed incidence of 23.9 per 100,000 PY (71 events detected) will be [18.7, 30.1] for a follow-up 5.2 years.**

46. **Section 9.5.2 - Sample size for meningitis monitoring:** With T = 10 (estimated as the cumulative number of meningitis cases based on EPI-MAL-002 background incidence, EPI-MAL-003 cohort size and period of follow-up of 1 year following dose 3), a true RR = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters ~~in a follow-up time corresponding to an observed RR equal to 3.~~

47. Section 9.5.3.1 – Before -after design

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]

Period at-risk	Baseline incidence 13000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	~~1.77~~ 2.63	~~3.87~~ 2.2
6 weeks	~~1.85~~ 1.4	~~2.36~~ 1.7
3 months	~~1.62~~ 1.3	~~1.97~~ 1.5
6 months	~~1.45~~ 1.2	~~1.68~~ 1.4
12 months	~~1.32~~ 1.17	~~1.47~~ 1.25
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	~~2.60~~ 1.8	~~3.80~~ 2.2
6 weeks	~~1.83~~ 1.4	~~2.33~~ 1.6
3 months	~~1.60~~ 1.3	~~1.93~~ 1.5
6 months	~~1.43~~ 1.2	~~1.66~~ 1.3
12 months	~~1.30~~ 1.17	~~1.45~~ 1.24

48. Section 9.5.3.2 – Cluster design**Table 12 Detectable relative risk for mortality overall and by gender with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]**

Period at-risk	Baseline incidence 13000/100000 PY - 80% power	
	Overall	Per gender
50% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	~~1.77~~ 2.65	~~2.23~~ 3.88
6 weeks	~~1.44~~ 1.86	~~1.66~~ 2.37
3 months	~~1.33~~ 1.63	~~1.49~~ 1.98
6 months	~~1.24~~ 1.45	~~1.36~~ 1.69
12 months	~~1.18~~ 1.32	~~1.26~~ 1.48
75% of the children with primary schedule received a 4 th dose of RTS,S/AS01 _E		
2 weeks	~~1.76~~ 2.60	~~2.20~~ 3.80
6 weeks	~~1.43~~ 1.83	~~1.65~~ 2.33
3 months	~~1.32~~ 1.61	~~1.48~~ 1.94
6 months	~~1.24~~ 1.44	~~1.35~~ 1.66
12 months	~~1.17~~ 1.31	~~1.25~~ 1.46

49. Section 9.5.4.2 – Impact using the before-after design

Table 14 presents the total effect which could be detected with 80% of power, going from ~~16%~~ 14 to ~~23%~~ 20 for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

50. Section 9.5.5.2 – Impact using the before-after design

Table 17 presents the total effect which could be detected with 80% of power, going from ~~1.51~~ 1.44 to ~~1.82~~ 1.72 for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

51. Section 9.5.6 - Sample size for the effectiveness and impact on mortality rate, overall and per gender

- Reference mortality rate: **1/100PY 3%***

*In real-life setting under 5 years mortality in SSA is estimated to be 3% (WHO) to 5% (World Bank). 3% is considered to take the conservative approach.

52. Section 9.5.6.1 – Effectiveness (direct effect)

Table 19 presents the direct effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going ~~1.561.30~~ to ~~2.001.50~~ for overall and from ~~1.881.44~~ to ~~2.661.76~~ per gender, and depending on the scenario.

Table 19 Detectable direct effect in terms of mortality rate ratio, overall and per gender with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

	Mortality	Correlation of covariates					
		Overall			Per gender		
		0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	~~0.010.03~~	~~1.861.43~~	~~2.001.50~~	~~2.231.59~~	~~2.401.66~~	~~2.661.76~~	~~3.101.93~~
D3-> D4+1Y (50%)	~~0.010.03~~	~~1.511.27~~	~~1.591.31~~	~~1.701.36~~	~~1.791.40~~	~~1.921.46~~	~~2.121.55~~
D3-> D4+1Y (75%)	~~0.010.03~~	~~1.491.26~~	~~1.561.30~~	~~1.681.35~~	~~1.761.39~~	~~1.881.44~~	~~2.071.53~~

53. Section 9.5.6.2 – Impact using before-after design

Table 20 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from ~~1.341.16~~ to ~~1.531.25~~ for overall and from ~~1.511.23~~ to ~~1.821.37~~ per gender, and depending on the scenario.

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]

	Mortality	Correlation of covariates					
		Overall			Per gender		
		0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	~~0.010.03~~	~~1.471.25~~	~~1.531.28~~	~~1.631.33~~	~~1.711.37~~	~~1.821.42~~	~~1.991.50~~
D3-> D4+1Y (50%)	~~0.010.03~~	~~1.341.19~~	~~1.391.21~~	~~1.461.25~~	~~1.511.27~~	~~1.581.31~~	~~1.701.36~~
D3-> D4+1Y (75%)	~~0.010.03~~	~~1.301.16~~	~~1.341.19~~	~~1.401.22~~	~~1.451.24~~	~~1.511.27~~	~~1.601.32~~

54. Section 9.5.6.3 – Impact using the cluster design

Table 21 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from ~~1.351.19~~ to ~~1.541.29~~ for overall and from ~~1.521.28~~ to ~~1.821.42~~ per gender, and depending on the scenario.

Table 21 Detectable total effect in terms of mortality rate ratio, overall and per gender in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

	Mortality	Correlation of covariates					
		Overall			Per gender		
		0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.010.03	1.471.25	1.541.29	1.641.34	1.721.37	1.821.42	2.001.50
D3-> D4+1Y (50%)	0.010.03	1.351.19	1.401.22	1.481.26	1.531.28	1.601.32	1.721.38
D3-> D4+1Y (75%)	0.010.03	1.311.17	1.351.19	1.411.22	1.451.24	1.521.28	1.611.32

55. **Section 9.7 – Data analysis:** Sensitivity analyses will be conducted including **all** subjects **from EPI-MAL-002 study (i.e. subjects** from both age groups (6-12 weeks, 5-17 months)) using an adjustment on the age.

56. Section 9.7.2 – Study participant disposition

- ~~Number of subjects with at least one AE leading to hospitalisation or death and number of AE leading to hospitalisation or death;~~

57. Section 9.7.5.2.1 – Incidence rate of AESI and other AE leading to hospitalisation or death

The incidence rate of each AESI and other AE leading to hospitalisation ~~or death~~ will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time

~~For other AE leading to hospitalisation or death the at-risk period for the analyses will be defined with the support of the GSK safety physicians and the panel of experts. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.~~

Incidence rates of these composite endpoints will be calculated as described for individual AESI ~~other AE leading to hospitalisation or death~~; in case of multiple cases in a study participant, only the first event will be considered in this analysis.

58. **Section 9.7.6.3 – Incidence rate of cerebral malaria:** Incidence rate (and 95% CI) of cerebral malaria will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

59. **Section 9.7.6.4 – Mortality rate:** Mortality rate and 95% CI (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), both overall and by gender, will be estimated with the same approach as for an AESI as described in Section 9.7.5.2 using the entire follow-up as at-risk period.

60. Section 9.7.6.5 - Cause of hospitalisation due to AESI, meningitis or malaria and death in children < 5 years vaccinated with RTS,S/AS01E and unvaccinated children < 5 years

~~AE and AESI will be grouped as described above in Section 9.7.5.2.1 (Subsection on: Incidence for children < 5 years). In the same way,~~

61. Section 9.7.6.6 - Other AE leading to hospitalisation

Incidence rate (and 95% CI) of other AE leading to hospitalisation will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

All other AE leading to hospitalisation will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary and presented by System Organ Class (SOC) and Preferred Term (PT).

62. Section 9.7.6.7.1 – Before-after comparison

Further analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) (see Section 9.7.5.2) will consist of a comparison of its incidence rate before (i.e. unvaccinated EPI-MAL-002 from active surveillance) and after (vaccinated EPIMAL003 from active surveillance) introduction of RTS,S/AS01_E vaccine by means of a Poisson regression model with the study site as an adjusted factor.

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the before cohort (EPI-MAL-002)
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the before cohort (EPI-MAL-002).

Exposure determinants and potential risk factors for AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) could also be collected at study entry and evaluated using univariate and multivariable Poisson regression models only for the incidence following immunisation.

Of note, multivariable models will be conducted for a specific AESI, MedDRA SOC and PT of other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) if a signal is detected (i.e. the null hypothesis is rejected) and if a minimum number of cases of AESI, other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) is observed (at least 10 cases in total).

The attributable risk in the vaccinated study participants will be derived for AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) as (Risk Ratio-1)/Risk Ratio [Cole, 1971].

Finally, a model with study site considered as random effect will be performed as sensitive analysis for the analysis of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) (Section 9.6.9.1.2).

63. Section 9.7.6.7.2 – Cluster design comparison

Analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of the exposed and the unexposed clusters from EPI-MAL-003 by means of a random-effect Poisson regression model with the clusters as random effect.

64. Section 9.7.6.7.3 – Exposed clusters comparison

For the exposed clusters only, analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of vaccinated study participants from the exposed clusters of EPI-MAL-003 and unvaccinated study participants from the exposed clusters of EPI-MAL-003 by means of a Poisson regression model with the study site as an adjusted factor.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

65. Section 9.7.13 – Statistical analyses during special circumstances

Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.

66. Section 9.9 - Limitations of the research methods

The enhanced hospitalisation surveillance should help to identify additional cases of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and any severe malaria occurring in children living in the study area but not enrolled in the active surveillance.

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation ~~or death~~, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified.

~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of at least 20,250 RTS,S/AS01_E recipients. Similarly,~~

Detecting the occurrence of AESI, ~~other AE leading to hospitalisation or death~~, and meningitis cases following immunisation with RTS,S/AS01_E after its introduction in vaccination programmes are the primary objectives of this study.

~~Introduction of an alert system using mobile phones to ease communications between the health care staff and the study staff will enable the adherence to national~~

~~recommendations for diagnosis during the study. However, meningitis cases based on clinical symptoms only, or suspected cases, can be expected.~~

The co-primary objectives will provide estimates of the incidence of AESI ~~of other AE leading to hospitalisation or death~~, and of aetiology-confirmed meningitis.

67. Section 11.4 – Reporting of adverse events not via eCRF

- Any AE which, in the opinion of the investigator, is suspected to be related to a GSK licensed product other than RTS,S/AS01_E must be reported, within 24 hours of awareness, directly to GSK Safety for entry in GSK's safety database, and potential expedited reporting to **relevant National Health** authorities.
- Any AE which, in the opinion of the investigator, is suspected to be related to RTS,S/AS01_E and which is not collected per study protocol, must be reported to relevant National Health authorities following the local pharmacovigilance legislation.**

68. Section 13 – References

AMP: Agence de Médecine Préventive. <https://fr.linkedin.com/company/agence-de-medecine-preventive> <http://amp-vaccinology.org/>. Accessed 06 September 2017 **03 April 2024**.

Tinto H, Otieno W, Gesase S, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis 2019;19: 821–32

United Nations. Sex differentials in childhood mortality, New York, 2011. <https://www.un.org/en/development/desa/population/publications/pdf/mortality/SexDifferentialsChildhoodMortality.pdf>. Accessed 06 September 2017
<http://www.un.org/esa/population/publications/SexDifChildMort/SexDifferentialsChildhoodMortality.pdf>

69. Annex 1 - List of stand-alone documents

No.	Document Reference No	Date	Title
8.	115056 (EPI-MAL-003 VS AME)	15 October 2020	Protocol Amendment 2 sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	15 October 2020	Protocol Amendment 2 investigator agreement

70. Annex 5 – Case definitions for protocol-defined AESI and Surveillance Indicators

GENERALIZED CONVULSIVE SEIZURE	The etiological work up is negative: (i.e. ~~febrile seizure~~, acute intoxication, trauma, severe malaria etc. have all been excluded).

GLAXOSMITHKLINE BIOLOGICALS VACCINE VALUE & HEALTH SCIENCE (VVHS) Protocol Amendment 3	
eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Amendment number:	Amendment 3
Amendment date:	24 Oct 2024
Co-ordinating author:	PPD, Medical Writer
Rationale/background for changes: The context in which the EPI-MAL-003 study was initially designed has changed. The Malaria Vaccine Implementation Programme (MVIP) was designed to evaluate the public health use of the RTS,S vaccine in Ghana, Kenya and Malawi and was completed at the end of 2023. Since initiation in 2019, more than 2 million children have been vaccinated. Implementation resulted in a substantial drop in all-cause mortality (13%) among children age-eligible for the vaccine and a reduction in severe malaria hospitalisations [WHO. The RTS,S Malaria Vaccine. November 2023. https://cdn.who.int/media/docs/default-source/immunization/mvip/who_mvi_infographic-jan2024-01_approved.pdf?sfvrsn=43d3653a_2&download=true]. There was no evidence of a causal relationship with any of the safety signals observed after the Phase III trial (meningitis, cerebral malaria and a gender-based imbalance in deaths), and no new safety signals were identified. The success of the MVIP, and lessons learned through the pilot programme, informed considerations by the WHO and facilitated more efficient development of future malaria vaccines. Protocol Amendment 3 reflects the findings of the MVIP by simplifying the final analyses of the study, but was not feasible for the interim analyses (planned for Q1 2024) due to the timing of completion of the MVIP, as follows: - The EPI-MAL-002 study included univariate and multivariate Poisson regression models for analysis of potential risk factors for AESI, aetiology-confirmed meningitis, cerebral malaria and death if there were a minimum of 10 cases. Due to the low number of events, analyses were only conducted for mortality. The value of these analyses is considered to be limited for EPI-MAL-003 and they have been removed from the Final Analysis. - All-cause hospitalisation was assessed and reported following Phase III evaluation [The RTS,S Clinical Trials Partnership. Lancet 2015;386(9988):31-45]. Analyses of “Other causes leading to hospitalisation” in EPI-MAL-003 was considered to not be required and has been removed from the Final Analysis	

- The data from 12 clusters will be used in the cluster randomised design which compares to only 3 clusters in the before-after analysis using data from the EPI-MAL-002 study. As the before-after design analyses is therefore considered to be prone to biases compared to the temporaneous cluster randomised design, which will have a much larger enrolled population available for analyses, these analyses have been removed from the Final Analysis.
- Febrile convulsion was a recognised AESI of RTS,S/AS01_E during Phase III evaluation [Mendoza YG. Hum Vaccin Immunother 2019;15(10):2386-98], and is included in the Risk Management Plan as an accepted risk. The Mosquirix label includes febrile convulsions (within 7 days post-vaccination) as an uncommon AE. As this is an accepted risk and there is no proposal to remove febrile convulsions from the label, there is no requirement for further analyses of febrile convulsion, reference to which has been removed for the Final Analysis.

Following an in-depth safety review of the Phase III study (MALARIA-055) [Mendoza YG. Hum Vaccin Immunother 2019;15(10):2386-98], the at-risk period within 3 days after vaccination for febrile convulsion was added, and the 1-month period was removed.

As exposure data to RTS,S/AS01_E in the Enhanced Hospital Surveillance (EHS) population is missing, or is uncertain, for approximately 70% of enrolled children of eligible age for vaccination, comparison of vaccinated vs unvaccinated groups will likely introduce substantial bias. The unreliability of the exposure data precludes any meaningful analyses using statistical models. Furthermore, results of the Interim Analysis were reassuring; safety signals were not confirmed and there was impact on all-cause mortality and malaria-related mortality with no gender imbalance. Revisions to the protocol have been made to address the concerns over the vaccination status data for the EHS cohort as follows:

- The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality). Data will not be cleaned for other safety endpoints.
- The EHS population will not be included in estimates of incidence rates and effectiveness and impact analyses in the Final Analysis.
- Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

The initial recommended age for the administration of the 4th dose was 22 months in Malawi and 24 months in Ghana and Kenya. During the course of the EPI-MAL-003 study, it was observed that much older children received the 4th dose. For unvaccinated participants, the planification of home visits are based on the recommended vaccination schedule. Therefore, for the calculation of the study end per site, a maximum age of 30 months for the 4th dose (or equal point in time for unvaccinated children) will be used. This will ensure an equivalent surveillance period between vaccinated and unvaccinated participants and will limit the age gap between vaccinated and unvaccinated participants. The definition of the study end has been revised as follows:

- Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) given at a maximum age of 30 months.

In addition, to align with the current protocol template (V03), the GSK logo and Company address have been deleted from the title page, the Investigator Agreement has been simplified, and the Back-up Study Contact for Reporting AEs details (Section 11.4.1) have been updated.

Amended text has been included in bold italics and deleted text in ~~strikethrough~~ in the following sections:



~~Study Protocol~~
Sponsor:
~~GlaxoSmithKline Biologicals~~
Rue de l'Institut 89
~~1330 Rixensart, Belgium~~

1. Section 1 - PASS INFORMATION

Date of last version of the protocol:	<i>Amendment 2: 15 October 2020</i>
Countries of study:	 In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ~~will~~ was to be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GlaxoSmithKline (GSK) Phase IV studies ~~have been~~ were selected from the 3 countries where the RTS,S/AS01_E vaccine ~~will~~ was to be implemented. Sites from Ghana and

	Kenya that were part of study EPI-MAL-002 <i>(unexposed clusters)</i> ~~should become~~ <i>became exposed cluster</i> study sites in study EPI-MAL-003 ~~which will be exposed clusters.~~
Authors:	Coordinating authors: • ~~PPD [REDACTED] (GSK Biologicals)~~ • ~~PPD [REDACTED], Lead Scientific Writer (GSK Biologicals)~~ Main GSK Biologicals contributing authors: • ~~PPD [REDACTED], Senior Epidemiology Lead—Malaria (GSK Biologicals)~~ • ~~PPD [REDACTED], Epidemiology Lead—Malaria (GSK Biologicals)~~ • ~~PPD [REDACTED], Epidemiology Lead—Malaria (GSK Biologicals)~~ • ~~PPD [REDACTED], Statistician (4Clinics for GSK Biologicals)~~ • ~~PPD [REDACTED], Lead Statistician (GSK Biologicals)~~ • ~~PPD [REDACTED] Statistician (4Clinics for GSK Biologicals)~~ • ~~PPD [REDACTED], Safety Physician (GSK Biologicals)~~ • ~~PPD [REDACTED], Oversight Data Manager (GSK Biologicals)~~ • ~~PPD [REDACTED], Safety Physician (GSK Biologicals)~~ • ~~PPD [REDACTED] / (ICON for GSK Biologicals / PPD [REDACTED], Data Management (Business and Decision Life Sciences for GSK Biologicals)~~ • ~~PPD [REDACTED], Clinical and Epidemiological Project Lead (GSK Biologicals)~~ • ~~PPD [REDACTED] Global Epidemiology (GSK Biologicals)~~

	• PPD [REDACTED], Global Epidemiology (GSK Biologicals) • PPD [REDACTED], Safety Scientist (GSK Biologicals) • PPD [REDACTED], Epidemiology Lead—Malaria (previously Statistician, GSK Biologicals) • PPD [REDACTED], Senior Epidemiologist, (ManiAfriCare for GSK Biologicals) Other GSK Biologicals contributing authors: • PPD [REDACTED] [REDACTED] Project Delivery Lead (GSK Biologicals) • PPD [REDACTED], Senior Study Delivery Lead (GSK Biologicals) • PPD [REDACTED] for Africa (GSK Biologicals) • PPD [REDACTED] Local Delivery Lead (GSK Biologicals) • PPD [REDACTED] [REDACTED], Local Medical Leads (GSK Biologicals) • PPD [REDACTED] Clinical Laboratory Sciences Clinical Read-out Team Lead (GSK Biologicals) • PPD [REDACTED], Clinical Laboratory Sciences Study Manager (Business & Decision for GSK Biologicals) • PPD [REDACTED], Clinical Operations (GSK Biologicals) • PPD [REDACTED], Senior Manager, Clinical Operations (GSK Biologicals) • PPD [REDACTED], Clinical Laboratory Sciences Study Manager (CVO Europe for GSK Biologicals) • PPD [REDACTED], Clinical Laboratory Sciences Study Manager (Altran for GSK Biologicals) • PPD [REDACTED], Global Regulatory Lead Malaria Vaccines (GSK Biologicals)

	• ~~PPD [REDACTED], Study Delivery Lead (GSK Biologicals)~~ • ~~PPD [REDACTED] - Study Delivery Lead (GSK Biologicals)~~ ~~Other non-GSK Biologicals contributors:~~ ~~Representatives of the Principal Investigators and co-chairs of the Safety Post Approval Program Partnership Committee.~~ ~~Other non-GSK Biologicals partners:~~ • ~~Réseau en Afrique Francophone pour la Télémédecine (RAFT) (represented by Professor PPD [REDACTED] - Geneva, Switzerland)~~ • ~~Agence de Médecine Préventive (AMP) Regional Office for Africa (represented by Dr. PPD [REDACTED], Abidjan, Ivory Coast)~~ • ~~Second line laboratory: Clinical Laboratory Services (CLS) (represented by PPD [REDACTED], Johannesburg, South Africa)~~

2. Section 2 - OPINION HOLDER

Opinion holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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3. List of Abbreviations

AIC Akaike's Information Criterion

SBC Schwarz Bayesian Criterion

4. Section 3 - RESPONSIBLE PARTIES

~~PPD [REDACTED] (PhD; PPD [REDACTED] – Epidemiology – Malaria) and PPD [REDACTED] (PhD; PPD [REDACTED] – Epidemiology Lead – Malaria) and PPD [REDACTED] (MD; PhD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.~~

5. Section 4 – ABSTRACT

Main authors

PPD [REDACTED] (PhD; PPD [REDACTED] – *Epidemiology– Malaria*) and
 PPD [REDACTED] PhD; PPD [REDACTED] - *Epidemiology
 Lead Malaria*). PPD [REDACTED] (Senior Epidemiology Lead–
 Malaria) and PPD [REDACTED] (Epidemiology Lead– Malaria)

Rationale and background

..... In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ~~will~~ **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GSK Phase IV studies ~~have been~~ **were** selected from the 3 countries where the RTS,S/AS01_E vaccine ~~will~~ **was to** be implemented. Sites from Ghana and Kenya that were part of ***the completed pre-implementation (i.e., before vaccine implementation) surveillance study, EPI-MALARIA-002 VS AME (115055) (referred to as EPI-MAL-002 in the remainder of the protocol)*** study EPI-MAL-002 are exposed clusters in EPI-MAL-003. The first vaccine introduction started in April 2019 in Malawi and Ghana, ***and in September 2019 in Kenya***. The RTS,S/AS01_E vaccine contains new components, including a novel adjuvant that is not present in currently licensed vaccines. ~~If recommended for use, it would be launched solely in malaria endemic countries in SSA.~~ ***In 2021, the WHO recommended widespread use of the RTS,S/AS01_E malaria vaccine for children living in regions with moderate to high P. falciparum transmission, based on the MVIP results [WHO recommends groundbreaking malaria vaccine for children at risk. October 2021].***

.....
 A ~~pre-implementation (i.e. before vaccine implementation) surveillance study, EPI-MALARIA-002 VS AME (115055) (referred to as~~ ***The EPI-MAL-002 in the remainder of the protocol), study*** ~~will~~ **measured** the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, ~~will~~ **was** also be estimated.

.....
 In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MALARIA-005 BOD AME [116682], referred to as EPI-MAL-005 in the remainder of the protocol) ***is being*** conducted to measure malaria transmission intensity and other malaria control interventions as confounding factors in the study site areas.

**Research
question and
objectives**

The three studies are *being/were* conducted in similar if not identical settings and with the same methodology for identification and characterisation of the events of interest. A strong capacity development component *is was* included in the baseline study EPI-MAL-002 *and EPI-MAL-003*.

Secondary objectives**Safety**

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E):

-
- To estimate the incidence of other AEs leading to hospitalisation*.
- ~~To describe risk factors for AESI, meningitis, and malaria.~~
- To describe the causes of hospitalisation (including AESI, meningitis and malaria)*.
- To assess the risk of febrile convulsions during *the 3-day period and* the 7-day period ~~and 1-month period~~ following each dose of RTS,S/AS01_E*.

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E)**:

-
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and AESI, by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.

- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01E with the incidence of these events in children not vaccinated with RTS,S/AS01E^{**}.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01E with the incidence of these events in children not vaccinated with RTS,S/AS01E^{**}.
- To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01E with the incidence of these events in children not vaccinated with RTS,S/AS01E^{**}.

****Analyses of Other AE leading to hospitalisation, cause of hospitalisation and incidence of febrile convulsions will only be conducted for the Interim Analysis and not for the Final Analysis.***

*****Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

Study design

- A disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; ***Interim Analysis only***) and concurrent (cluster design comparison of exposed and unexposed clusters; ***Interim Analysis and Final Analysis***) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01E vaccination for those living in the exposed clusters.
- The design ~~will~~ includes active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities) and enhanced hospitalisation surveillance (continuous monitoring of hospitalisations) in both exposed and unexposed clusters. ***The enrolment to active surveillance was completed on 06 April 2021.*** ***Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for***

subjects diagnosed with an AESI, meningitis or cerebral malaria.

- The study ~~targets~~ **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 in exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants ~~will~~ **would** receive three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.
- The impact (indirect, total and overall effect) of the vaccine will be investigated, in the active surveillance, firstly by comparing the incidence of all malaria (including severe and cerebral malaria) events in EPI-MAL-002 to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect)*.

****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

- Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) ***given at a maximum age of 30 months.***

Population, including the setting and study population

The study population is defined as study participants < 5 years of age living in a geographically limited area with a demographic surveillance system in place, and a well-developed infrastructure to monitor population health and vaccination programmes. ~~All EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005 studies sites have been identified.~~

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01_E in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria ~~have enrolled~~ **participants** for EPI-MAL-002 (Ghana [Kintampo and Navrongo], Kenya [Kombewa], and Burkina Faso [Sapone, Nouna]), ***and the study has completed.***

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ~~will~~ **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. In order to align with the MVIP, the study sites for the GSK Phase IV studies ~~have been~~ **were** selected from the 3 countries where the RTS,S/AS01_E vaccine ~~will~~ **was to** be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 ~~should become~~ **(unexposed clusters) became exposed cluster** study sites in EPI-MAL-003 ~~which will be exposed clusters~~.

Variables

Secondary endpoints

Safety endpoints

In children in active or enhanced hospitalisation surveillance:

-
- Occurrence of hospitalisation (including those attributed to an AESI, meningitis or malaria)* ~~or death~~.
- Occurrence of other AE leading to hospitalisation*.
- Occurrence of febrile convulsions during **the 3 day period (days 0-3) and** the 7-day period (Days 0-6) ~~and 1-month period (Days 0-29)~~ following each dose of RTS,S/AS01_E*.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation*.

****Occurrence of hospitalisation, other AE leading to hospitalisation, febrile convulsions and quality indicators will only be conducted for the Interim Analysis and not for the Final Analysis.***

Effectiveness and impact endpoints

In children in active surveillance:

-
- Occurrence of hospitalisation*

****Occurrence of all-cause hospitalisation will only be conducted for the Interim Analysis and not for the Final Analysis.***

Study size

- The study ~~targets~~ **targeted** enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children ~~are~~ **were** estimated to be enrolled in active surveillance,

assuming that the distribution according to the administration of RTS,S/AS01_E in the exposed clusters ~~will~~ **would** be 10% without any dose (2,250 unvaccinated children), 10% with an incomplete primary schedule (i.e. 1 or 2 doses; 2,250 partially vaccinated children), 80% with the full primary schedule (i.e. 3 doses; 18,000 vaccinated children).

The enrolment to active surveillance was completed on 06 April 2021.

-
- With the before-after design*, assuming 10 as the cumulative number of meningitis cases in EPI-MAL-002, based on cohort size and period of follow-up of 1 year following dose 3, a true relative risk (RR) = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters in a follow-up time corresponding to an observed RR equal to 3.
- With the before-after design*, and depending on the follow-up, the total effect for severe malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, ranges from 16% to 23%, and the direct effect, from 23% to 33%.
- With the before-after design*, and depending on the follow-up, the total effect for cerebral malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, expressed as RR ranges from 1.51 to 1.82, and the direct effect, from 1.55 to 1.88.

****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

Data analysis

.....

For the analysis of the secondary objectives, all comparisons will be performed separately for each of the two designs (i.e. before-after design and cluster design). As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters; and the cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters.

Note: Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

6. Section 5 - AMENDMENTS AND UPDATES

Amendment 1 Final: 24 April 2019.

Amendment 2 Final: 15 October 2020.

Amendment 3 Final: 24 Oct 2024.

The rationales for protocol amendment 1, & protocol amendment 2 **and protocol amendment 3** are provided in [Annex 7](#).

7. Section 6 – MILESTONES

The target population for the introduction of the RTS,S/AS01_E vaccine are children living in sub-Saharan Africa (SSA). The age group ~~for in which the vaccine will be administered~~ **administration** is 5 to 17 months of age.

The milestones below ~~will be adapted~~ **are** based on the timing of vaccine introduction in the intended study sites in the target SSA countries and the selected immunisation schedule (3-doses primary with a 4th dose). In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ~~will~~ **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVP.

The study ~~targets~~ **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants ~~will~~ **would** receive three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact ~~In the participating sites, the vaccine coverage is not expected to be low. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children in the exposed clusters is reached. The length of recruitment in active surveillance is assumed to be approximately 18 months from first study participant first visit to last study participant first visit at each site.~~

.....

The milestones for dates in the future in the following table are therefore tentative.

Milestone	Planned date
.....	
Protocol Amendment 1	April 2019
Protocol Amendment 2	October 2020
Protocol Amendment 3	April 2024
End of data collection	Q4 Q2 2025*
Interim epoch analysis	Q2 2023* Q1 2024 and ad hoc (if triggered by a safety signal)
Registration in the EU PAS register	23 March 2019 Updated 17 March 2023 EUPAS28541
NCT Number	NCT03855995 27 February 2019
Statistical analysis completed	Q4 2025*
Final report of study results	Q1 2026*

*Tentative date; depending on recruitment timelines and implementation of vaccination by the Ministries of Health

8. Section 7.1 – RATIONALE AND BACKGROUND – Background

In most SSA countries endemic for malaria, pharmacovigilance reporting systems are either in development phase, poorly functional or non-existent. As RTS,S/AS01_E will be distributed in SSA countries, GSK Biologicals deems crucial to expand the data on vaccine safety without relying solely on a passive reporting system once the vaccination ~~will be~~^{is} implemented. Therefore, GSK Biologicals ~~has~~ developed a Post Approval Plan ~~comprised~~^{comprising} of a set of complementary prospective studies ~~that will~~^{to} be conducted in similar if not identical settings.

The pre-implementation (i.e. before vaccine implementation) surveillance study EPI-MAL-002, ~~will~~^{measured} the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, ~~will be~~^{was} estimated. The events measured in EPI-MAL-002 ~~are~~^{were} based on data generated from MALARIA-055 described below (see Section 7.2 and Section 7.3), or ~~are~~^{were} events that have historically been associated with vaccines other than RTS,S/AS01_E, or may hypothetically be associated with RTS,S/AS01_E due to the fact that this vaccine has components which are new compared to current widely used vaccines. The EPI-MAL-002 study ~~has~~ started in Q4 2015. The RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries (Ghana, Kenya and Malawi) in 2019. As the vaccine ~~becomes~~^{became} available in the study sites that are exposed clusters, EPI-MAL-003 ~~will be~~^{was} initiated. EPI-MAL-002 and EPI-MAL-003 ~~are~~^{were} partly run concomitantly in the same study sites.

EPI-MAL-003 is intended primarily as a post-implementation safety study as reflected in the co-primary and secondary objectives. Additionally, vaccine effectiveness and impact estimations are included as secondary objectives. **The protocols for** EPI-MAL-002 and -003 ~~will be conducted with~~^{include} the same methodology for identification and characterisation of the events of interest. A strong capacity development component ~~is~~^{was} included in the baseline study EPI-MAL-002 **and -003**.

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MAL-005) is **being** conducted to measure malaria transmission intensity (MTI) and other malaria control interventions as confounding factors in the study site areas. ~~This study began in Q4 2014, at the first malaria transmission peak season, in the West African sites with peak in the second half of the year, and will run until the completion of EPI-MAL-003.~~

The three studies ~~were~~^{are} **being** conducted in similar if not identical settings. Sites selection ~~has been~~^{was} done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO [WHO, 2017] (refer also to Section 9.2.1), in order to ensure synergy between the latter and those three studies.

Through this programme, the malaria vaccine ~~will be~~^{is} **being** routinely delivered in sub-national areas of the pilot implementation countries by Ministries of Health (MoH) According to the MVIP, the RTS,S/AS01_E vaccine ~~will be~~^{is} given as a four dose schedule with the first dose administered as soon after 5 months of age as possible, followed by doses two and three at approximately one month intervals, and a fourth dose 15-18 months after dose three. **After study start, Mosquirix was prequalified by the**

WHO on 15 July 2022, with the WHO recommendation for administration from 5 months of age, as a 3-dose primary schedule with a minimum interval of 4 weeks between doses and a fourth dose provided approximately 12–18 months after the third dose. The recommendations also allow for flexibility in the schedule to optimize delivery, e.g. to align the fourth dose with other vaccines given in the second year of life.

Vaccine implementation ~~will be conducted~~**was** based on a cluster-randomized design, in which some areas (clusters) introduced RTS,S/AS01_E at the beginning of the programme and other clusters, initially without RTS,S/AS01_E, acted ~~as~~**ed** as comparison areas. In terms of vaccine evaluation, GSK ~~will~~ monitors vaccine safety, effectiveness and impact in some of those clusters while the WHO ~~will~~ monitored vaccine safety, effectiveness/impact and programmatic feasibility in the remaining ones The division of clusters into intervention or comparison areas ~~will be~~**was** randomized; with the exception of sites where the EPI-MAL-002 and EPI-MAL-003 **studies were** ~~are~~**are**/will be running, which ~~will be~~**was** purposely selected by the MoHs according to WHO guidance. From each pilot country, about 256,000 children ~~are~~**were** expected to be included into the pilot implementation programme (about 128,000 children in the RTS,S/AS01_E clusters [exposed clusters] and about 128,000 in the comparison arm [unexposed clusters]). Identical monitoring systems ~~will be~~**were** set up to record the outcomes of interest in both intervention and comparison areas.

9. Section 7.2 – Safety results of the clinical development of RTS,S/AS01_E

.....

- Background mortality rates per gender vary significantly across SSA countries. Under circumstances where boys and girls have the same access to resources such as food and medical care, boys have higher mortality rates than girls during childhood. ~~Western Africa had the most countries (five) with evidence of excess female child mortality in the 2000s as well as several countries of Eastern Africa and Middle Africa [United Nations, 2011].~~

10. Section 7.4 – Summary of the study rationale

.....

The WHO's SAGE and MPAC recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. They did not recommend the use of the malaria vaccine in the 6–12 weeks age group [WHO, 2015(a)]. In this post-implementation safety study EPI-MAL-003, only the 5-17 months age group ~~will be~~**was** kept. The first vaccine introduction occurred in 2019 after approval and recommendation by local health authorities. The RTS,S/AS01_E vaccine was implemented in selected areas/clusters of 3 SSA countries and ~~plan to expand~~**was expanded** the RTS,S/AS01_E vaccination programme ~~from 2023 is under discussion.~~

.....

In addition to the efficacy data provided by the MALARIA-055 ~~pre-authorisation clinical trial~~, evidence on the impact and effectiveness of RTS,S/AS01_E when administered post-implementation most close to routine medical practice is needed. Although primarily designed as a post-implementation safety study to detect potential rare and uncommon AEs following vaccination with RTS,S/AS01_E, the secondary objectives of EPI-MAL-003 also aim to evaluate the effectiveness (direct effect) and impact (indirect, total and overall effects) of RTS,S/AS01_E when administered ~~post-implementation~~ **in a setting matching most close to routine medical practice in SSA.** ...

It is important to note that background data on AEs are limited for malaria-endemic countries in SSA. This makes the assessment of risks potentially associated with the new vaccine following its implementation challenging. More specifically, the incidence and onset of autoimmune diseases and some of the other AESI are not known for African populations. Thus, an epidemiological study (EPI-MAL-002) to collect AESI data ~~has been~~ **was** initiated in Q4 2015 in the same study sites. The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation), of approximately 30,000 children in several sites in SSA countries (with at least 20,000 children enrolled where the RTS,S/AS01_E vaccine will be implemented), ~~will~~ **measured** the baseline incidence of AESI, other AE leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, ~~will~~ **was** also ~~be~~ estimated. In addition, EPI-MAL-005 ~~will be~~ **is being** conducted in parallel to EPI-MAL-002 and EPI-MAL-003, to measure MTI and record malaria control interventions at **the** community level in the study site areas on a yearly basis.

As much as possible, sites ~~have been~~ **were** selected for EPI-MAL-002 and EPI-MAL-005 based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system. The capacity of the study sites to detect AESI and meningitis ~~will be~~ **was** strengthened early in EPI-MAL-002.

GSK Biologicals ~~intends~~ **intended** to enrol 30,000 unvaccinated study participants in EPI-MAL-002 (with at least 20,000 in sites where the RTS,S/AS01_E vaccine will be implemented). The EPI-MAL-003 study ~~targets~~ **targeted** enrolling at least 45,000 children in active surveillance, including 22,500 children in the exposed clusters; with a minimum of 20,250 children vaccinated with RTS,S/AS01_E for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact (assuming that 80% of the 22,500 study participants in the exposed clusters ~~will~~ **would** receive three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose; see Section 9.2.7.1.1. for details of procedures if a child selected to be unvaccinated receives RTS,S/AS01_E vaccine); and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact. **The enrolment to active surveillance was completed on 06 April 2021.**

Considering the limited number of sites where the safety study ~~may be~~ **could have been** performed and following feasibility assessment with respect to recruitment target and practical conduct of the study, GSK ~~considers~~ **considered** that a sample size of around 45,000 study participants ~~is~~ **was** the highest possible.

.....

11. Section 8.2.1 – Secondary objectives – Safety

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E):

-
- To estimate the incidence of other AE leading to hospitalization*.
- ~~To describe risk factors for AESI, other AE leading to hospitalisation, meningitis, and malaria.~~
- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria)*.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following each dose of RTS,S/AS01_E*.

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01_E or not vaccinated with RTS,S/AS01_E)**:

-
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and AESI by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.
- To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.

****Analyses of Other AE leading to hospitalisation, cause of hospitalisation and incidence of febrile convulsions will only be conducted for the Interim Analysis and not for the Final Analysis.***

*****Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

12. Section 8.2.2 – Secondary objectives – Effectiveness and impact

-
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on:
 -
 - the incidence of ~~all-cause hospitalisations~~ and hospitalisations attributed to malaria (including *P. falciparum*).
 -

13. Section 9.1 – Study design

The EPI-MAL-003 study is a disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002; ***Interim Analysis only***) and concurrent (cluster design comparison of exposed and unexposed clusters; ***Interim Analysis and Final Analysis***) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters. The design ~~will~~ includes active surveillance (corresponds to a prospective cohort monitoring) and enhanced hospitalisation surveillance (Figure 1) in both exposed and unexposed clusters (see Annex 2 for definitions).

Active surveillance: First, a cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children, ~~will~~ ***was expected to*** be recruited in the exposed clusters (assuming that 80% of the 22,500 vaccinated study participants ~~will~~ ***would*** receive three doses of RTS,S/AS01_E, 10% ~~will~~ ***would*** receive one or two doses and 10% ~~will~~ ***would*** not have any dose). Second, a cohort of at least 22,500 children ~~will~~ ***was expected to*** be recruited in the unexposed clusters. In both exposed and unexposed clusters, the children ~~will be~~ ***are*** actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Parents/ legally acceptable representative(s) (LARs) (according to local requirements) ~~will be~~ ***were*** invited to enrol their child into the active surveillance as follows:

- **DTP group:** Children identified at any administration of DTP/HepB/Hib (usually given at 6, 10 and 14 weeks of age) or at hospitalisation before administration of 3rd dose of DTP/HepB/Hib and vaccinated with at least one dose of DTP/HepB/Hib. That group ~~will~~ includes both RTS,S/AS01_E vaccinated and unvaccinated children (from exposed or unexposed clusters);

- **Catch-up group:** Children identified at 1st RTS,S/AS01_E dose administration (schedule ~~depends~~ **dependent** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and ~~are~~ **were** older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group ~~will~~ includes only RTS,S/AS01_E vaccinated children from exposed clusters. Indeed, the objective of this catch-up is **was** to include all the children who ~~will~~ **would** receive the RTS,S/AS01_E vaccine and who could not be recruited at the time of DTP/HepB/Hib administration because the study had not yet started.

There ~~is~~ **was** no predefined number of study participants to be enrolled in each group. All children meeting the inclusion criteria ~~are~~ **were** expected to be enrolled in the study within the recruitment period.

.....

Note: The enrolment to active surveillance was completed on 06 April 2021.

Enhanced hospitalisation surveillance:

Since the MoHs of the countries participating in the MVIP according to the SAGE/MAPC recommendation ~~planned~~ to expand the RTS,S/AS01_E vaccine implementation to the unexposed clusters from 2023, clusters that were initially unexposed ~~will become~~ **became** exposed with regards to RTS,S/AS01_E vaccination. This change in vaccine implementation directly ~~impacts~~ **impacted** the current study plan. Therefore, the enrolment of subjects in the enhanced hospitalisation surveillance ~~will~~ **was** stopped **on 01 November 2022** in clusters that were not involved in the EPI-MAL-002 study (i.e. all clusters in Malawi; unexposed clusters in Ghana and 1 exposed and 2 unexposed clusters in Kenya) as from 01 ~~January 2023~~ **November 2022**. Subjects already enrolled in EHS ~~will~~ **continued** to be followed ~~until study conclusion~~, in order to capture information on their subsequent hospitalisations. Study conclusions ~~are being~~ **will be** conducted in a timely manner from 01 January 2023. ~~As initially planned, the enrolment of subjects in EHS will be pursued until the end of study in clusters involved in the EPI-MAL-002 study because this will provide relevant information for the before/after comparison.~~ **Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.**

.....

Enrolled in:

Active Surveillance

RTS,S Vaccinated

Unvaccinated

Enh. hosp. Surv.

Continuous monitoring of health care facility visits

Continuous monitoring of hospitalisations*

Continuous monitoring of hospitalisations*

Legend:

- RTS,S Vaccinated
- Unvaccinated
- Continuous monitoring of health care facility visits
- Continuous monitoring of hospitalisations*

• • • • •

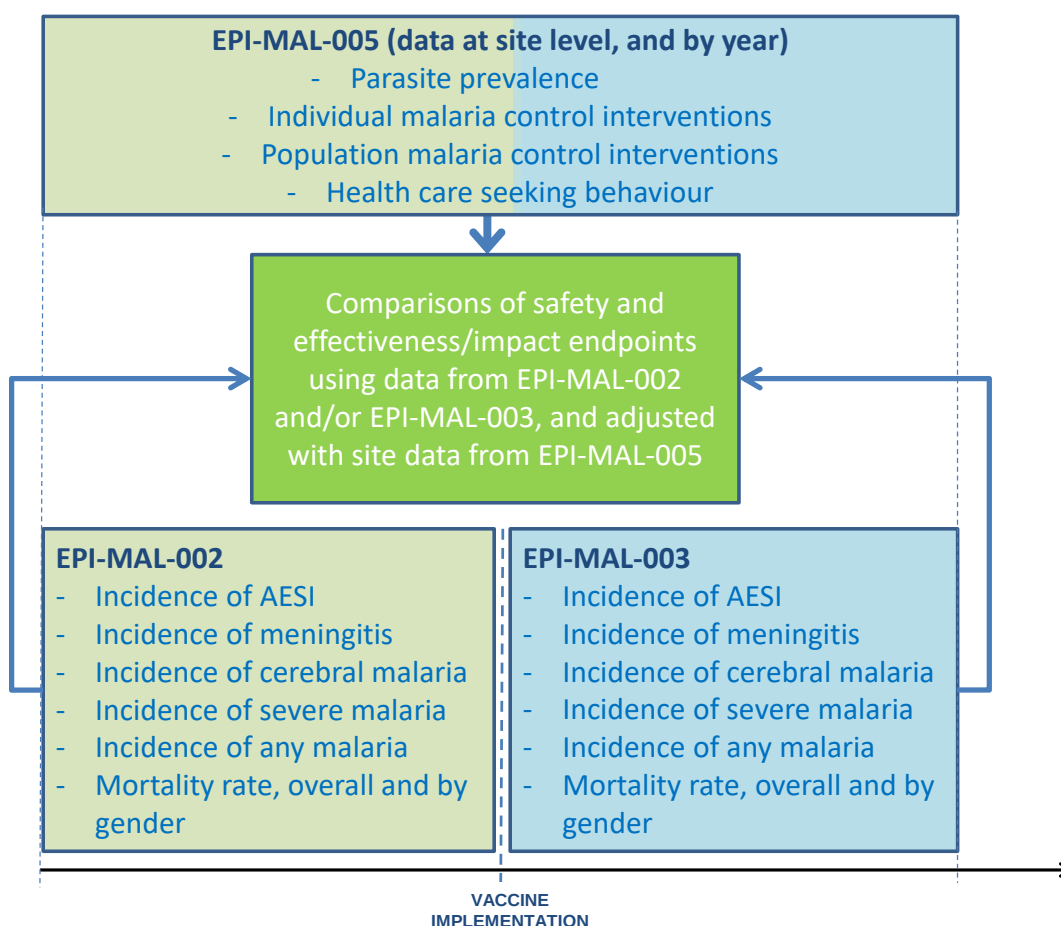
****Before-after comparison with the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.***

• • • • •

223

other AE leading to hospitalisation, meningitis, and malaria morbidity and mortality. The mortality rate, overall and by gender, ~~will~~ **was** also ~~be~~ estimated. ~~Studies~~ **Study** ~~EPI-MAL-002 and EPI-MAL-003 is~~ **will** collecting data in a similar manner **as in study EPI-MAL-002** to ensure their comparability. Capacity building of sites ~~will be~~ **was** provided before **the** start of EPI-MAL-002 and throughout the studies, to strengthen early case finding and diagnosis of the events of interest. **In parallel to studies EPI-MAL-002 and EPI-MAL-003, study** EPI-MAL-005 ~~will run in parallel with EPI-MAL-002 and EPI-MAL-003, and~~ aims to estimate the annual parasite prevalence and record malaria control measures, providing information on potential confounding factors relevant to interpreting EPI-MAL-002/-003 malaria outcome measures. In addition, as the vaccine ~~will~~ **was** to be implemented using a cluster design (sites in Kenya and Ghana where the EPI-MAL-002 ~~is~~ **was conducted** ~~running were expected to~~ **should** become part of the intervention areas, and new sites ~~have been~~ **were** selected to be part of the comparison areas of the EPI-MAL-003 **study**), a concurrent unvaccinated cohort ~~may be~~ **was** added as a comparator. For study sites of EPI-MAL-003 which are unexposed clusters of EPI-MAL-003 and where the EPI-MAL-002 was not conducted, the same capacity building ~~will be~~ **was** provided before **the** start of EPI-MAL-003 and throughout the study.

Figure 2 Evaluation of safety, effectiveness and impact using data collected in studies EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005



Note: comparison of endpoint data between EPI-MAL-002 and EPI-MAL-003 will only be conducted for the Interim Analysis and not for the Final Analysis.

Active surveillance

Note: as the last participant enrolled to active surveillance on 06 April 2021, some of the below protocol instructions are no longer applicable.

.....

An important function of the active surveillance component is to ensure referral of sick children to the health care facilities. Due to EPI-MAL-002 activities, the active surveillance processes should already **have been** effective when EPI-MAL-003 ~~begins~~ **began** enrolment, allowing for identification of AEs at an early stage of this study. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building ~~will be~~ **was** provided before **the** start of EPI-MAL-003 and throughout the study.

Enhanced hospitalisation surveillance

Note: following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

.....

Selected study sites ~~are~~ **were** expected to have a HDSS or equivalent surveillance system in place. If a site ~~does~~ **did** not have a HDSS in place, the **International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH)** procedures for demographic census ~~might be~~ **could have been** implemented to ensure consistency across study sites. In addition, being part of the ~~International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH)~~ (or seeking membership to INDEPTH) is an asset to ensure standard health and demographic surveillance practices, thereby enabling standardised calculation of incidence rates.

15. Section 9.2.1 – Study population

The three studies EPI-MAL-002, -003 and -005 ~~are~~ **were** ~~planned to be~~ anchored when possible on the INDEPTH health and demographic survey platform (<http://www.indepth-network.org>) or equivalent surveillance system to provide both population and health facility linkage [INDEPTH].....

....

Note: If a site ~~is~~ **was** not part of the INDEPTH network, the INDEPTH procedures for demographic census ~~might be~~ **could have been** implemented to ensure consistency across study sites.

..... other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01_E vaccine ~~is~~ **was** planned to be implemented according to MVIP, were added to the already defined study sites for EPI-MAL-002 as described below.

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01_E vaccine ~~will~~ **was to** be first introduced in 3 countries (Ghana, Kenya and Malawi) through MVIP. Each of the 3 countries ~~will~~ **were to** decide on the districts and regions to be included in the MVIP. High malaria burden areas ~~will~~ **were to** be prioritized [WHO, 2017]. In order to align with the MVIP, the study sites for the GSK's baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) ~~have been~~ **were** selected as follows:

- Sites ~~have been~~ **were** selected from the 3 countries where the RTS,S/AS01_E vaccine ~~will~~ **was to** be implemented in the framework of the MVIP. Burkina Faso sites that started EPI-MAL-002 ~~have~~ early terminated the study activities on 06 June 2018 (with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI). Burkina Faso sites ~~will~~ **were** not ~~be~~ included in EPI-MAL-003 because the MVIP ~~was~~ **will** not **planned to** take place in the country.
- As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 ~~should become~~ **(unexposed clusters) became exposed cluster** study sites in EPI-MAL-003 ~~which will be exposed clusters~~.
- Currently, as per MVIP and WHO guidance, 4 study sites (corresponding to 4 clusters of the MVIP) in each of the 3 countries selected for the RTS,S/AS01_E pilot implementation programme (12 study sites/clusters in total) ~~are~~ **were** planned to be part of EPI-MAL-003: 2 of them ~~should to~~ become exposed clusters and 2 of them ~~should to~~ become unexposed clusters. ~~As~~ Phase IV vaccine evaluation ~~being~~ **was** fully embedded in the MVIP, selection of the unexposed clusters ~~that will be~~ included in study EPI-MAL-003 ~~depends~~ **depended** on the cluster identification process led by the MoH in collaboration with the WHO. Of note, the clusters, once pre-identified by the MoHs ~~are~~ **were** submitted to a comprehensive scientific and operational study site assessment conducted by GSK, which ~~will~~ **determined** study feasibility in those sites. Exposed and unexposed clusters ~~will~~ **were to** be comparable in terms of malaria transmission, health facilities level, geographical region and population size.
 - As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 ~~should become~~ **(unexposed clusters) became exposed cluster** study sites in EPI-MAL-003 ~~which will be exposed clusters~~.
 - Selection of the remaining study sites/clusters ~~that will be~~ included in the EPI-MAL-003 study ~~is completed and is~~ **was** fully embedded in the MVIP.
- In summary: currently, a total of 3 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa]) ~~have~~ enrolled study participants in the EPI-MAL-002 study. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 sites have become exposed study sites/clusters in EPI-MAL-003. Selection of the remaining study sites/clusters ~~that will be~~ included in the EPI-MAL-003 study ~~is completed and is~~ **was** fully embedded in the MVIP. Study feasibility in all sites/clusters ~~is~~ **was** assessed through a comprehensive scientific and operational study site assessment.

Taking into account a global birth cohort of 23,000 children at the time of EPI-MAL-002 study preparation, and the refusal rate of parents for their children to join the study, an expected number of at least 45,000 children, including 22,500 children in the exposed clusters (with minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children) and 22,500 children in the unexposed clusters ~~will~~ **were planned to** be part of the active surveillance of the study. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. ~~If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children in the exposed clusters is reached. The number of children enrolled per site will depend on the birth cohort at each site.~~

16. Section 9.2.2. – Eligible population

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The WHO's SAGE on Immunization and the MPAC recommended pilot implementations of RTS,S/AS01_E in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. At the start of the malaria vaccine implementation, children aged 5-12 months ~~will be~~ **were** eligible for dose 1 of RTS,S/AS01_E. In some countries a large number of children aged 5-12 months may therefore ~~be~~ **have been** vaccinated at the start of the pilot implementation programme. Once the malaria vaccine implementation ~~is reached~~ **a** steady state, the majority of children receiving dose 1 ~~will~~ **would** have only ~~recently~~ **just** grown into the eligible age range. Co-administration could ~~have happened~~ **have** happened such as measles or yellow fever vaccines, scheduled in older infants at 9 months of age.

For the active surveillance, children from both exposed and unexposed clusters ~~will be~~ **were** enrolled. At least 22,500 children in the exposed clusters, including a minimum of 20,250 children vaccinated with RTS,S/AS01_E, and a minimum of 2,250 unvaccinated children, ~~are~~ **were** targeted to be enrolled (assuming that 80% of study participants ~~will~~ **would** receive at least three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose). At least 22,500 children in the unexposed clusters ~~will~~ **were to** be enrolled into the active surveillance when presenting for administration of DTP/HepB/Hib vaccine. Parents/ LARs ~~will be~~ **were** invited to enrol their child into the active surveillance when children ~~are~~ **were** presenting for administration of DTP/HepB/Hib vaccine (DTP group), regardless **of** whether they subsequently decided to vaccinate their child with RTS,S/AS01_E or not. In addition, parents/ LARs ~~will be~~ **were** invited to enrol their child into the active surveillance when children ~~are~~ **were** presenting for 1st administration of RTS,S/AS01_E vaccine and who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and ~~are~~ **were** older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start (catch-up group).

The enrolment to active surveillance was completed on 06 April 2021.

For enhanced hospitalisation surveillance, ...:

- If a child, who ~~is~~ **was** first identified during hospitalization by study staff, ~~fulfills~~ **fulfilled** the eligibility criteria for enrolment in active surveillance (within the

recruitment period), enrolment in active surveillance ~~will be~~**was** proposed. If the parents/LARs declined enrolment in active surveillance and if the child ~~fulfills~~**fulfilled** the eligibility criteria for enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance ~~will be~~**was** proposed.

- If a child, who ~~is~~**was** first identified during hospitalization by study staff, ~~is~~**was** not eligible for enrolment in active surveillance but ~~fulfills~~**fulfilled** the eligibility criteria for enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance ~~will be~~**was** proposed.

..... ~~This issue will be addressed by identifying the type of health care facility (either hospital or primary health care facility) in case of hospitalisation. The type of health care facility will be included as covariate in the analyses, where appropriate.~~

~~There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003. Children~~ **who were** enrolled in active surveillance of EPI-MAL-002, and **were** not eligible for RTS,S/AS01_E vaccination or ~~declining~~**declined** RTS,S/AS01_E vaccination, ~~will~~ **were** continued to be followed up to the study conclusion visit in EPI-MAL-002. Children enrolled in active surveillance of EPI-MAL-002, and ~~becoming~~ vaccinated with RTS,S/AS01_E, ~~will have~~**had** their study conclusion of EPI-MAL-002. Thereafter, these children ~~can~~ **could have been** enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

For children enrolled in enhanced hospitalisation surveillance of EPI-MAL-002, ~~the~~ study conclusion of EPI-MAL-002 ~~will be~~**was** done at start of study EPI-MAL-003 (as the vaccine ~~becomes~~ **became** available in the study sites that ~~are~~ **were** exposed clusters). Thereafter, these children ~~can be~~ **could have been** eligible and enrolled in active surveillance or in enhanced hospitalisation surveillance of EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

Note: Enrolment to EHS will stop following site Ethics Committee approval of Protocol Amendment 3.

17. Section 9.2.3 – Inclusion criteria

Note: the enrolment to active surveillance was completed on 06 April 2021; reference to inclusion criteria at study entry to active surveillance is no longer applicable.

.....

18. Section 9.2.5 – Study period

Taking into account a global birth cohort of 23,000 children at the time of EPI-MAL-002 study preparation (11,500 children in the exposed clusters, and 11,500 children in the unexposed clusters), a period of approximately 18 months ~~is~~ **was** assumed to be sufficient to enrol at least 45,000 children in active surveillance of EPI-MAL-003, including 22,500 children in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children assuming that 80% ~~will~~ **would** receive three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose) and 22,500 in the unexposed clusters. The

vaccine coverage in the exposed clusters and enrolment ~~will be~~**were** monitored through the progress reports. ~~In the participating sites, the vaccine coverage is not expected to be low. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children is reached.~~

The recruitment period ~~will~~**was to** be adapted according to the birth cohorts of the different sites at the time of study start. The duration of the recruitment ~~will~~**was also to** be adjusted according to the recommended schedule of the vaccine and the vaccine coverage in the exposed clusters, the time the participating countries started implementing the vaccine (which may **have been** different between countries), and potential unanticipated logistical issues.

The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months. Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01_E (or equal point in time for unvaccinated children) **given at a maximum age of 30 months.**

Note: ~~There might be an~~**Due to the** overlap of studies EPI-MAL-002 and EPI-MAL-003, some children enrolled in EPI-MAL-002 ~~will have~~**had** the possibility to be part of EPI-MAL-003. First, the study conclusion of EPI-MAL-002 for children enrolled in enhanced hospitalisation surveillance ~~will be~~**was** done at the start of study EPI-MAL-003 (as the RTS,S/AS01_E vaccine ~~becomes~~**became** available in the sites that are exposed clusters; See Section 9.2.2.). In addition, children enrolled in active surveillance of EPI-MAL-002, and ~~becoming~~ vaccinated with RTS,S/AS01_E, ~~will have~~**had** their study conclusion of EPI-MAL-002. Thereafter, these children ~~can~~**could have been** enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

19. Section 9.2.6.3 - Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria)

.....

Collection of hospitalisations for an AE other than AESI or meningitis or any malaria or severe malaria (including cerebral malaria) ~~will be~~**were** stopped as of 01 ~~January 2023~~**November 2022** in subjects previously enrolled in EHS in sites not involved in EPI-MAL-002 study. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria) will continue to be collected as part of continuous monitoring for subjects enrolled in AS in all sites, or EHS in sites involved in **the** EPI-MAL-002 study **until enrolment to EHS is stopped following site Ethics Committee approval of Protocol Amendment 3.**

20. Section 9.2.7.1 – Active surveillance

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Note: the enrolment to active surveillance was completed on 06 April 2021; the below instructions relating to enrolment and some of the protocol instructions are no longer applicable.

21. Section 9.2.7.1.6. – Outline of study procedures

Table 4 List of study procedures for participants in active surveillance

Footnote:

Note: the enrolment to active surveillance was completed on 06 April 2021; instructions relating to enrolment and some of the visit instructions are no longer applicable.

22. Section 9.2.7.2. - Enhanced hospitalisation surveillance

.....

Note: following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.

23. Section 9.2.7.2.15. - Study conclusion

Note: For subjects enrolled in EHS, data collection of other AE leading to hospitalisation ~~will be~~**was** stopped as from 01 ~~January 2023~~**November 2022** in sites not participating in EPI-MAL-002. For those subjects, a study conclusion visit ~~will be~~**was to** be conducted in a timely manner from 01 ~~January 2023~~**November 2022**. For subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge. ***Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop in sites not participating in EPI-MAL-002, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for subjects diagnosed with an AESI, meningitis or cerebral malaria.***

24. Section 9.2.7.2.16. - Outline of study procedures

Table 5 List of study procedures to be conducted in the event of hospitalisation

Footnote:

****For subjects enrolled in EHS in sites not participating in EPI-MAL-002, a study conclusion visit ~~will be~~ was conducted in a timely manner from 01 ~~January 2023~~ November 2022.***

25. Section 9.2.7.4. – Case ascertainment

For the purpose of this study, a panel of experts ~~will be~~**was** set up and a charter ~~will be~~ defined.

26. Section 9.2.7.4.2. – AESI

A panel of experts in the different fields ~~will be~~**was** established and ~~will~~ **assessed** whether the aetiology of the AESI is confirmed or not and whether the date of first symptoms of the disease falls within the risk period.

27. Section 9.2.7.7. – Capacity building

Capacity building from the sites ~~conducting~~ **that conducted** EPI-MAL-002 ~~that~~ **will** ~~which~~ also participated in EPI-MAL-003 ~~will be~~ **was** utilized to strengthen early case finding and diagnosis of the events of interest. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building ~~will be~~ **was** provided before ~~the~~ start of EPI-MAL-003 and throughout the study.

- Training

The Agence de Médecine Préventive [AMP, ~~http://amp-vaccinology.org~~] will provide

In addition, all sites will have access to online continued medical education, training packages (including training on AESI, meningitis, HIV and hemoglobinopathies) and a telemedicine system established by the Réseau en Afrique Francophone pour la Télémédecine [RAFT, Geneva; ~~http://raft.globalhealthforum.net~~].....

In EPI-MAL-002, health care (including EPI staff) and study staff ~~will be~~ **were** trained in pharmacovigilance procedures.....

28. Section 9.3.2.1. – Safety endpoints

In children included in active or enhanced hospitalisation surveillance*:

-
- Occurrence of hospitalisation (including those attributed to an AESI, ~~other AE,~~ meningitis or malaria)*.
- Occurrence of febrile convulsions during the **the 3-day period (Days 0-3) and** 7-day period (Days 0-6) ~~and 1-month period (Days 0-29)~~ following each dose of RTS,S/AS01E (see Section 9.2.6.5 for case definition)*.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation (see Section 9.2.6.10 for case definitions)*.
- Occurrence of other AE leading to hospitalisation (see section 9.2.6.3 and section 9.2.6.9 for definitions)*.

****Occurrence of hospitalisation, other AE leading to hospitalisation, febrile convulsions and quality indicators will only be conducted for the Interim Analysis and not for the Final Analysis.***

29. Section 9.3.2.2. – Effectiveness and impact endpoints

In children included in active surveillance:

-
- Occurrence of hospitalisation*

****Occurrence of all-cause hospitalisation will only be conducted for the Interim Analysis and not for the Final Analysis.***

30. Section 9.3.3.2. – Recorded in EPI-MAL-005

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~~In addition, the malaria control intervention use and health care seeking behaviour will also be included in the model of the study EPI-MAL-003, as centre level covariates estimated in study EPI-MAL-005 per year.~~

31. Section 9.4.1. – HDSS (or equivalent surveillance system) databases

..... From this database, the listing of children at the beginning of the study ~~will~~ provided the study site with a basis for recruitment of children <18 months old for active surveillance and for the total number of children < 5 years of age recorded at least once a year during the study duration. During the study, further newborns may *have been* identified by one of several possible mechanisms (depending on the site):

32. Section 9.4.2 - Active surveillance and enhanced hospitalisation surveillance

Note: the enrolment to active surveillance was completed on 06 April 2021; the below instructions for screening and enrolment of study participants are no longer applicable.

.....

33. Section 9.4.3. – Baseline study EPI-MAL-002

The study EPI-MAL-002 ~~is~~ *was* designed to estimate baseline incidence rates of AESI, other AE leading to hospitalisations, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality prior to introduction of RTS,S/AS01_E. It ~~will~~ also served as the platform for capacity building for EPI-MAL-003, with the overall goal to increase the sensitivity and specificity of capturing rare safety events post vaccination.

34. Section 9.4.4. - Malaria transmission intensity study EPI-MAL-005

....

EPI-MAL-005 started in Q4 2014, is ~~planned~~ *being conducted* to run in parallel with EPI-MAL-002 and EPI-MAL-003, in similar if not identical settings, and will assess the following parameters:

35. Section 9.5. – Study size

The study ~~targets~~ *targeted* enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children ~~are~~ *were* estimated to be enrolled in active surveillance, assuming that the distribution according to the administration of RTS,S/AS01_E in the exposed clusters ~~will~~ *would* be the following:

- 10% without any dose, corresponding to 2,250 unvaccinated children (in the exposed clusters);

- 10% with an incomplete primary schedule (i.e. 1 or 2 doses), corresponding to 2,250 partially vaccinated children;
- 80% with the full primary schedule (i.e. 3 doses), corresponding to 18,000 vaccinated children. Among those children, two scenarios ~~are~~ **were** considered with regards to the uptake of the 4th dose of RTS,S/AS01_E: either 50% (i.e. 9,000 children), or 75% (i.e. 13,500 children).

Note that the size of each exposed/unexposed cluster ~~is~~ **was** assumed to be around 4,000 children, leading to a total of less than 20 clusters (~~currently~~ 12 clusters ~~are~~ **were** planned).

36. Section 9.6. – Data management

...

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator ~~will be provided with a CD-ROM of the final version of~~ **can download** the data generated at his/her investigational site **directly from the electronic data collection tool**.

37. Section 9.7. – Data analysis

.....

As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters from the same countries (sites) and same age group **(Interim Analysis only)**. ~~Sensitivity analyses will be conducted including all subjects from EPI-MAL-002 study (i.e. subjects from both age groups (6-12 weeks, 5-17 months)) using an adjustment on the age.~~ The cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters **(Interim Analysis and Final Analysis)**.

38. Section 9.7.3. - Demographics and characteristics at study entry

.....

In the same way, the subjects from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-002 Analysis set will be compared **(Interim Analysis only)**.

39. Section 9.7.4. – Exposure description

.....

The exposure to other vaccines will be compared between the baseline cohort (EPI-MAL-002) and the EPI-MAL-003 exposed clusters **(Interim Analysis only)** as well as between the EPI-MAL-003 unexposed clusters and the EPI-MAL-003 exposed clusters **(Interim Analysis and Final Analysis)**.

40. Section 9.7.5.1 – Analysis for co-primary objectives - Analysis population

The population will include the study participants from the active surveillance of the exposed clusters of the EPI-MAL-003 study.

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance. The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints. ~~A secondary population will include the study participants from the active and enhanced hospitalisation surveillance of the exposed clusters of the EPI-MAL-003 study, computing incidence for all children < 5 years.~~

41. Section 9.7.5.2.1. – Statistical approach - Incidence rate of AESI

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance.

Incidence following immunisation

.....

Incidence rates of these composite endpoints will be calculated as described for individual AESI in case of multiple cases in a study participant, only the first event *after each dose* will be considered in this analysis.

~~Incidence for children < 5 years~~

~~In addition, the incidence will be estimated for all children < 5 years. In such case, the numerator will be the number of cases of specified events during the study. The person-time denominators for each rate will be reflective of the entire community population in the age group of interest. Each child will contribute person-time until the relevant age (at study end or at 5 years, whichever occurs first).~~

42. Section 9.7.5.2.2. – Incidence rate of aetiology-confirmed meningitis

Incidence rate (and 95% CI) of aetiology-confirmed meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for an AESI.

43. Section 9.7.6. – Analysis for secondary safety objectives

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance. The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.

44. Section 9.7.6.1. – Analysis population

....

Study participants from the active surveillance of the EPI-MAL-002 study, ~~and study participants from the active and enhanced hospitalisation surveillance of the EPI-MAL-002 study~~ will be used for comparison purposes with the exposed clusters of EPI-MAL-003 study in a before-after design (***Interim Analysis only***). Subjects from the 5-17 months age group of the EPI-MAL-002 study will be included ~~and a sensitive analysis will be conducted with subjects from both age groups (6-12 weeks, 5-17 months), using an adjustment on the age.~~

Moreover, study participants from the active ~~and enhanced hospitalisation~~ surveillance of the unexposed clusters of the EPI-MAL-003 study will be used for comparison with the exposed clusters of the EPI-MAL-003 study in a cluster design.

45. Section 9.7.6.2.2. – Meningitis cases monitoring

....

..... For interim analysis and at the end of the study, if the threshold is not reached, the comparisons between vaccinated and unvaccinated study participants using the before-after design (***Interim Analysis only***) and the cluster design (***Interim Analysis and Final Analysis***) will be done anyway.

.....

46. Section 9.7.6.5. - Cause of hospitalisation due to AESI, meningitis or malaria and death in children < 5 years vaccinated with RTS,S/AS01E and unvaccinated children < 5 years

Descriptive analysis of the causes of hospitalisation (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) will consist in computing the number of cases, person-time and incidence (with 95% CI).

Note: these analyses will only be conducted for the Interim Analysis and not for the Final Analysis.

47. Section 9.7.6.6 – Other AE leading to hospitalisation

.....

All other AE leading to hospitalisation will be coded using ~~Medical Dictionary for Regulatory Activities (MedDRA)~~ Dictionary and presented by ~~System Organ Class (SOC) and Preferred Term (PT).~~

Note: these analyses will only be conducted for the Interim Analysis and not for the Final Analysis.

48. Section 9.7.6.7.1. – Before-after comparison

Before-after comparison using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

Whether for incidence following immunisation or for incidence for children < 5 years, two comparisons will be performed, in addition to the different analysis populations mentioned in Section 9.7.6.

.....

~~Exposure determinants and potential risk factors for AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) could also be collected at study entry and evaluated using univariate and multivariable Poisson regression models only for the incidence following immunisation.~~

Of note, multivariable models will be conducted for a specific AESI, MedDRA SOC and PT of other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) if a signal is detected (i.e. the null hypothesis is rejected) and if a minimum number of cases of AESI, other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) is observed (at least 10 cases in total).

~~The adjusted covariates are described in Section 9.3.3:~~

- ~~• Demographic parameters such as age at reference date and gender.~~
- ~~• Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drugs exposure, toxic agent exposure.~~
- ~~• Comorbidity factors such as premature birth, history of trauma.~~
- ~~• Health care seeking behaviour and distance to health care facilities.~~
- ~~• Type of health care facility.~~
- ~~• Neighbourhood of residence (urban/rural area).~~
- ~~• Total number of outpatient visits per centre.~~

~~This list may be adapted according to the data generated from EPI-MAL-002.~~

~~The categorisation of covariates will be described in the SAP when the final CRF is available.~~

~~Covariates occurring in less than 5% of the study participants (percentage will be computed over both cohorts) will not be included in the model.~~

~~Some predefined clinical relevant covariates might be forced into the models and will be listed in the SAP with the rationale (e.g. prior knowledge from literature).~~

~~Covariates selection will be done using both statistical significance and change in estimate method. Confounders will be included in the multivariable models if univariate p-value will be less than 20% or if their inclusion in bivariate model along with the exposure variable (i.e. vaccine status) and study site as fixed effect, change the coefficient of the exposure variable by 10% or more.~~

~~Co-linearity (i.e. correlation among predictor covariates) will be assessed on the full model including forced-in covariate and the other selected with the variance inflation factor (level of 10% [Hair, 1995]). If it is necessary to drop a variable due to co-linearity, the decision will be made on order of clinical importance.~~

~~Then the selected set of covariates will be entered in the final model without transformations.~~

.....

49. Section 9.7.6.7.2 – Cluster design comparison

Analyses of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis or cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of the exposed and the unexposed clusters from EPI-MAL-003 by means of a random-effect Poisson regression model with the clusters as random effect.

~~Univariate and multivariable Poisson regression will also be conducted using the same strategy (Section 9.7.6.7.1) for selection of covariates.~~

50. Section 9.7.6.7.3. – Exposed clusters comparison

For the exposed clusters only, analyses of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis and cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of vaccinated study participants from the exposed clusters of EPI-MAL-003 and unvaccinated study participants from the exposed clusters of EPI-MAL-003 by means of a Poisson regression model with the study site as an adjusted factor.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation (**Interim Analysis only**), meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

~~Univariate and multivariable Poisson regression will also be conducted using the same strategy (Section 9.7.6.7.1) for selection of covariates.~~

51. Section 9.7.6.8. – Febrile convulsion

The frequency (with 95% CI) of febrile convulsion within **3 and 7** and ~~30~~ days post vaccination will be reported in all study participants from the exposed clusters (**Interim Analysis only**).

~~In addition, the risk of febrile convulsions will be assessed using a SCCS analysis. Only the cases recorded in the vaccinated study participants during the active surveillance will be used. Two risk periods after vaccination will be considered: 0-6 and 7-29 days. Incidence rate with its 95% CI will be computed (see details of the statistical model in Section 9.7.9).~~

52. Section 9.7.6.9. – Surveillance indicator analysis

The analysis done on AESI will also be conducted on the incidence of foot positional deformations as a birth defect (negative control) and abscess at the injection site (positive control) (*Interim Analysis only*).

53. Section 9.7.7.1. – Analysis for secondary effectiveness and impact objectives - Analysis population

....

Comparisons will be performed using the direct effect design, the before-after design (*Interim Analysis only*) and the cluster design.....

54. Section 9.7.7.1.2. – Impact using the before-after design

Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

.....

55. Section 9.7.7.2. – Comparison of incidence rate of effectiveness or impact endpoints

.....

~~Univariate and multivariable Poisson regression models will be conducted. Those adjusted covariates are described in Section 9.3.3:~~

- ~~• Demographic parameters such as age at reference date and gender.~~
- ~~• Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drug exposure, toxic agent exposure.~~
- ~~• Use of malaria control measures such as bednets, indoor residual spraying, seasonal malaria chemoprevention.~~
- ~~• Comorbidity factors such as premature birth, history of trauma.~~
- ~~• Health care seeking behaviour and distance to health care facilities.~~
- ~~• Type of health care facility.~~
- ~~• Neighbourhood of residence (urban/rural area).~~
- ~~• Total number of outpatient visits per centre.~~

- ~~Seasonal MTI (i.e. parasite prevalence) estimated in study EPI-MAL-005 on the vaccine ineligible group (see Annex 2 for definition).~~
- ~~Other centre level covariates estimated in study EPI-MAL-005 per year: malaria control intervention use, bednet use and health care seeking behaviour.~~

The same strategy as described in Section 9.7.6.7.1 will be used for covariates selection to be included in the multivariable model.

.....

Table 22 Incidence rate and prevalence calculations for effectiveness and impact objectives (children enrolled in active surveillance)

Endpoints	Numerator	Denominator
.....		
Hospitalisation due to AESI (<i>Interim Analysis only</i>), meningitis, malaria	# of children hospitalised for AESI, during study period Source: Hospitalisations	Person-years contribution of enrolled children
....		

56. Section 9.7.7.3. – Comparison of time to event of effectiveness or impact endpoints

The first occurrence of each effectiveness and impact endpoint event will be coded as a binary variable (Yes/No).

For each effectiveness and impact outcome:

- ~~The time between reference date and date of event will be analysed using Kaplan-Meier method and Cox regression models.~~
- ~~The reference date will be adapted according to the analysis population (e.g. the date of third RTS,S/AS01E vaccination for the vaccinated cohort, and the equivalent date for the unvaccinated cohort).~~
- ~~The date of event will be the date of first occurrence of the event or date of death for death endpoint.~~
- ~~The date of censoring will be the date of end of study period, date when the child reaches 5 years, date of death (for endpoints other than death), date of last contact, or migration date, whichever comes first.~~

~~Kaplan-Meier curves presenting the cumulative probability of an event will be displayed and compared between groups for risk factors of interest using the Log-rank test (univariate analyses).~~

~~Univariate Cox regression models will also be performed in order to obtain unadjusted hazards ratios of the risk factors of interest. In addition, a multivariable Cox regression model will be performed in order to estimate the relative contribution of each risk factor~~

adjusting for the simultaneous effects of the other covariates. Those adjusted covariates are described in Section 9.3.3:

- Demographic parameters such as age at reference date and gender.
- Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drug exposure, toxic agent exposure.
- Use of malaria control measures such as bednets, indoor residual spraying, seasonal malaria chemoprevention.
- Comorbidity factors such as premature birth, history of trauma.
- Health care seeking behaviour and distance to health care facilities.
- Type of health care facility.
- Neighbourhood of residence (urban/rural area).
- Total number of outpatient visits per centre.
- Seasonal MTI (i.e. parasite prevalence) estimated in study EPI-MAL-005 on the vaccine ineligible group (see Annex 2 for definition).
- Other centre level covariates estimated in study EPI-MAL-005 per year: malaria control intervention use, bednet use and health care seeking behaviour.

For covariates selection to be included in the multivariable Cox model, the same strategy as described in Section 9.7.6.7.1 for Poisson Regression will be used.

Results from the multivariable time survival analyses (Cox model) will include mean and median (if estimable) time (with 95% CI) and hazards ratios (with 95% CI). The survival curves predicted by the model will be displayed.

57. Section 9.7.7.3.2. – Impact using the before-after design

Before-after design analyses using data from the EPI-MAL-002 study will only be conducted for the Interim Analysis and not for the Final Analysis.

.....

58. Section 9.7.8.1. – Handling of missing data

A worst case allocation will be done for suspected events (i.e. suspected AESI, suspected malaria) for which confirmation of the outcome is not available. In such case a sensitivity analysis will be done considering these unresolved events as confirmed.

For the determinants included in multivariable models, a complete cases analysis will be performed as primary analysis (i.e. missing data will not be substituted).

As sensitivity analysis, a precise diagnosis of missing pattern will be done to describe the kind of missing data (i.e. missing at random, missing completely at random and missing not at random). Considering the diagnosis an appropriate method of imputation will be conducted and will only concern the covariates forced in the models. The strategy will be the following:

- ~~For continuous covariates, a multiple imputation [Rubin, 1987] method will be applied to handle missing value if missing at random mechanism is confirmed. Indeed, as noted by Sterne et al [Sterne, 2009], multiple imputations may give misleading results in case data are missing not at random;~~
- ~~For categorical covariates, missing indicator method will be done (i.e. a specific category of missing value will be created).~~

~~Of note, if the “complete cases” analysis contains 90% of the study participants, no imputation will be done. In the case that for a single covariate more than 50% of values are missing, the covariate will not be included in the model.~~

~~The method of imputation will be detailed in the SAP.~~

59. Section 9.7.9.1.2. – Mixed regression

~~Sensitivity analysis of the before-after design will use Mixed Poisson model including study site as random-effect. For the cluster design, Mixed-Poisson model will also be used including clusters as random-effect. Those models will be conducted using the SAS GLIMMIX procedure.~~

60. Section 9.7.9.3. – Cox proportional hazards model

~~The Cox model will be computed using the SAS PHREG procedure. The dependent variable is the time between the reference date and the event. The reference date will be adapted according to the analysis population (e.g. the date of third RTS,S/AS01_E vaccination for the vaccinated cohort, and the equivalent date for the unvaccinated cohort). The unvaccinated study participants could be obtained from EPI-MAL-002 or from EPI-MAL-003, either in the exposed or the unexposed clusters.~~

~~Time to event for a study participant with no event will be censored at the earliest of the following time points:~~

- ~~End of study period~~
- ~~Lost to follow-up~~
- ~~Death (for endpoint other than death).~~

~~For the before-after design, the first model will include the exposure status (vaccinated study participants versus unvaccinated study participants both from EPI-MAL-003) as a binary independent variable and the study site as a class covariate (see Section 9.7.7 for further models). The adjusted hazard ratio will be derived as the exponential of the coefficient associated with the exposure status and its 95% Wald CI.~~

~~A survival curve will be estimated for the vaccinated and unvaccinated study participants (using the Option Plots (overlay)=survival in the SAS PHREG procedure).~~

~~For the cluster design, as described in section 9.7.7.3.3, The COVS(AGGREGATE) will be specified in SAS PHREG procedure to compute the robust sandwich covariance matrix estimate.~~

The choice of the best fitted model will be based on the consistency of the effects of the covariates observed in the different multivariable models and the Akaike's Information Criterion (AIC) and the Schwarz Bayesian Criterion (SBC).

61. Section 9.7.9.4. Self-controlled case-series

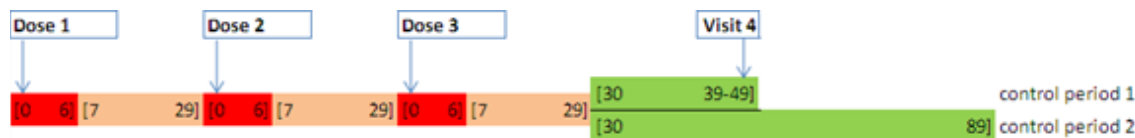
Section 9.7.9.4.1. Background

The SCCS was developed to investigate associations between vaccination and acute potential AE [Farrington, 1995]. The SCCS is based only on cases, and provides consistent estimates of the relative incidence rate. The effect estimate is calculated as the ratio of the incidence rate of events during a given post-exposure period (risk period), to the incidence rate of events during the absence of the exposure (control period).

Section 9.7.9.4.2. Risk and control periods

Two periods at-risk will be defined: Day 0 to Day 6, and Day 7 to Day 29, with Day 0 defined as the day of vaccination. These two periods will be compared to two different control periods: a 2-week period (between Day 30 and day of the visit 4 [Day 39-49]) and a two-month control period (between Day 30 and Day 89) after vaccination. Two different control periods are utilised as the probability to report an event decreases after the day of Visit 4 (recall bias). The first risk period will be primarily used to analyse the risk of febrile convulsions.

Figure 6 Conceptual representation of the risk periods and two control periods



If there is more than one month between 2 doses, control periods will be considered after dose 1 and dose 2 with the same timeframe as the dose 3.

For the study participants who received several doses, risk and control periods will be defined after each dose. The risk period after Dose 1 (Dose 2) will be censored at the time of the second (third) dose vaccination in case of a second (third) dose vaccination less than 30 days after the first (second) dose vaccination. The control period after the first (respectively second) dose will be censored at the time of the second (respectively third) dose vaccination.

The post-vaccination period will be censored at the date of death or date of last contact (lost to follow-up) or date when the child reaches 5 years.

It cannot be ruled out that the probability to be vaccinated could be impacted by the occurrence of the event. However, this assumption will be assessed because the SCCS analyses will be done in a cohort setting, vaccination rate for second / third dose will be computed for the children who experience febrile convulsions after first / second dose and compared with the vaccination rate in children who don't experience febrile convulsion. In case this comparison suggests lower probability for vaccination after

occurrence of febrile convulsion, the SCCS method for curtailed post-event exposure [Farrington, 2009] will be used.

Section 9.7.9.4.3. Statistical calculations

The statistical calculation will be done in SAS 9.2 or higher using the specific SAS macro developed by Whitaker et al [Whitaker, 2006] and available online from <http://statistics.open.ac.uk/sees>.

Section 9.7.9.4.4. Mathematical model

Due to the relatively short duration of the period of observation (3 months) compared to a possible age effect, no age effect will be included in the model.

Each individual i is observed within a time interval (a_i, b_i) . This interval is the observation period for the individual i . The observation period for individual i is then partitioned into $k=0,1$ periods. Risk period, $k=1$, corresponds to an increased risk relative to control period which is coded $k=0$.

Conditioning on the exposure history over the entire observation period, it is assumed that events of interest for individual i arise as a non-homogeneous Poisson process with rate λ_{ik} . If n_{ik} is the number of events arising for individual i and risk period k , then

$$n_{ik} \approx \text{Poisson}(\lambda_{ik} e_{ik})$$

Conditioning on the total number of events

$$n_i = \varphi_i + \beta_k$$

arising in (a_i, b_i) , the log-likelihood contribution of individual i is

$$l_i = \sum_k n_k \log \left(\frac{\lambda_k e_{ik}}{\sum_s \lambda_s e_{is}} \right)$$

With a log-linear model for the Poisson rate of the form

$$\log(\lambda_{ik}) = \varphi_i + \beta_k$$

Where φ_i is an individual effect, and β_k is the exposure effect associated with risk period. The parameter β_k is the log relative incidence.

The log-likelihood estimate of β_k is

$$l(\beta) = \sum_i n_{ik} \log \left(\frac{\exp(\beta_k) e_{ik}}{\sum_r \exp(\beta_r) e_{ir}} \right)$$

~~The analysis will compare the incidence rate in the 0-6 day risk period and in the 7-29 day risk period with the overall incidence rate in the two control periods: a 2-week period (between Day 30 and day of the visit 4 [Day 39-49]) and a two-month control period after (between Day 30 and Day 89) vaccination.~~

~~Point estimates of the relative incidence rate and its 95% CI will be derived.~~

62. Section 9.7.10. – Conuct of analysis

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the **SAP** / final study report.

63. Section 9.7.12. – Statistical considerations for interim analysis

.....

Final analysis will be carried out on clean data collected up to study conclusion. ***The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the Final Analysis (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.***

.....

64. Section 9.9. – Limitations of the research methods

.....

This study ~~will~~ **targeted** enrolling at least 20,250 vaccinated children for evaluation of the safety of RTS,S/AS01_E (in total, 22,500 children ~~are~~ **were** estimated to be enrolled in active surveillance in the exposed clusters, assuming that 80% of study participants in the exposed clusters ~~will~~ **would** receive at least three doses of RTS,S/AS01_E, 10% ~~will~~ **would** receive one or two doses and 10% ~~will~~ **would** not have any dose even though they are assigned to the exposed clusters cohort).

....

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified. Training of physicians and field staff ~~will~~ **started** during the pre-implementation study (EPI-MAL-002). For the study sites of EPI-MAL-003 where the EPI-MAL-002 was not conducted, training ~~will be~~ **was** provided before **the** start of EPI-MAL-003. All efforts will be made to ensure an optimal standardised way of collecting data across the different sites. Progress reports every 6 months will help in monitoring the participation rate, the vaccination coverage and the trends in event detection. ~~In the participating sites where the RTS,S/AS01_E vaccine will be implemented at the beginning of the pilot implementation programme (exposed clusters), the vaccine coverage is not expected to be low. If the~~

~~vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children (in the exposed clusters) is reached.~~

.....

Longitudinal detection of events such as meningitis might also be difficult to interpret because of the changing meningitis disease epidemiology. The study ~~will take place in~~ **includes** some countries of the “meningitis belt”, which is affected yearly by bacterial meningitis epidemics (mostly meningococcal meningitis). This zone comprises 22 countries from Senegal in the West to Ethiopia in the East. ~~During 1993–2012, nearly one million suspected meningitis cases were reported; 80% of epidemics were caused by *Neisseria meningitidis* serogroup A. From 1928 to 2018, 2,628,283 cases including 151,808 deaths were reported to WHO-AFRO in the 53 African countries during the meningitis epidemics period, with a mean case-fatality rate of 5.77% [Mazamay, 2021]. The highest case numbers were reported in 1996 (184,487 cases). The mean incidence of meningitis cases in Africa from 1928 to 2018 was 216 per 100,000 inhabitants (SD ± 14.8). Epidemic meningococcal group A disease outbreaks have recorded incidence rates up to 100 per 100,000 [Soeters, 2019].~~ Despite successful introduction of a meningococcal A conjugate vaccine in the African meningitis belt since 2010 [Novak, 2012], meningococcal meningitis outbreaks ~~may occur~~ **was a possibility** in some study sites during the EPI-MAL-002 and EPI-MAL-003 study periods, due to other *Neisseria meningitidis* serogroups, or if the study site is in a region/country which has not yet introduced the vaccine. Therefore, the interpretation of differences in meningitis incidence rates should take into account the epidemiological context of each site. As for AESI, all efforts will be made to standardize meningitis diagnosis and reach an optimal proportion of laboratory confirmed cases to establish the aetiology. The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts (blinded to RTS,S vaccination status as much as possible). ~~Additional epidemiological investigations (such as case-control or SCCS designs) might be necessary to establish causality if meningitis cases are reported more frequently in EPI-MAL-003 than in EPI-MAL-002 or in EPI-MAL-003 exposed clusters than in EPI-MAL-003 unexposed clusters.~~ In addition, other evidence such as data generated by the meningitis surveillance in place in those countries, or the monitoring of meningitis in the older non-vaccine eligible children will be taken into account for the analysis of the events.

Because surveillance will be conducted in study areas covering mainly rural areas, children who are severely ill might die before being transported to hospital. In EPI-MAL-002 and EPI-MAL-003, in the event of death, the cause of death ~~will be~~ **is** systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital. However, ascertaining the cause of death remains a concern considering the limitation of the verbal autopsy methods in the field, ~~this~~ **and** is why all-cause mortality is an important endpoint to consider in this study.

*If a site is not part of the INDEPTH, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

All efforts ~~were/are being~~**will be** made to standardize data collection during EPI-MAL-002 and EPI-MAL-003, both in exposed and unexposed clusters. However, due to the long duration of both studies, changes in diagnostic procedures, implementation of malaria control measures such as seasonal malaria chemoprevention [WHO, 2012(a)], and changes in treatment measures will have to be considered during the analyses of the safety and effectiveness/impact data. Potential confounders ~~were~~**will** be collected at individual level during EPI-MAL-002 and EPI-MAL-003 and at community level during EPI-MAL-005. Some study participants might also leave the study area during the study period but this is regularly documented through demographic census (scheduled at least once a year during the study periods).

In addition to the 22,500 children in the unexposed clusters, this study ~~will~~**targeted** enrolling at least 2,250 unvaccinated children in the exposed clusters for evaluation of effectiveness and impact of RTS,S/AS01_E. ~~The uncertainty about recruitment of a sufficiently large unvaccinated group in the exposed clusters will be clarified when vaccine recommendations by the respective MoH will be known.~~ To be able to compare the groups, parents/ LARs ~~were~~**will** be invited to enrol their child into the active surveillance when children **presented** for administration of DTP/HepB/Hib vaccine, regardless of whether they subsequently decided to vaccinate their child with RTS,S/AS01_E or not. In addition, the same follow-up will be conducted (same study period, same timing for the inclusion visit and same number of home visits) and the same data collection will be prospectively implemented. However, the objective is to be able to collect data to estimate both the direct effect and the vaccine impact (indirect, total and overall effects). Considering the low proportion of vaccinated study participants in the population at the beginning of the vaccination programme implementation where EPI-MAL-003 ~~will be~~**is being performed****conducted**, there is some likelihood that an indirect effect (also named herd effect) will not be estimable in this study.

.....

In the framework of the secondary objectives, the comparisons will be done considering the before-after design (comparing occurrence of events in subjects from EPI-MAL-002 with subjects from the exposed clusters of EPI-MAL-003; **Interim Analysis only**), and considering the cluster design (comparing occurrence of events in subjects from the unexposed clusters of EPI-MAL-003 with subjects from the exposed clusters of EPI-MAL-003; **Interim Analysis and Final Analysis**). Both comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

Integrating the Phase IV in the MVIP and adding a concurrent unvaccinated cohort (unexposed clusters) to EPI-MAL-003 have some impact on study designs but also allow strengthening the post-approval plan of RTS,S/AS01_E. The latter now considers two comparisons (before-after and cluster design comparisons) allowing adjustment for both temporal and geographical variability in terms of, **for example**, malaria transmission, disease incidence, access to care, **and** use of other malaria control measures,.... On one

hand, temporal bias might occur due to *factors such as* seasonality and year to year variations, or due to variation in control measures,~~....~~, *amongst others*~~....~~. On the other hand, geographical bias might occur due to, *for example*, differences in health care infrastructure/facilities between sites, due to the epidemiology of several diseases, especially of infectious disease, or due to variation in controls measures,~~....~~. Therefore, the two comparisons are considered complementary and should provide more robust results.

~~The before-after design enables a more powerful continuous monitoring of meningitis through MaxSPRT analysis as well as a more powerful comparison at the time of the interim analysis. Indeed, the enrolment of the unvaccinated comparator arm (before) is complete at the moment the EPI-MAL-003 study starts. It will therefore provide precise estimates of the different incidences.~~

..... Also, cluster trials with fewer than five clusters per arm are, in general, inadvisable, since parametric tests may be unreliable with such small numbers [~~Medical Research Council, 2002~~*Puffer, 2005*]. In addition, the clusters that are/will be allocated to the Phase IV studies have not been randomized to allow before-after comparison (EPI-MAL-002 sites that will provide baseline incidences of the endpoints of interest ~~will be~~ *were to become* clusters implementing RTS,S/AS01_E vaccine). Moreover,...

Finally, since the Phase IV is fully integrated in the ~~malaria vaccine pilot implementation programme~~*MVIP*,.....

65. Section 10.1 - Regulatory and ethical considerations, including the informed consent process

....

GSK ~~will~~ *obtained* favourable opinion/approval to conduct the study prior to a site initiating the study in any country, according to local requirements, or ~~will was to~~ document that neither a favourable opinion nor an approval to conduct the study *is was* needed.

....

GSK Biologicals ~~will~~ *prepared* a model ICF which ~~will embody~~ *embodies* the applicable ICH GCP or other applicable guidelines, and GSK Biologicals required elements.

66. Section 11.4.1. - Back-up system in case the electronic reporting system does not work

Back-up Study Contact for Reporting AEs
24/24 hour and 7/7 day availability: Email: ~~RIX-CT-Safety-Vac@gsk.com~~ <i>ogm28723@gsk.com</i> GSK Biologicals Clinical Safety & Pharmacovigilance Fax: ~~+32 2 656 51 16 or +32 2 656 80 09~~ <i>+32 2 656 8009</i>

67. Section 11.5. – Follow-up of adverse events

-

Note: enrolment to EHS and data collection will stop following Ethics Committee approval of Protocol Amendment 3; for subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge.

.....

68. Section 13. – REFERENCES

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69. Annex 1 – List of stand-alone documents

No.	Document Reference No	Date	Title
1.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	List of stand-alone documents
2.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Glossary of terms
3.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Trademarks
4.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Sponsor Information
5.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Case definitions for protocol-defined AESI and surveillance indicators
6.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Study specific guidance document
7.	115056 (EPI-MALARIA-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Amendment to the protocol
8.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Protocol Amendment ~~23~~ sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	Protocol Amendment ~~23~~ investigator agreement
10.	115056 (EPI-MAL-003 VS AME)	~~15 October 2020~~ 24 Oct 2024	ENCePP Checklist for study protocols

70. Annex 8 – Protocol Amendment 3 Sponsor Signatory Approval

Sponsor signatory

François Roman, Clinical **Project Lead, Discovery Projects/Adjuvants** and Epidemiological Project Lead, DDW Vaccines

71. Annex 9 – Protocol Amendment 3 Investigator Agreement

I agree:

- ~~To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals~~
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, ‘Good Clinical Practice’ (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- ~~To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.~~ ***To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.***
- ~~That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator’s ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.~~

Hence I:

- ~~Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).~~
- ~~Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.~~
- ~~Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.~~

Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

Annex 8 Protocol Amendment 3 Sponsor Signatory Approval

**eTrack study number and
Abbreviated Title**

115056 (EPI-MALARIA-003 VS AME)

Date of protocol Amendment

Amendment 3 Final: 24 Oct 2024

Detailed Title

A prospective study to evaluate the safety,
effectiveness and impact of the RTS,S/AS01_E
vaccine in young children in sub-Saharan Africa.

Sponsor signatory

François Roman, Clinical Project Lead, Discovery
Projects/Adjuvants

Signature

Date

Annex 9 Protocol Amendment 3 Investigator Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- *To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.*

eTrack study number and Abbreviated Title 115056 (EPI-MALARIA-003 VS AME)

Date of protocol Amendment Amendment 3 Final: 24 Oct 2024

Title A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01_E vaccine in young children in sub-Saharan Africa.

Investigator name _____

Signature _____

Date _____

Annex 10 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ⁴	☒	☐	☐	30
1.1.2 End of data collection ⁵	☒	☐	☐	30
1.1.3 Study progress report(s)	☒	☐	☐	30
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	30

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	31-43
2.1.2 The objective(s) of the study?	☒	☐	☐	44-46
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	54-59
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	116-118
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

This is primarily a safety surveillance study				
Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	46-53
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	89-90
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk,	☒	☐	☐	111-130

⁴ Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

⁵ Date from which the analytical dataset is completely available.

excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)				

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	53-58
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	58-59
4.2.2 Age and gender?	☒	☐	☐	53-58
4.2.3 Country of origin?	☒	☐	☐	53-58
4.2.4 Disease/indication?	☒	☐	☐	53-58
4.2.5 Co-morbidity?	☒	☐	☐	53-58
4.2.6 Seasonality?	☒	☐	☐	53-58
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	58-59, 70-73

Comments:

To address seasonality change and other malaria control interventions, EPI-MAL-005 will run in parallel with EPI-MAL-003 on a yearly basis				
Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	91-95
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	91-95
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	91-95
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	112-128
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	60-69, 91-92
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	91-92

Comments:

<u>Section 7: Confounders and effect modifiers</u>	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	90-91
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	90-91

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	89-91
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	89-91
8.1.3 Covariates?	☒	☐	☐	89-91
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	89-91
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	89-91
8.2.3 Covariates? (e.g. age, gender , clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	89-91
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	Part of GSK safety procedure
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	Not applicable
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

For standardised case definition for protocol-defined AESI, see Annex 5

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	94-108

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	112-134
10.2 Is the choice of statistical techniques described?	☒	☐	☐	112-134
10.3 Are descriptive analyses included?	☒	☐	☐	112-134
10.4 Are stratified analyses included?	☒	☐	☐	112-134
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	112-134
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	112-134

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	126-127
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	109, 136
11.3 Are methods of quality assurance described?	☒	☐	☐	133-134
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	133-134
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

There is a system for independent review of the cases by a panel of expert physicians (see pages 83-86)

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	135-140
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	135-140
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	53-58
12.3 Does the protocol address other limitations?	☒	☐	☐	135-140

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	140-141
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	134

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	29

Comments:

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	146-147
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	146-147

Comments:

NOTE: SPONSOR CONFIRMS HIS/HER AGREEMENT WITH THE COMPLETED ENCEPP CHECKLIST BY SIGNING THE PROTOCOL SPONSOR APPROVAL PAGE.

Signature Page for 115056 TMF-20112174 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 24-Oct-2024 16:14:14 GMT+0000

Signature Page for TMF-20112174 v1.0

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01_E vaccine in young children in sub-Saharan Africa.

Scope Final Analysis

Study Number: 115056

Abbreviated Title: EPI-MALARIA-003 VS AME

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

EU PAS Register No: EUPAS28541

TABLE OF CONTENTS

	PAGE
TITLE PAGE	1
VERSION HISTORY	7
1. INTRODUCTION.....	8
1.1. Objectives and Endpoints	8
1.2. Study Design	11
2. STATISTICAL HYPOTHESES	14
2.1. Multiplicity Adjustment	14
3. ANALYSIS SETS	14
3.1. Enrolled set.....	14
3.2. Analysis set	14
3.2.1. Impact Analysis set.....	15
3.3. Summary	16
4. STATISTICAL ANALYSES.....	16
4.1. General Considerations	16
4.1.1. Groups.....	17
4.1.2. General Methodology	18
4.1.2.1. Poisson regression model	18
4.1.2.2. Logistic model	18
4.1.3. Methodology for computing confidence intervals.....	19
4.1.4. Handling missing data.....	19
4.1.5. Number of decimals.....	19
4.1.6. Descriptive statistics	19
4.2. Primary Endpoint(s) Analyses.....	20
4.2.1. Definition of endpoint(s).....	20
4.2.1.1. Confirmed AESI.....	20
4.2.1.2. Aetiology confirmed meningitis	20
4.2.2. Main analytical approach	20
4.2.2.1. Incidence following immunisation (actual or virtual vaccination primary schedule).....	20
4.2.2.1.1. Individual follow-up period and at- risk period.....	20
4.2.2.1.2. Management of the at-risk period	22
4.2.2.2. Comparison vaccinated and unvaccinated populations.....	24
4.2.2.2.1. Cluster design comparison	24
4.2.2.2.2. Exposed clusters comparison	24
4.2.2.2.3. Summary of the comparisons	25
4.3. Secondary Endpoint(s) Analyses	25
4.3.1. Secondary safety endpoint(s)	25
4.3.1.1. Definition of endpoint(s).....	25
4.3.1.1.1. Meningitis	25
4.3.1.1.2. Cerebral malaria	25
4.3.1.1.3. Death.....	25

4.3.1.2.	Main analytical approach	26
4.3.1.2.1.	Incidence rate following immunisation (actual or virtual vaccination primary schedule)	26
4.3.1.2.2.	Comparison of vaccinated and unvaccinated populations	27
4.3.2.	Secondary effectiveness and impact endpoints analyses	27
4.3.2.1.	Definition of endpoints	28
4.3.2.1.1.	Malaria	28
4.3.2.1.1.1	Uncomplicated malaria	28
4.3.2.1.1.2	Severe malaria	29
4.3.2.1.1.3	Cerebral Malaria	30
4.3.2.1.2.	Anaemia	30
4.3.2.1.3.	Hospitalisation	30
4.3.2.1.4.	Death.....	30
4.3.2.2.	Main analytical approach	30
4.3.2.2.1.	Derivation of incidence rate and prevalence	30
4.3.2.2.2.	Comparison of incidence rate of effectiveness or impact endpoints	32
4.3.2.2.2.1	Effectiveness (direct effect).....	32
4.3.2.2.2.2	Impact using the cluster design	33
4.3.2.2.3.	Summary of the comparisons	34
4.4.	Exploratory Analyses	35
4.4.1.	Prevalence of malaria among anaemic children and comparison	35
4.4.2.	Averted cases based on Total effect	35
4.4.3.	Vaccine Impact (Total effect) accounting for Malaria Transmission Intensity (MTI) estimated in EPI-MAL-005 study	36
4.5.	Other Analyses	36
4.6.	Interim Analyses	37
4.6.1.	Data in scope.....	37
4.6.1.1.	EPI-MAL-003 study	37
4.7.	Changes to Protocol Defined Analyses	38
5.	SAMPLE SIZE DETERMINATION	38
6.	SUPPORTING DOCUMENTATION	39
6.1.	Appendix 1 Study Population Analyses.....	39
6.1.1.	Study participant disposition	39
6.1.2.	Demographics and characteristics at study entry	39
6.1.3.	Signs and symptoms, and medical history	40
6.1.4.	Exposure description	40
6.1.5.	Protocol Deviations.....	40
6.1.6.	Additional Analyses Due to the COVID-19 Pandemic	41
6.2.	Appendix 2 Data Derivations Rule	41
6.2.1.	Age	41
6.2.2.	Number of RTS,S/AS01 _E vaccine dose received	41
6.2.3.	Cause of death	42
6.2.4.	Reference date: Vaccination/Virtual vaccination date	42
6.2.4.1.	Vaccinated children with RTS,S/AS01 _E vaccine	42

6.2.4.2.	Unvaccinated children	43
6.2.4.2.1.	Handling of missing visit dates.....	43
6.2.5.	Date of occurrence	43
6.2.6.	Management of consecutive visits and/or hospitalisations	43
6.2.6.1.	AESI, meningitis	44
6.2.6.2.	Malaria	44
6.2.7.	Last contact date & Migration/Return date	45
6.2.8.	Protocol amendment approval dates.....	47
7.	REFERENCES.....	48

LIST OF TABLES

		PAGE
Table 1	Elimination codes	14
Table 2	Definition of at-risk period for AESI.....	21
Table 3	Follow-up period definition after each dose	21
Table 4	Summary of the comparisons for safety endpoints analyses	25
Table 5	Definition of at-risk period for safety events:.....	27
Table 6	Follow-up period definition for other secondary endpoints.....	31
Table 7	Incidence rate and prevalence calculations for other secondary objectives (children enrolled in active surveillance)	31
Table 8	Summary of the comparisons for effectiveness and impact endpoints	35
Table 9	Changes to Protocol Defined Analysis Plan	38
Table 10	Management of consecutive hospitalisations for malaria cases.....	44
Table 11	Protocol amendment 2 approbation dates.....	47

LIST OF FIGURES

	PAGE
Figure 1	
Diagram on effectiveness (adapted from Halloran and Longini [Halloran, 1997]).....	33
Figure 2	
Diagram on impact presenting the different vaccine effects for the cluster design (adapted from Halloran and Longini [Halloran, 1997]).....	34

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	29 September 2022	Protocol amendment 2 (22 October 2020)	Not Applicable	SAP for Interim Analysis
SAP	17 Apr 2025	Protocol amendment 3 (24 October 2024)	Changes made to describe the planned final analysis following protocol amendment 3. To incorporate the changes made during the interim analysis for clarifying the analysis section and the selection of regression models, and to include the additional analyses performed following the interim analysis.	SAP for Final Analysis

1. INTRODUCTION

The purpose of this SAP is to describe the planned final analysis following protocol amendment 3. All data from Active Surveillance will be included for the final analysis. The Enhanced Hospital Surveillance (EHS) cohort data will only be used for descriptive statistics of the main safety endpoints in the final analysis (Adverse Events of Special Interest [AESI], meningitis, malaria and mortality).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To estimate the incidence of AESI¹ in children vaccinated with RTS,S/AS01_E.	Occurrence of AESI
To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E.	Occurrence of aetiology-confirmed meningitis
Secondary safety	
In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01 _E or not vaccinated with RTS,S/AS01 _E):	
To estimate the incidence of aetiology-confirmed and/or probable meningitis (final classification²).	- Occurrence of aetiology-confirmed meningitis - Occurrence of probable meningitis (final classification²)
To estimate the incidence of probable meningitis (final classification²).	Occurrence of probable meningitis (final classification²)
To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification²).	- Occurrence of aetiology-confirmed meningitis - Occurrence of probable meningitis (final classification²) - Occurrence of clinically suspected meningitis (final classification²)
To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy).	Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
To estimate the incidence of other AE leading to hospitalisation*	Occurrence of other AE leading to hospitalisation

Objectives	Endpoints
To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including <i>P. falciparum</i>]), overall and by gender.	Occurrence of death, All causes and malaria attributed deaths (including <i>P. falciparum</i> malaria attributed death)
To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria)*.	Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis or malaria).
To describe the causes of death, overall and by gender.	Occurrence of death (All causes, death due to AESI, other AE, meningitis or malaria including <i>P. falciparum</i> malaria attributed death)
To assess the risk of febrile convulsions during the 3-day period and the 7-day period following each dose of RTS,S/AS01_E*.	Occurrence of febrile convulsions during the 3 day period (days 0-3) and the 7-day period (Days 0-6) following each dose of RTS,S/AS01_E
In children enrolled in EPI-MAL-003 studies (vaccinated with RTS,S/AS01 _E or not vaccinated with RTS,S/AS01 _E)**:	
To monitor trends over time of meningitis cases identified at site level (first line laboratory).	Occurrence of meningitis cases identified at site level (first line laboratory)
To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.	Occurrence of aetiology-confirmed meningitis
To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.	- Occurrence of aetiology-confirmed meningitis - Occurrence of probable meningitis (final classification²)
To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.	- Occurrence of aetiology-confirmed meningitis - Occurrence of probable meningitis (final classification²) - Occurrence of clinically suspected meningitis (final classification²)
To assess the potential association between vaccination and AESI by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E**.	Occurrence of AESI
To assess the potential association between vaccination and cerebral malaria by comparing the incidence of this event in	Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).

Objectives	Endpoints
children vaccinated with RTS,S/AS01 _E with the incidence of this event in children not vaccinated with RTS,S/AS01 _E ^{**} .	
To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of death in children vaccinated with RTS,S/AS01_E with the incidence of death in children not vaccinated with RTS,S/AS01_E^{**}.	Occurrence of death (All causes, death due to AESI, other AE, meningitis or malaria attributed deaths including <i>P. falciparum</i> malaria attributed death)
To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01_E with the incidence of these events in children not vaccinated with RTS,S/AS01_E^{**}.	Occurrence of other AE leading to hospitalisation
Secondary effectiveness and impact	
To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01_E on the incidence of any malaria (including <i>P. falciparum</i> malaria), severe malaria (including <i>P. falciparum</i> malaria) and cerebral malaria diagnosed by RDT and/or microscopy.	- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy - Any malaria (including <i>P. falciparum</i> malaria) - Severe malaria (including <i>P. falciparum</i> malaria) - Cerebral malaria
To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01 _E on:	
the prevalence of anaemia among hospitalised children.	Occurrence of anaemia at hospital entry among hospitalised children
the incidence of all-cause hospitalisations and hospitalisations attributed to malaria (including <i>P. falciparum</i>).	Occurrence of hospitalisation, All causes and hospitalisations for any malaria (including <i>P. falciparum</i> malaria), severe malaria (including <i>P. falciparum</i> malaria) and cerebral malaria
the mortality rate (all-cause mortality and deaths attributed to malaria [including <i>P. falciparum</i>]) overall and by gender.	Occurrence of death, All causes and malaria attributed deaths (including <i>P. falciparum</i> malaria attributed death)

¹Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode (HHE), generalised convulsive seizure

Intussusception, hepatic failure or renal insufficiency

Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease

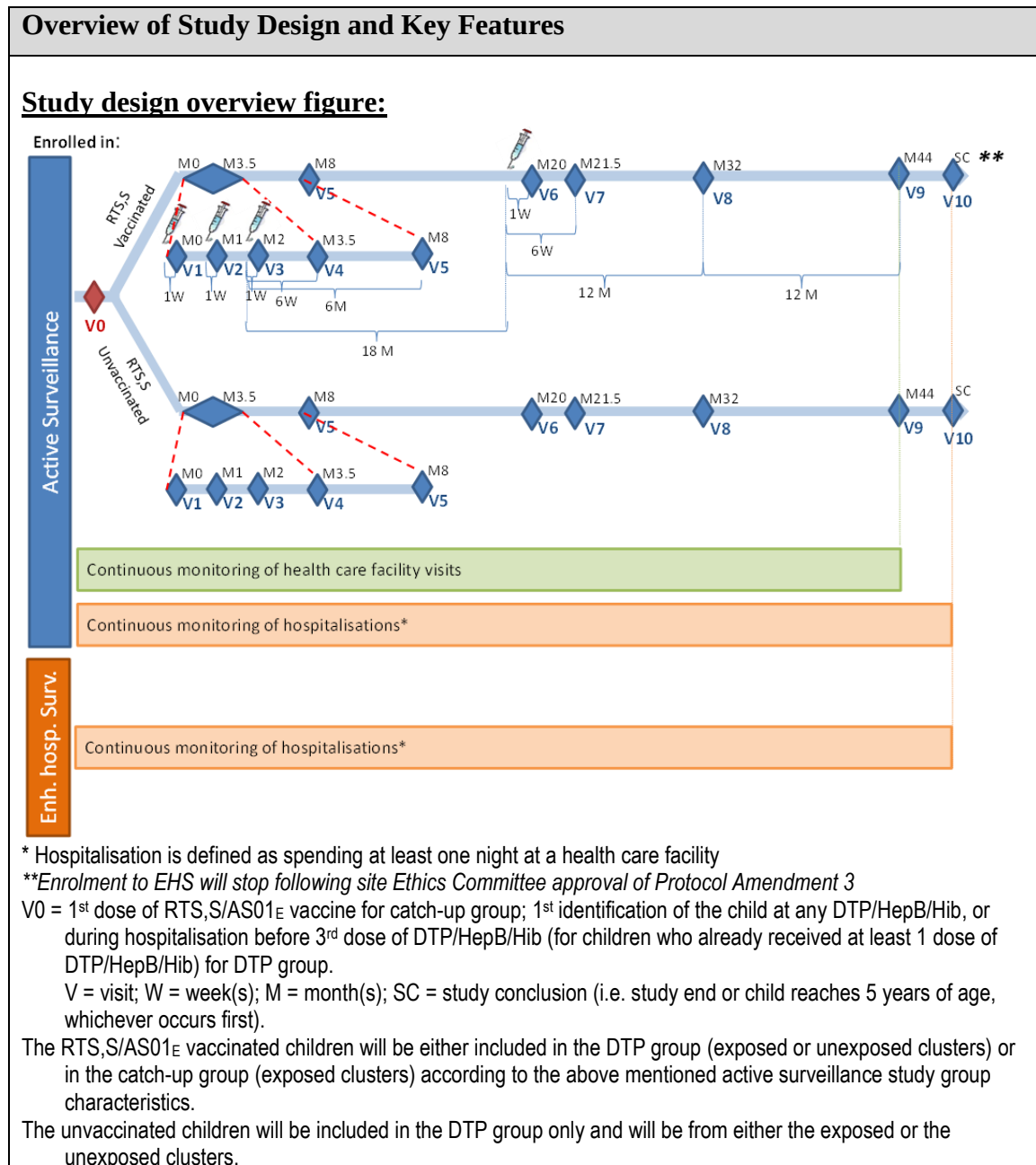
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

²Final classification of meningitis cases will be based on second line laboratory results (when available) and after external panel of experts review

*Analyses of Other AE leading to hospitalisation, cause of hospitalisation and incidence of febrile convulsions were only conducted for the Interim Analysis and will not be conducted for the Final Analysis.

**Before-after design analyses using data from the EPI-MAL-002 study were only conducted for the Interim Analysis and will not be conducted for the Final Analysis.

1.2. Study Design



For the children enrolled in active surveillance in the DTP group, enrolment is at any administration of DTP/HepB/Hib vaccine or at hospitalisation before 3rd administration of DTP/HepB/Hib vaccine and vaccinated with at least one dose of DTP/HepB/Hib. This group includes both RTS,S/AS01_E vaccinated and unvaccinated children from exposed or unexposed clusters. The catch-up group of the active surveillance will include a group of children identified at 1st RTS,S/AS01_E dose administration (schedule depends on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group includes RTS,S/AS01_E vaccinated children from exposed clusters. For the children vaccinated with RTS,S/AS01_E, the home visits will take place approximately 1 week after administration of each dose of primary schedule of RTS,S/AS01_E (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose; and 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after administration of the 4th dose of RTS,S/AS01_E. For the children not vaccinated with RTS,S/AS01_E, the home visits will be scheduled at equal points in time. A last home visit (V10) will be conducted at study conclusion. Continuous monitoring of outpatient visits at health care facilities will be done up to the end of active follow-up for children enrolled in active surveillance. For active surveillance, continuous monitoring of hospitalisations will be done throughout the whole study period. For EHS, the continuous monitoring of hospitalisations will be done throughout the whole study period for clusters involved in EPI-MAL-002 study. For the other clusters not involved in EPI-MAL-002 study, enrolment into EHS was stopped and study conclusion conducted in a timely manner from 01 November 2022.	<table border="1"> <tr> <td data-bbox="233 835 440 1915"> Design Features </td><td data-bbox="440 835 1378 1915"> • Disease surveillance study with prospective cohort event monitoring • Temporal (before-after comparison with EPI-MAL-002; interim analysis only) and concurrent (cluster design comparison of exposed and unexposed clusters; interim and final analyses) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated participants living in exposed or unexposed clusters located in sub-Saharan Africa (SSA) countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters. • The design includes active surveillance (corresponds to a prospective cohort monitoring) and enhanced hospitalisation surveillance in both exposed and unexposed clusters. – <u>Active surveillance:</u> • A cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children, was expected to be recruited in the exposed clusters • A cohort of at least 22,500 children was expected to be recruited in the unexposed clusters. • In both exposed and unexposed clusters, the children are actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. For vaccinated children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01_E vaccine, up to 2 years after the last dose. </td></tr> </table>	Design Features	• Disease surveillance study with prospective cohort event monitoring • Temporal (before-after comparison with EPI-MAL-002; interim analysis only) and concurrent (cluster design comparison of exposed and unexposed clusters; interim and final analyses) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated participants living in exposed or unexposed clusters located in sub-Saharan Africa (SSA) countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters. • The design includes active surveillance (corresponds to a prospective cohort monitoring) and enhanced hospitalisation surveillance in both exposed and unexposed clusters. – <u>Active surveillance:</u> • A cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children, was expected to be recruited in the exposed clusters • A cohort of at least 22,500 children was expected to be recruited in the unexposed clusters. • In both exposed and unexposed clusters, the children are actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. For vaccinated children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01_E vaccine, up to 2 years after the last dose.
Design Features	• Disease surveillance study with prospective cohort event monitoring • Temporal (before-after comparison with EPI-MAL-002; interim analysis only) and concurrent (cluster design comparison of exposed and unexposed clusters; interim and final analyses) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated participants living in exposed or unexposed clusters located in sub-Saharan Africa (SSA) countries, and eligible for RTS,S/AS01_E vaccination for those living in the exposed clusters. • The design includes active surveillance (corresponds to a prospective cohort monitoring) and enhanced hospitalisation surveillance in both exposed and unexposed clusters. – <u>Active surveillance:</u> • A cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01_E and a minimum of 2,250 unvaccinated children, was expected to be recruited in the exposed clusters • A cohort of at least 22,500 children was expected to be recruited in the unexposed clusters. • In both exposed and unexposed clusters, the children are actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. For vaccinated children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01_E vaccine, up to 2 years after the last dose.		

	For children not vaccinated with RTS,S/AS01_E, visits will be scheduled at equal points in time. – <u>Enhanced hospitalisation surveillance:</u> • All children who are at least 6 weeks and <5 years of age, within the study areas in both exposed and unexposed clusters, not already enrolled in the active surveillance (because parents/ legally acceptable representatives [LARs] declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance at the time of hospitalisation, are eligible for enrolment in enhanced hospitalisation surveillance. • Following site Ethics Committee approval of Protocol Amendment 3, enrolment to EHS and data collection will stop, with the exception of planned check-up visits at 1 month, 6 months and 1 year after hospital discharge for participants diagnosed with an AESI, meningitis or cerebral malaria. • The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months
Study intervention	Not applicable: Observational study
Study intervention Assignment	Not applicable: Observational study
Interim Analysis	Interim analysis done only on Active Surveillance data 12 months post dose 3.

2. STATISTICAL HYPOTHESES

Unless specified otherwise, all the statistical tests will be two-sided at alpha level of 0.05.

2.1. Multiplicity Adjustment

All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

3. ANALYSIS SETS

3.1. Enrolled set

The **Enrolled set** will include all children enrolled in the study (i.e. either from exposed or unexposed clusters), through active surveillance or EHS, and will include a mix of children vaccinated with RTS,S/AS01_E and unvaccinated.

3.2. Analysis set

The **Analysis set** will include all evaluable study participants (i.e. those meeting all eligibility criteria, complying with the enrolment procedures defined in the protocol, with no elimination criteria during the study). This analysis set will be used for primary endpoint analyses (see section 4.2) and secondary safety endpoints analyses (see section 4.3.1). The Table 1 below describes the elimination codes:

Table 1 Elimination codes

Analysis sets	Elimination codes
Enrolled set	900* Invalid informed consent or fraudulent data
Analysis set	2010 Inclusion criteria - Participants' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol. - Written informed consent provided from either the parent(s) or LAR of the participant. - Participant living in the HDSS or equivalent surveillance system area. - For enrolment in the active surveillance (DTP group & Catch-up group): children must be < 18 months of age OR For enrolment in the enhanced hospitalisation surveillance: Children must be < 5 years + 2 weeks of age and hospitalised at any time during the study. Children enrolled after protocol amendment 2 approval (see Table 11) must be ≥ 6 weeks of age Exclusion criteria - Child in care

Analysis sets	Elimination codes
	2501 Participants recruited in the group active surveillance DTP group: • Participants without DTP or without DTP vaccine dates available eliminated • Participants eliminated if ICF signed more than 10 days after 3rd DTP • Participants eliminated if ICF signed at first visit available or after first visit • Participants for whom the hospitalisation admission date is before 3rd DTP and : ○ If hospital discharge date is known then participants with ICF signed more than 7 days after hospital discharge are eliminated. ○ If hospital discharge date is missing with ICF signed more than 7 days after hospital admission are eliminated.
	2502 Participants recruited in the group active surveillance catch up group: • Participants from unexposed clusters eliminated • Participants without DTP or without DTP vaccine dates available eliminated • Participants without RTS,S or without RTS,S vaccine dates available eliminated • Participants eliminated if ICF signed after first available visit • Participants eliminated if ICF signed more than 10 days after first RTS,S vaccine dose
	2503 Participants recruited in the group enhanced hospitalisation surveillance (EHS) : • Participants eliminated if no hospitalisation recorded or without hospitalisation admission dates available • Participants with ICF before hospitalisation date -1 day are eliminated • Participants for whom the hospitalisation admission date is before ICF and: – If hospital discharge date is known then participants with ICF signed more than 7 days after hospital discharge are eliminated. – If hospital discharge date is missing with ICF signed more than 7 days after hospital admission are eliminated.

3.2.1. Impact Analysis set

A subset of the Analysis set will be defined for the secondary effectiveness and impact endpoints analyses (see section 4.3.2) to select children receiving the RTS,S/AS01_E vaccine according to the recommended schedule. Indeed, the **Impact Analysis set** will include all study participants from the Analysis set who have received their third dose of RTS,S/AS01_E vaccine or virtual dose (see section 6.2.4) before 12 months of age and/or the 4th dose of RTS,S/AS01_E vaccine or virtual dose before 30 months of age. Children receiving at least one of their first 3 doses of RTS,S/AS01_E vaccine after 12 months of age will not be considered for the analysis.

Note that:

- Children unvaccinated are included only if they have their Visit 3 and/or Visit 6 for the final analysis
- Children vaccinated with incomplete primary schedule are excluded from the Impact Analysis set
- Children vaccinated with complete primary schedule (at least 3 doses) and dose 4: all those included in the Analysis set, with the first 3 doses done before 12 months of age and the 4th dose before 30 months of age will be included in the Impact Analysis set.

3.3. Summary

Unless specified otherwise:

- Safety endpoints for the Cluster design will be analysed using the Analysis set.
- Impact and effectiveness endpoints for the Cluster design will be analysed using the Impact Analysis set.

	Cluster design	
	Analysis set	Impact analysis set
Primary endpoints analyses	X	
Secondary safety endpoints analyses	X	
Secondary effectiveness and impact endpoints analyses		X

4. STATISTICAL ANALYSES

4.1. General Considerations

SAS version 9.4 or above will be used for statistical analysis.

Main descriptive statistics (i.e.: demographic characteristics) will be computed by study group, RTS,S/AS01_E vaccination status, study site and overall.

Categorical variables will be summarised by the frequency and the percentage of each category. 95% confidence intervals (CIs) might also be presented and will be described in the Tables, Figures, Listings (TFLs). The following statistics will be presented for continuous variables: number of non-missing observations, mean, standard deviation, median and range (minimum and maximum).

Incidence rate computations will be conducted for study participants from active surveillance but not study participants from EHS. The EHS cohort data will only be used for descriptive statistics of the main safety endpoints (AESI, meningitis, malaria and mortality); data will not be cleaned for other safety endpoints.

4.1.1. Groups

The following group names will be used for the final statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
Study site		
1	235635_GH_KHRC_EXP	Kintampo exposed: Kintampo North, Kintampo South, Nkoranza North and Techiman North - exposed (Ghana)
2	235635_GH_KHRC_UNEXP	Kintampo unexposed: Nkoranza South and Techiman South - unexposed (Ghana)
3	235636_GH_NHRC_EXP	Navrongo exposed: Kassena-Nankana West and East - exposed (Ghana)
4	235636_GH_NHRC_UNEXP	Navrongo unexposed: Builsa North and South - unexposed (Ghana)
5	235638_KE_Kombewa_EXP	Kombewa exposed (Kenya)
6	235641_KE_Nyando_UNEXP	Nyando unexposed (Kenya)
7	235637_KE_Gem_EXP	Gem exposed (Kenya)
8	235637_KE_Bondo_UNEXP	Bondo unexposed (Kenya)
9	235639_MA_Chikwawa_UNEXP	Chikwawa unexposed (Malawi)
10	235639_MA_StMonfort_EXP	St Monfort exposed (Malawi)
11	235640_MA_Mangochi_EXP	Mangochi exposed (Malawi)
12	235640_MA_MonkeyBay_UNEXP	Monkey Bay unexposed (Malawi)
Study group for Active Surveillance		
1	AS DTP group	Active Surveillance DTP group
2	AS catch-up group	Active Surveillance catch-up group
Study group for EHS		
1	EHS	Enhanced Hospital Surveillance
Exposure status		
1	Exposed	Exposed clusters
2	Unexposed	Unexposed clusters
RTS,S Vaccination status		
1	RTS,S Vaccine	Participants vaccinated with at least one dose of RTS,S/AS01 _E vaccine
2	Unvaccinated	Participants without RTS,S/AS01 _E vaccine reported in eCRF

4.1.2. General Methodology

4.1.2.1. Poisson regression model

Incidence rate ratios will be computed using Poisson regression models. The Poisson regression model expresses the natural logarithm of the event or outcome of interest as a linear function of a set of predictors. The dependent variable is the number of events (Y). The model will include the study country [Z] and the vaccine exposure status [X] as fixed effects.

The risk ratio will be derived as the exponential of the coefficient associated with the covariate status and its 95% Wald CI.

Crude IRRs (ratios of IRs) and 95% CI will also be reported.

Poisson regression may be conducted using the SAS GENMOD procedure:

```
PROC GENMOD DATA=<filename>;  
  CLASS X Z;  
  MODEL Y=X Z /OFFSET=Ln(PY) DIST=poisson LINK=log;  
RUN;
```

For each model, the following assumptions will be checked to interpret the results obtained from the Poisson regression: the outcome variable follows a Poisson distribution and does not have an excessive number of zeros. The deviance will measure the adequacy of the model. If the scaled deviance is close to one, the regression model is adequate. Otherwise, the validity of the model is questionable. A value greater than 1 indicates overdispersion.

In case of overdispersion (the variance value of data is greater than the mean value), negative binomial models will be used instead of Poisson regression models.

Of note, the same procedure PROC GENMOD may be adapted by specifying option DIST=negbinomial in the model statement:

```
PROC GENMOD DATA=<filename>;  
  CLASS X Z;  
  MODEL Y=X Z /OFFSET=Ln(PY) DIST=negbin LINK=log;  
RUN;
```

4.1.2.2. Logistic model

The prevalence of anaemia will be studied with Logistic models. To describe the nature of the relationship between the dependent variable [Y] (probability of having anaemia) and vaccination status [X] adjusted on study country [Z] a logistic regression model will be used.

The odds ratio (OR) will be derived as the exponential of the coefficient associated with the covariate status and its 95% Wald CI.

Crude OR and 95% CI will also be reported.

Logistic regression may be conducted using the PROC LOGISTIC procedure:

```
PROC LOGISTIC DATA=<filename>;
  CLASS X Z;
  MODEL Y=X Z ;
  RUN;
```

4.1.3. Methodology for computing confidence intervals

Except specified otherwise, all CIs will be two-sided 95% CI computed using the exact method [[Clopper, 1934](#)].

The asymptotic 95% CIs for a mean within a group will be calculated when applicable.

4.1.4. Handling missing data

No imputation of missing data will be done in the context of EPI-MAL-003 study final analyses.

However if the three first home-visits planned according to the recommended primary vaccination schedule are missing among unvaccinated children, the first virtual vaccination date will be set based on the schedule (see details in section [6.2.4.2.1](#)).

4.1.5. Number of decimals

The following decimal description will be used for the analyses.

Parameters	Number of decimal digits
% of count, including LL & UL of CI	1
p-value	3
Minimum, maximum, range	Number of decimals in the raw data
Mean, median	Number of decimals in the raw data +1
SD	Number of decimals in the raw data +2

LL = Lower Limit; UL = Upper Limit; CI = Confidence Interval; SD = Standard deviation

4.1.6. Descriptive statistics

Unless otherwise specified, continuous data will be summarised using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum.

Categorical data will be summarised as the number and percentage of participants in each category.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoint(s)

4.2.1.1. Confirmed AESI

Each AESI will first be analysed separately after case ascertainment on confirmed cases (hospitalised cases) classified by case definition according to final diagnosis (external expert diagnosis or Principal Investigator (PI) diagnosis if external expert diagnosis not available).

Note: The confirmed AESI cases are those AESI with an available ICD10 code (i.e.: variable ICD10 code not equal to “Not confirmed”, as per convention in the eCRF guidelines).

4.2.1.2. Aetiology confirmed meningitis

Aetiology confirmed meningitis final diagnostic (external expert diagnosis or PI diagnosis if external expert diagnosis not available) will not be grouped with other AESI and will be considered as a single endpoint.

4.2.2. Main analytical approach

Incidence rate computations will be conducted for study participants from active surveillance but not study participants from enhanced hospital surveillance.

4.2.2.1. Incidence following immunisation (actual or virtual vaccination primary schedule)

Analyses of incidence following RTS,S/AS01_E vaccine or virtual vaccination (see section 6.2.3 for details) will only be performed on children enrolled in the active surveillance Analysis set.

These analyses will be computed on each confirmed co-primary endpoint as the number of first events reported post each dose over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable. Incidence per 100,000 person-years will be presented overall.

Incidence rates after the secondary schedule/virtual secondary schedule (i.e. combining the 4 first doses/virtual doses) and after the dose 4/virtual dose 4 will be presented.

4.2.2.1.1. Individual follow-up period and at-risk period

The total person-years will be computed as the sum of individual follow-up periods expressed in years. The computation of follow-up periods (start and end dates) is defined in Table 2.

For each endpoint, the follow-up period will be calculated separately depending on the at-risk period and the vaccine/virtual vaccine administration. The at-risk period will follow any dose, with a censoring of participants when they receive the following dose/virtual dose.

Table 2 Definition of at-risk period for AESI

AESI	Risk period identified (for other licensed vaccines)*	Risk period applied
ADEM	NA	6 weeks
Encephalitis	6 weeks and 2 weeks	
Guillain-Barre Syndrome	3-5 days to 6-10 weeks	3 months
Generalized convulsive seizures	0-7 days	2 weeks
Hypotonic Hypo responsive Episode	immediately to 48h	2 weeks
Intussusception	1 to 7 days	2 weeks
Hepatic Insufficiency	1-10 days	2 weeks
Renal Insufficiency	1-10 days	2 weeks
Juvenile Chronic Arthritis	≤6 months	6 months
SJS & TEN	1-3 weeks	6 weeks
Henoch Schonlein purpura	NA	6 months
Kawasaki Disease	1 month	6 weeks
Diabetes mellitus type 1	≤6 months	6 months
Anaphylaxis	0-48 hours	2 weeks
Thrombocytopenia	12-25 days	6 weeks

* from Table 3 of the protocol

AESI = Adverse Event Of Special Interest; ADEM = Acute Disseminated Encephalo-Myelitis; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; NA = not available

Of note:

- The predefined list of AESI with expected at-risk period is available in the current Table 3 of the protocol
- The at-risk period of 12 months will be used for meningitis.

Table 3 Follow-up period definition after each dose

Risk period applied	Start	Stop earliest (i.e.: date of censoring)
2 weeks	Reference date*	• Date of first diagnosis of event of interest • Date of death • Date of next dose • Date of end of risk period • Date of last contact** • Date of migration • Date when child reaches 5 years or end of the study
6 weeks		
3 months		
6 Months		
12 Months		

*Reference date: see definition detailed in section 6.2.4

**Date of last contact: see definition detailed in section 6.2.7

Notes:

- a child may come back into the study after a certain period of lost-to follow-up. In such a case, the person-year will only consider the duration when the child was present on site (e.g. from reference date to migration date, then from return date to the end). To do so, a migration date will be derived using migration date from:
 - Date of migration:
 - From Study continuation
 - From Study conclusion

A return date will be derived using return date from:

 - Date of return:
 - From Study continuation
 - From Study conclusion

In case of several migrations/returns, several migration/return dates will be computed. For such participants, the last contact date will be computed according to migration/return dates.

In case of any inconsistencies regarding the migration/return dates, the return will not be considered and the participant will be censored at the first migration date.
- If the Informed Consent Form (ICF) is signed after the first reference date, the individual follow-up period will be computed as the difference +1 between the follow-up end date and the ICF date. The follow-up end date remains the same as for participants with an ICF signed before the first reference date.

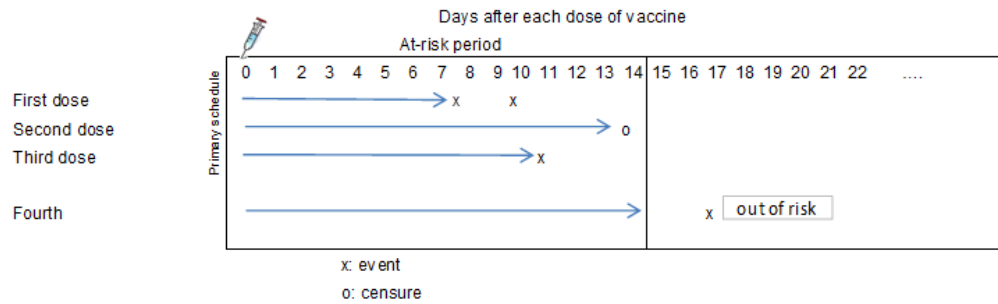
4.2.2.1.2. Management of the at-risk period

- Events occurring outside of the at-risk period (before or after) will be censored for the main analysis.
- In case an AESI had several at-risk periods, the longest will be considered for analysis:

Example: Guillain-Barré Syndrome: expected at-risk period from 3-5 days to 6-10 weeks, as a consequence an at-risk period of 3 months will be applied
- In case an AESI occurs after the specified at-risk period, it will be censored at the time-point (e.g.: 2 weeks in the example below).

First example of AESI with 2 weeks at-risk period:

The following diagram represent a theoretical scenario for one participant presenting a first AESI 7 days after the first dose, a second AESI 9 days after the first dose, a third AESI 10 days after the third dose and a fourth AESI 16 days after the fourth dose.

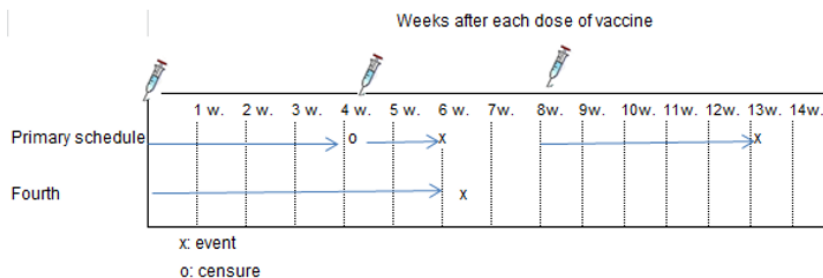


Of note, in case of recurrence of the event after a specified dose, the person year computation will stop at first occurrence.

When computing incidence rate for the primary schedule, the follow-up period corresponding to each dose should be summed. In our example: the follow-up period to consider for the primary schedule is: 7 days + 14 days + 10 days and two events will be considered (i.e.: the first one after each dose).

Second example of AESI with 6 weeks at-risk period:

The following diagram represent a theoretical scenario for one participant presenting a first AESI 6 weeks (42 days) after the first dose corresponding also to 2 weeks (14 days) after the second dose, a second AESI 5 weeks (34 days) after the third dose and a third AESI more than 6 weeks (45 days) after the fourth dose.



As mentioned earlier, the at-risk period will follow any dose, with a censoring of participants when they receive the following dose. Then in our example the follow-up period to consider for:

- First dose: 28 days with no event*
- Second dose: 14 days with one event
- Third dose: 34 days with one event
- Primary schedule: 28 days + 14 days + 34 days with two events considered.
- Virtual fourth dose: censoring at 6 weeks
- Secondary schedule: 28 days + 14 days + 34 days + 42 days with two events.

* Note: In case no event occurred between doses, the exact number of days between the two doses will be considered to compute the follow-up period.

4.2.2.2. Comparison vaccinated and unvaccinated populations

Incidence rate ratios following primary schedule, adjusted for country, will be computed for the cluster design comparison and exposed clusters comparison as described below. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002]. The method is described in section 4.1.2.1.

4.2.2.2.1. Cluster design comparison

Analyses of primary endpoints will consist of a comparison of the vaccinated children from exposed and the unvaccinated children from unexposed clusters from EPI-MAL-003 by means of a Poisson or Negative binomial regression model with the study country as fixed effect.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of primary endpoints in the RTS,S/AS01_E vaccinated cohort from exposed clusters (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort from unexposed clusters (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of primary endpoints in the RTS,S/AS01_E vaccinated cohort from exposed clusters (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort from unexposed clusters (EPI-MAL003).

4.2.2.2.2. Exposed clusters comparison

For the exposed clusters comparisons, analyses of primary endpoints will consist of a comparison of vaccinated study participants from the exposed clusters of EPI-MAL-003 and unvaccinated study participants from the exposed clusters of EPI-MAL-003 by means of a Poisson or Negative binomial regression model with the study country as a fixed effect.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of primary endpoints in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of primary endpoints in the RTS,S/AS01_E vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

4.2.2.2.3. Summary of the comparisons

The summary of the comparisons for safety endpoints is given in the following table:

Table 4 Summary of the comparisons for safety endpoints analyses

Unvaccinated Children	Vaccinated Children from Exposed clusters
from Unexposed clusters	Cluster design comparison
from Exposed clusters	Within Exposed clusters comparison

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary safety endpoint(s)

4.3.1.1. Definition of endpoint(s)

4.3.1.1.1. Meningitis

Final classification (based on second line laboratory results and after external panel of experts review) will be used; the meningitis cases will be analysed as follows:

- Aetiology confirmed meningitis
- Probable meningitis,
- Clinically suspected meningitis
- Aetiology confirmed, and/or probable meningitis,
- Aetiology confirmed, probable and/or clinically suspected meningitis.

Please note that Aetiology confirmed meningitis, Probable meningitis and Clinically suspected meningitis are mutually exclusive categories.

4.3.1.1.2. Cerebral malaria

Cerebral malaria is defined as severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children $\geq$ 2 years of age or Blantyre coma score < 3 in children < 2 years of age);

AND

If malaria with seizure and coma: coma persisting for > 30 min after the seizure.

4.3.1.1.3. Death

The details of the cause of death are extracted from the 'study conclusion' screen and the fatality confirmed in the 'check for study continuation' screen.

A participant may experience several AEs during an outpatient visit or during a hospitalisation resulting in a fatal outcome. However, the cause of death is considered to be the event reported by the PI in the study conclusion screen. Cause of death is either established from the medical records when occurring at a healthcare facility, or through verbal autopsy for children who died in the community.

Death cases will be defined as:

- Death – all cause
A fatality (of any cause).
- Malaria attributed death (including *P. falciparum* malaria)
A fatality for which malaria (including *P. falciparum* malaria) is being listed as the cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.
P. falciparum Malaria attributed deaths: A fatality for which Malaria is listed as a cause of death and the malaria type is identified as *P. falciparum*.
- Deaths attributed to an AE
A fatality for which an AE is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.
The following endpoints will be described:
 - Deaths attributed to an AESI
 - Death attributed to Meningitis
 - Deaths attributed to another AE (i.e. other than AESI, meningitis or malaria)

* Note that if a site is not part of the INDEPTH network, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites

Please note that these categories are mutually exclusive (see section 6.2.3 for details).

4.3.1.2. Main analytical approach

Incidence rate computations will be conducted for study participants from active surveillance, but not study participants from enhanced hospital surveillance.

4.3.1.2.1. Incidence rate following immunisation (actual or virtual vaccination primary schedule)

Incidence rate following primary schedule for secondary endpoints: meningitis, cerebral malaria and death (overall death and death by gender) will be computed using the same method as for primary endpoints (see section 4.2.2.1).

Analyses of the occurrence of death, including/excluding specific causes such as death associated with malaria, deaths associated with accidents and poisonings will be conducted overall and by gender.

Please find the at-risk periods for the safety events in the following table.

Table 5 Definition of at-risk period for safety events:

Event	Risk period applied
Meningitis	12 months
Cerebral malaria	12 months
Death	12 months

4.3.1.2.2. Comparison of vaccinated and unvaccinated populations

Incidence rate ratios following primary schedule for secondary endpoints: meningitis, cerebral malaria and death will be computed as using the same method as for primary endpoints (see section 4.2.2.2).

For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons concludes on an observed imbalance in mortality in girls, the following sensitivity analyses might be conducted:

- Additional comparisons by subgroups:
Characteristics at study entry will be compared between boys and girls. This may allow defining subgroups based on which additional comparison may be conducted.
- Analysis according to the last vaccine administered or co-administered vaccines.
- Analyses of the cause of death:
Depending on the distribution of the causes of death (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria), analyses of the occurrence of death will be conducted including/excluding specific causes of death overall and by gender.

4.3.2. Secondary effectiveness and impact endpoints analyses

The analyses of effectiveness and impact will be performed only on children enrolled in the active surveillance for both exposed and unexposed clusters.

The main analysis on effectiveness and impact endpoints will be performed (see definition of Impact Analysis set section 3):

- One year after the 4th dose of RTS,S/AS01_E evaluated from 3rd dose, and for children who have received the 3 doses before 12 months of age and the 4th dose of RTS,S/AS01_E before 30 months of age.

Additional analyses will be performed on effectiveness and impact endpoints at:

- Two years after the 3rd dose of RTS,S/AS01_E vaccine evaluated from 3rd dose (given before 12 months of age), and for children who did not receive the 4th dose of RTS,S/AS01_E,
- Two years after the 4th dose of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from the 1st dose of vaccine,
- Two years after the 4th dose of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from the 3rd dose of vaccine (received before 12 months of age),
- Two years after the 4th dose of RTS,S/AS01_E for children who received it before 30 months of age, evaluated from the 4th dose of vaccine.

Comparisons will be performed using the direct effect design and the cluster design. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons will conclude on an observed imbalance in mortality in girls, additional comparisons might be performed on subgroups. Those subgroups will be defined based on the observed difference between boys and girls in the characteristics at study entry first visit. In addition, an analysis according to last vaccine administered and/or co-administered will also be done.

4.3.2.1. Definition of endpoints

4.3.2.1.1. Malaria

The analysis of malaria cases included cases recorded during both outpatient visits and hospitalisations. Malaria cases are derived according to the protocol case definition. Any Malaria, Uncomplicated, severe, and cerebral malaria are presented as planned in the protocol.

The detailed derivation algorithm will be part of the ADAM specifications.

4.3.2.1.1.1 Uncomplicated malaria

Plasmodium parasitaemia > 0 detected by microscopy and/or RDT

AND

Presence of fever (temperature $\geq 37.5^{\circ}\text{C}$), as reported by the parent(s)/LAR(s) or recorded at the time of presentation

OR

Occurring in a child who is unwell and brought for treatment to a health care facility.

AND

Without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

4.3.2.1...1.2 Severe malaria

- Severe *falciparum* malaria [WHO, 2015]

P. falciparum parasitaemia > 0 detected by microscopy and/or RDT

AND

One or more of the following, occurring in the absence of an identified alternative cause:

- Impaired consciousness: a Glasgow coma score < 11 in children ≥ 2 years of age or a Blantyre coma score < 3 in children < 2 years of age;
- Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;
- Multiple convulsions: more than two episodes within 24 h;
- Acidosis: a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);
- Severe malarial anaemia: haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age with a parasite count > 10,000/μL;
- Renal impairment: plasma or serum creatinine > 265 μmol/L (3 mg/dL) or blood urea > 20 mmol/L;
- Jaundice: plasma or serum bilirubin > 50 μmol/L (3 mg/dL) with a parasite count > 100,000/μL;
- Pulmonary oedema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation;
- Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena;
- Shock: compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill);
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/μL).

Severe *vivax* malaria is defined as for severe *falciparum* malaria but with no parasite density thresholds [WHO, 2015]

4.3.2.1.1.3 Cerebral Malaria

Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children $\geq$ 2 years of age or Blantyre coma score < 3 in children < 2 years of age);

AND

If malaria with seizure: coma persisting for > 30 min after the seizure.

4.3.2.1.2. Anaemia

Cases of anaemia will be defined as follow:

- All anaemia: haemoglobin <11g/dL.
- Severe anaemia: haemoglobin <7g/dL.

4.3.2.1.3. Hospitalisation

Hospitalisations will be defined as:

- Hospitalisation for malaria (including *P. falciparum* malaria)
A hospitalised participant with malaria (including *P. falciparum* malaria)
- Hospitalisation for *P. falciparum* malaria
A hospitalised participant with *P. falciparum* malaria.

4.3.2.1.4. Death

See section [4.3.1.1.3](#).

4.3.2.2. Main analytical approach

Analysis will be performed on the secondary impact endpoints (i.e.: malaria, anaemia, hospitalisation and death) as described in [Table 7](#).

4.3.2.2.1. Derivation of incidence rate and prevalence

For all endpoints listed in [Table 7](#) incidence rate will be calculated by dividing the number of all events over the follow-up period by person-year as defined in the [Table 7](#).

If a participant had several cases during the period defined, all episodes will be reported.

The number of person-years will be computed as the sum of participants follow-up period expressed in years.

Table 6 Follow-up period definition for other secondary endpoints

Analysis	Start	Stop (earliest)
D3 → D4 + 1Y	Dose 3 or virtual dose 3*	• One year after fourth dose • Date of death • Date of last contact** • Date of migration • Date when child reaches 5 years
D3 → D3 + 2Y (for children without dose 4/virtual dose 4)	Dose 3 or virtual dose 3*	• Two years after third dose • Date of death • Date of last contact** • Date of migration • Date when child reaches 5 years
D1 → D4 + 2Y	Dose 1 or virtual dose 1*	• Two years after fourth dose • Date of death • Date of last contact** • Date of migration • Date when child reaches 5 years
D3 → D4 + 2Y	Dose 3 or virtual dose 3*	
D4 → D4 + 2Y	Dose 4 or virtual dose 4*	

* Virtual dose: for unvaccinated children (see section 6.2.4.2)

** Date of last contact: lost-to follow-up (see section 6.2.7)

The prevalence rate for anaemia among hospitalised children will be computed by dividing the number of hospitalised children with at least one event by the number of enrolled children.

Table 7 Incidence rate and prevalence calculations for other secondary objectives (children enrolled in active surveillance)

Endpoints	Numerator	Denominator
Any malaria	# cases of any malaria during the follow-up time of each analysis Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children during the follow-up time of each analysis
Any <i>P. falciparum</i> malaria	# cases of any malaria due to <i>P. falciparum</i> during the follow-up time of each analysis Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children during the follow-up time of each analysis
Severe malaria	# cases of severe malaria during the follow-up time of each analysis Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children during the follow-up time of each analysis
Severe <i>P. falciparum</i> malaria	# cases of severe malaria due to <i>P. falciparum</i> during the follow-up time of each analysis Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children during the follow-up time of each analysis
Cerebral malaria	# cases of cerebral malaria during the follow-up time of each analysis Source: Hospitalisations	Person-years contribution of enrolled children during the follow-up time of each analysis
Death – all cause	# deaths (due to any cause) during the follow-up time of each analysis	Person-years contribution of enrolled children during the follow-up time of each analysis

Endpoints	Numerator	Denominator
	Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register	
Malaria attributed deaths	# cases of deaths with malaria listed as a contributing cause during the follow-up time of each analysis Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register	Person-years contribution of enrolled children during the follow-up time of each analysis
<i>P. falciparum</i> Malaria attributed deaths	# cases of deaths with malaria due to <i>P. falciparum</i> listed as a contributing cause during the follow-up time of each analysis Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register	Person-years contribution of enrolled children during the follow-up time of each analysis
Malaria attributable hospitalisation	# of children hospitalised during the follow-up time of each analysis where malaria is listed as the primary diagnosis Source: Hospitalisations	Person-years contribution of enrolled children during the follow-up time of each analysis
<i>P. falciparum</i> Malaria attributable hospitalisation	# of children hospitalised during the follow-up time of each analysis where <i>P. falciparum</i> malaria is listed as the primary diagnosis Source: Hospitalisations	Person-years contribution of enrolled children during the follow-up time of each analysis
Anaemia in hospitalised children	# hospitalised children with anaemia Source: Hospitalisations	Number of enrolled children
Severe anaemia in hospitalised children	# hospitalised children with severe anaemia Source: Hospitalisations	Number of enrolled children

Note: For cerebral malaria, incidence following immunisation will be derived

4.3.2.2.2. Comparison of incidence rate of effectiveness or impact endpoints

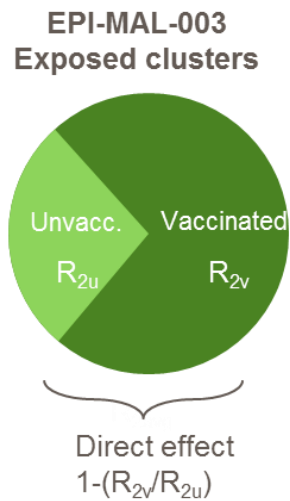
The incidence rates will be compared by means of Poisson regression / negative binomial models (the dependent variable will be the number of events), using the exposure status as a binary independent variable in the model and the country as a fixed effect. The details are given in Section 4.1.2.

4.3.2.2.2.1 Effectiveness (direct effect)

For any malaria, severe malaria and cerebral malaria, vaccine effectiveness (direct effect) will be estimated on adjusted models as explained in Figure 1 [Halloran, 1997] below.

In the same way, for occurrence of anaemia and mortality rate, direct effect will be estimated.

Figure 1 **Diagram on effectiveness (adapted from Halloran and Longini [Halloran, 1997])**



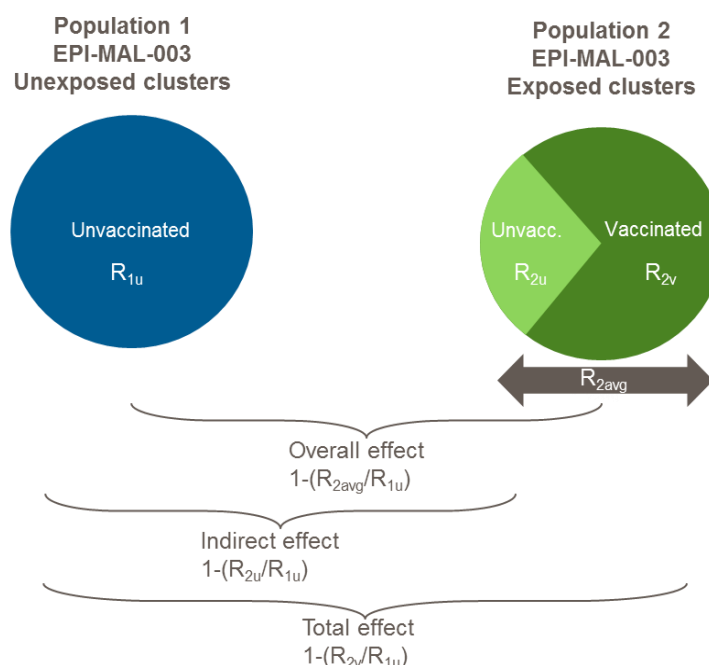
R_{2v} = risk of endpoint after vaccine introduction among vaccinated study participants
 R_{2u} = risk of endpoint after vaccine introduction among unvaccinated study participants

The direct effect will be computed on the exposed clusters of EPI-MAL-003 and is defined as the comparison between unvaccinated study participants and vaccinated study participants (from active surveillance).

4.3.2.2..2.2 Impact using the cluster design

For the same endpoints, impact of vaccination will be estimated as part of the cluster design on adjusted models as explained in [Figure 2 \[Halloran, 1997\]](#) below.

Figure 2 Diagram on impact presenting the different vaccine effects for the cluster design (adapted from Halloran and Longini [Halloran, 1997])



R_{1u} = risk of endpoint in the unexposed clusters

R_{2v} = risk of endpoint in the exposed clusters among vaccinated study participants

R_{2u} = risk of endpoint in the exposed clusters among unvaccinated study participants

R_{2avg} = risk of endpoint after vaccine introduction in the overall population (vaccinated and unvaccinated study participants)

The types of effect for the cluster design are detailed below:

- Indirect effect for the cluster design:

The indirect effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

- Total effect for the cluster design:

The total effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

- Overall effect for the cluster design:

The overall effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

4.3.2.2.3. Summary of the comparisons

The summary of the comparisons is given in the following table:

Table 8 Summary of the comparisons for effectiveness and impact endpoints

Unvaccinated Children	Children from EPI-MAL-003 Exposed clusters		
	Vaccinated Children	Unvaccinated Children	Children Overall
from EPI-MAL-003 Unexposed clusters	TOTAL EFFECT (Cluster design)	INDIRECT EFFECT (Cluster design)	OVERALL EFFECT (Cluster design)
from EPI-MAL-003 Exposed clusters	EFFECTIVENESS (Exposed clusters)	-	-

4.4. Exploratory Analyses

4.4.1. Prevalence of malaria among anaemic children and comparison

The prevalence of any malaria and severe malaria among hospitalized children with anaemia will be estimated as the number of hospitalized children with any malaria and severe malaria among those with anaemia, respectively. The same analysis will be performed among those with severe anaemia. A 95% CI will be computed using the exact binomial method.

The prevalence in vaccinated children from exposed and unvaccinated children from unexposed clusters will be compared using logistic regression model with the study country as fixed effect. The details are given in Section 4.1.2.

This analysis will be performed one year after the 4th dose of RTS,S/AS01_E, evaluated from 3rd dose (D3 → D4 + 1Y), as detailed in section 4.3.2.

4.4.2. Averted cases based on Total effect

This analysis will be performed to enhance the interpretation of vaccine impact in terms of cumulative number of cases averted per 1000 vaccinated participants.

The number of cases averted will be calculated as the difference in the estimated cases between the RTS,S vaccinated and unvaccinated groups. Estimated cases in each group will be calculated as the area under the curve of the incidence of cases over time and expressed as cumulative cases averted per 1000 participants followed up during the relevant period.

The number of averted cases of any malaria will be calculated (difference between incidences of RTS,S vaccinated and unvaccinated groups, expressed per 1000 population vaccinated) for each 3-month period and summed over the entire study period after dose 3.

95% Bootstrap confidence interval will be obtained (through 1000 resampling with the size equal to the number of participants, resampling with replacement, stratified by

vaccination status, computation of the cases averted in each of the 1000 samples and taking the 2.5% and 97.5% percentiles).

The same analysis will be performed for Uncomplicated Malaria, Severe Malaria cases, Death due to Malaria, All cause death and Hospitalisation due to Malaria.

SAS codes for generating bootstrap samples:

```
%let NumSamples = 1000;    /* number of bootstrap resamples */

PROC SURVEYSELECT DATA=sample NOPRINT SEED=123
  OUT=BOOTSSFREQ(RENAME=(REPLICATE=SAMPLEID))
  METHOD=URS           /* resample with replacement */
  SAMPRATE=1           /* each bootstrap sample has N observations */
  REPS=&NumSamples;    /* generate NumSamples bootstrap resamples */
  STRATA <RTSVA>;      /* resample stratified by vaccination status*/
RUN;
```

This analysis will be performed based on the Total effect estimated in the main analysis (D3 → D4 + 1Y) for the effectiveness and impact endpoints (section 4.3.2)

4.4.3. Vaccine Impact (Total effect) accounting for Malaria Transmission Intensity (MTI) estimated in EPI-MAL-005 study

For any malaria and severe malaria, the impact of vaccination using the cluster design (Total effect) will be estimated, accounting for seasonal MTI (i.e. parasite prevalence) estimated in EPI-MAL-005 study.

The year- and centre-specific MTIs computed for 6 months to < 5 years children will be included as additional covariates in the Poisson or Negative binomial regression model (detailed in Section 4.1.2) to account for annual fluctuations and/or changes due to other malaria control interventions per centre.

Each participant will be assigned an average MTI based on their follow-up period, using the corresponding year- and centre- specific MTI from the EPI-MAL-005 study.

This analysis will be performed two years after the 4th dose of RTS,S/AS01_E, evaluated from the 1st dose (D1 → D4 + 2Y), as detailed in section 4.3.2.

4.5. Other Analyses

Overall participant flow at each study visit by study group and study site among RTS,S/AS01_E vaccinated children, unvaccinated children and overall will be provided.

Participants having home visits, and participants who attended at least one outpatient visit, by study group and study site among RTS,S/AS01_E vaccinated children, unvaccinated children and overall will be provided.

Study enrolment by calendar month, and summary of study completion with reasons for withdrawals, by study group and study site will be provided.

Summary of HIV and haemoglobinopathy status, and frequency of CSF samples collected and tested, by study group will be provided.

Summary of number of participants and confirmed cases for the main safety endpoints (AESI, meningitis, cerebral malaria and death) will be tabulated for specific sub-populations such as children with haemoglobinopathy and HIV-positive children.

Cumulative number of the following cases that occurred after vaccine dose 1 or virtual dose 1 will be provided by RTS,S/AS01_E vaccination status for Exposed Clusters and Unexposed Clusters:

- Confirmed AESI cases according to final diagnosis by body system and protocol definition
- Meningitis cases (Final diagnosis)
- Malaria cases (Final diagnosis)
- Deaths
- Hospitalisation causes (Final diagnosis)
- Anaemia cases among hospitalised children

4.6. Interim Analyses

4.6.1. Data in scope

4.6.1.1. EPI-MAL-003 study

Data since the beginning of enrolment in EPI-MAL-003 study (i.e. 21 March 2019) are presented.

The interim analysis was done with data as clean as possible collected on all participants from active surveillance.

A cut-off date of 1 year post dose 3 was considered in order to allow all children to have 12 months of follow-up following the administration of RTS,S/AS01_E vaccine dose 3 or virtual dose 3.

The database freeze was done on 02 November 2023.

4.7. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in [Table 9](#).

Table 9 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Virtual vaccination dose date defined as the date of visit mimicking the vaccine schedule (visits 1,2,3,6) minus 1 week (see protocol section 9.7.5.2.1)	Virtual vaccination dose 1 defined as the age, computed for unvaccinated participants with missing visits 1,2,3 according to the country specific schedule (see section 6.2.4.2.1)	Unbalanced number of missing visit 1 between exposed and unexposed clusters
In the models for Cluster design comparison, the study site was planned to be considered as a random effect (see protocol section 9.7.6.7.2).	The model will include the study country as a fixed effect, instead of study site as random effect (see section 4.1.2).	In the Interim Analysis, random-effect model with the study site as random effect was rarely converging and is replaced by regression models with country as fixed effect.
For additional comparisons by subgroups for death events (analysis triggered by an observed imbalance in mortality in girls), the description of characteristics <u>at the first scheduled visit</u> compared between boys and girls was planned (see section 9.7.6.7 in the protocol).	In the SAP: the description of characteristics <u>at study entry</u> visit compared between boys and girls was planned (see section 4.3.1.2.2).	As the reference date is not the first visit for unvaccinated children this comparison is not useful.
Vaccine history will be collected from different sources (i.e. individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system). If any of the sources confirm RTS,S/AS01E vaccination, it will be assumed that vaccination has taken place.	We will consider all RTSS vaccine history for the analyses even if there is no source to confirm the vaccination.	This approach is more conservative regarding the safety of the vaccine.
The univariate and multivariable Cox model for the comparison of time to event of effectiveness or impact endpoints has been mentioned under the section 9.7.7.3.3.	The Cox model has been removed.	As per the Protocol Amendment 3, the comparison of time to event of effectiveness or impact endpoints has been removed.

5. SAMPLE SIZE DETERMINATION

Please refer to protocol amendment 3 section 9.5. Study size.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Study participant disposition

For the Enrolled set and Analysis set, study participant disposition will be summarised, by RTS,S vaccination status, by study site and overall, by computing for both exposed and unexposed clusters for children from the active surveillance and for children from the enhanced hospitalisation surveillance:

- Number of enrolled children;
- Number (%) of non-eligible children regarding inclusion and exclusion criteria (see Section 3.2)
- Number of children in Analysis set;
- Main results:
 - Number of participants with at least one AESI and number of AESI;
 - Number of participants with at least one meningitis case and number of meningitis cases;
 - Number of participants with at least one episode of any malaria and number of malaria cases;
 - Number of participants deceased.

The EHS cohort data will only be used for descriptive statistics of the main safety endpoints in the final analysis (AESI, meningitis, malaria and mortality).

6.1.2. Demographics and characteristics at study entry

Demographics (age at study entry, gender, site, country) will be summarised for the Enrolled set and the Analysis set separately for the exposed and the unexposed clusters, for the vaccinated and unvaccinated children enrolled in the active and enhanced hospitalisation surveillance using descriptive statistics.

Frequency tables will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

The participants from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-003 unexposed clusters Analysis set will be compared for their demographic characteristics.

6.1.3. Signs and symptoms, and medical history

- For Active surveillance, signs and symptoms, usual malaria preventive measures, and health care seeking behaviour will be tabulated by RTS,S Vaccination status and study site for all visits pooled.
 - The denominator will be the total number of visits and the numerator will be the number of participants with at least one symptom among the visits.
- For hospitalised children from Active Surveillance, malaria preventive measures, health care seeking behaviour, risk factors and comorbidity factors will be described by RTS,S Vaccination status and study site: the denominator will be the total number of hospitalisations and the numerator will be the number of participants with at least one risk among the hospitalisations.

6.1.4. Exposure description

For all study participants from the exposed clusters, the vaccine history will be summarised. The RTS,S/AS01_E vaccine coverage in the exposed clusters may be estimated.

In addition, the number of RTS,S/AS01_E doses received will be described for the vaccinated children. The age at each dose receipt and the time between doses will also be described using descriptive statistics.

The vaccination status will be described by type of surveillance, study site, and gender.

Exposure to other vaccines (Yes/No) during the study period will be summarised in frequency tables (n, %) for both exposed and unexposed clusters for the RTS,S/AS01_E vaccinated and unvaccinated children.

The exposure to other vaccines will be compared between the EPI-MAL-003 unexposed clusters and the EPI-MAL-003 exposed clusters.

6.1.5. Protocol Deviations

Important protocol deviations will be summarised.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion (see section 3.2 for the details of elimination codes) from the Analysis set will also be summarised.

Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADAM dataset (note these exclusions are not captured in the SDTM dataset).

In addition to the overall summary of important protocol deviations, separate summaries will be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively.

Visits missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarised in a table.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

No additional analyses due to the COVID-19 pandemic will be done for the final analysis.

6.2. Appendix 2 Data Derivations Rule

Programming specifications for the derivation of data are supporting the SAP.

6.2.1. Age

Age at time of enrolment in the study will be computed as the difference between the date of enrolment (date of ICF) and the date of birth.

Calendar age will be expressed in months and will be computed based on (the number of days/365.25)*12.

The age will be categorised as follows:

- 0-11: from birth to <1 year
- 12-23: 1 - <2 years
- 24-35: 2 - <3 years
- 36-47: 3 - <4 years
- 48-59: 4 - <5 years

6.2.2. Number of RTS,S/AS01_E vaccine dose received

The number of RTS,S/AS01_E vaccine dose received will be derived as the sum of non-missing RTS,S/AS01_E vaccine dose dates.

Note that the number of doses per participant could be more than 4 in case of duplicated doses, in that case the first 4 doses by date will be considered.

6.2.3. Cause of death

The following categories, required for analysis, are not directly available in the database:

- Death – AESI
- Death – AE
- Death – Meningitis
- Death – Malaria
- Death – *P. falciparum*

The process to retrieve them is detailed below:

1. To retrieve “DEATH – AESI”, BSP will identify the death attributed to an AESI in the study conclusion form.
2. To retrieve “DEATH – Malaria” and “Death – *P. falciparum*”, BSP will select the Malaria cases derived from outpatient visits and hospitalisations.

If MedDRA preferred term of cause of death includes “malaria” and if a malaria case was diagnosed during the last outpatient visits or hospitalisation before death and if the onset date or date of visits (when onset date missing) $\leq$ 14 days before death then considered the species from the visit:

- For Uncomplicated *P. falciparum* or severe *P. Falciparum* set to “Death – *P. falciparum*”
- Otherwise set to “Death – Malaria”

Of note:

If MedDRA preferred term of cause of death includes the word “*falciparum*” then set to “Death – *P. falciparum*”

If MedDRA preferred term of cause of death equal to “cerebral malaria” then set to “Death – *P. falciparum*”

3. Last steps:

If MedDRA preferred term of cause of death includes “meningitis” then set to “Death – meningitis”

For all other cases then set to “Death – AE”

6.2.4. Reference date: Vaccination/Virtual vaccination date

6.2.4.1. Vaccinated children with RTS,S/AS01_E vaccine

The reference date for vaccinated children with RTS,S/AS01_E vaccine will be the RTS,S/AS01_E vaccine dose date. It will be computed for vaccinated participants as follows.

The date of dose 1 will be derived as the first non-missing RTS,S/AS01_E vaccine dose date. The date of dose 2 will be derived as the second non-missing RTS,S/AS01_E vaccine dose date. The following dose dates will be derived using the same method.

6.2.4.2. Unvaccinated children

The reference date for unvaccinated children will be a virtual vaccine dose date. The date of virtual dose 1 will be derived as the Visit 1 date – 1 week; the date of virtual dose 2 as the Visit 2 date – 1 week; the date of virtual dose 3 as the Visit 3 date – 1 week; and the date of virtual dose 4 as the Visit 6 date – 1 week.

In case of missing visit date(s), the start date of the at-risk period will be the first non-missing date within primary schedule i.e. between virtual dose 1, 2 or 3 (based on the actual visit date(s)).

6.2.4.2.1. Handling of missing visit dates

The following will be applied:

In case of 3 missing dates among visit 1, visit 2 and visit 3, the virtual vaccine dose 1 will be set according to the country specific schedule:

- In Kenya and Ghana: The date of virtual dose 1 will be derived as the date of birth + 6 months
 - In Malawi: The date of virtual dose 1 will be derived as the date of birth + 5 months
- Visit 2 and visit 3 will not be computed.

6.2.5. Date of occurrence

The dates of occurrence of events are defined as follows depending on the endpoint:

- Confirmed AESI and meningitis reported at hospital:
 - Onset date of event
- Confirmed malaria cases:
 - Onset date of event for hospitalised cases
 - Admission date at outpatient visit otherwise
- Death:
 - Date of death reported in study conclusion

6.2.6. Management of consecutive visits and/or hospitalisations

In case of consecutive outpatient visits or hospitalisations of the same participant and for the same event, the following rules were considered for the onset dates to avoid counting the same event more than once.

6.2.6.1. AESI, meningitis

Multiple hospitalisations for 1 participant with the same MedDRA PT that have the same onset date or onset date + 1 day will be considered as the same event. In such cases, each of the events will contribute to several hospitalisations but will be considered as a single event.

The rationale for limiting the difference between the onset dates of consecutive events to 1 day is due to the changing severity of the symptoms for most AESI and meningitis. According to the investigators, in case of referral to another hospital, the transfer would occur on the same day or the day after. Moreover, for meningitis, if 2 or more hospitalisations, with different clinical definitions as per protocol, are reported with the same onset dates or onset date + 1 day, then a worst-case scenario based on the clinical definition will be considered in the analysis. The following order, starting with the worst-case scenario, will be applied:

- Bacterial confirmed meningitis / Aetiology confirmed meningitis
- Probable meningitis
- Clinically suspected meningitis

6.2.6.2. Malaria

Multiple events for 1 participant with a difference between the admission date for outpatient visit or the onset date for hospitalised malaria cases ≤ 14 days and with the same species identified either with rapid diagnostic test or slide reading, will be considered as 1 event. A worst-case allocation is attributed according to the following order (starting from worst):

- Severe malaria (with the same species)
- Uncomplicated malaria (with the same species)
- Clinically diagnosed malaria

Of note, cerebral malaria is also counted as severe malaria.

For example, considering participant ^{PP}_D and participant ^{PP}_D in Table 10:

Table 10 Management of consecutive hospitalisations for malaria cases

Participants	Locations	Dates of admission	Onset date	Diagnosis
^{PP} _D	Outpatient visit	07 April 2017	NA	Uncomplicated <i>P. falciparum</i>
	Outpatient visit	10 April 2017	NA	Severe <i>P. falciparum</i>
	Outpatient visit	17 April 2017	NA	Severe <i>P. falciparum</i>
	Outpatient visit	07 April 2017	NA	Suspected malaria under cleaning
	Hospitalisation	13 April 2017	07 April 2017	Uncomplicated <i>P. falciparum</i>

NA = Not applicable; *P. falciparum* = *Plasmodium falciparum*

- For participant^{PPD} the severe *Plasmodium falciparum* (*P. falciparum*) (worst-case within same species) is considered as 3 visits within 14 days and therefore a single event.
- For participant^{PPD} the uncomplicated *P. falciparum* (worst-case) is considered as 2 visits/hospitalisations within 14 days and therefore a single event.

6.2.7. Last contact date & Migration/Return date

Last contact date will be derived as following:

- For deceased participants the last contact date will be set as the death date.
- For participants who have finished their participation in the study and for whom their participation did not finish prematurely, the last contact date will be set as the last contact date from study conclusion CRF page (in such cases true last contact date encoded)
- For the other participants the last contact date will be defined as the latest date between:
 - Date of consent
 - Last date of hospitalisation
 - Last discharge date of hospitalisation
 - Last check-up visit after discharge
 - Last date of outpatient visit
 - Last home visit
 - Date of migration:
 - From Study continuation
 - From Study conclusion

Please note that:

- The last contact date should not be after the child reach 5 years + 2 weeks
- Since all the participants should have at least 1 day of follow-up after vaccination, the last contact date should be equal or superior to the date of first dose of RTS,S/AS01_E vaccine or virtual dose.
- The last contact date from study conclusion CRF page will not be used to compute last contact date for participants apart from participants who have finished their participation in the study and for whom their participation did not finish prematurely, because in the CRF this date corresponds to the statement: “Please record date of last contact or date when the last information was collected on the study participant’s condition”.
- The last contact date will not be computed using start and end date of symptoms associated with events.
- Some inconsistencies could be found between these dates due to the level of data cleaning.

Moreover, a child may come back into the study after a certain period of lost-to follow-up. In such a case, the person-year will only consider the duration when the child was present on site (e.g. from first vaccine dose or virtual dose date to migration date, then from return date to the end of follow-up period). To do so, a migration date will be derived using migration date from:

- Date of migration:
 - From Study continuation
 - From Study conclusion
- A return date will be derived using return date from:
 - Date of date of return:
 - From Study continuation
 - From Study conclusion

In case of several migration/return, several migration/return dates will be computed. For such participants, the last contact date will be computed according to migration/return dates.

In case of any inconsistencies regarding the migration/return dates, the return will not be considered and the participant will be censored at the first migration date.

6.2.8. Protocol amendment approval dates**Table 11 Protocol amendment 2 approbation dates**

Study site label	SITEID	Date of protocol amendment 2 approbation
235635_GH_KHRC_EXP	235635	06 September 2021
235635_GH_KHRC_UNEXP	235635	06 September 2021
235636_GH_NHRC_EXP	235636	23 March 2021
235636_GH_NHRC_UNEXP	235636	23 March 2021
235638_KE_Kombewa_EXP	235638	23 August 2021
235641_KE_Nyando_UNEXP	235641	23 July 2021
235637_KE_Gem_EXP	235637	12 July 2021
235637_KE_Bondo_UNEXP	235637	12 July 2021
235639_MA_Chikwawa_UNEXP	235639	31 March 2021
235639_MA_StMontfort_EXP	235639	31 March 2021
235640_MA_Mangochi_EXP	235640	31 March 2021
235640_MA_MonkeyBay_UNEXP	235640	31 March 2021

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Table of Content

Table of Content	1
SCREENING ()	3
ENROLLMENT ()	4
DEMOGRAPHY ()	5
INFORMED CONSENT ()	7
ELIGIBILITY CRITERIA(ACTIVE SURVEILLANCE) ()	9
ELIGIBILITY CRITERIA (ENHANCED HOSPITALISATION SURVEILLANCE) ()	10
CHECK FOR STUDY CONTINUATION ()	11
SIGNS AND SYMPTOMS ()	12
USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR ()	15
MALARIA PREVENTION &C" HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD ()	16
SIGNS AND SYMPTOMS ()	17
USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR ()	20
SIGNS AND SYMPTOMS ()	21
CHECK FOR STUDY CONTINUATION ()	24
SIGNS AND SYMPTOMS ()	26
USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR ()	29
MALARIA PREVENTION &C" HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD ()	30
LOG STATUS ()	31
MEDICATION () - Repeating Form	32
VACCINATION () - Repeating Form	35
OUTPATIENT VISIT STATUS ()	36
OUTPATIENT VISIT () - Repeating Form	37
HOSPITALIZATION	41
USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR ()	42
MALARIA PREVENTION &C" HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD ()	43
HOSPITALISATION MEDICAL HISTORY ()	44
AESI - MENINGITIS &C" SAE ()	46
MALARIA ()	49
OTHER DISEASES SIGNS AND SYMPTOMS ()	52
OTHER DISEASES	54
DIAGNOSIS AT DISCHARGE ()	57
ENCEPHALITIS /ADEM ()	63
GUILLAIN BARRE SYNDROME ()	70
MENINGITIS ()	78
GENERALIZED CONVULSIVE SEIZURES ()	87
DIABETES MELLITUS ()	92
HEPATIC INSUFFICIENCY ()	97
RENAL INSUFFICIENCY ()	106
JUVENILE CHRONIC ARTHRITIS ()	112
STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN) ()	118
ANAPHYLAXIS ()	123
THROMBOCYTOPENIA ()	126
HYPOTONIC HYPORESPONSIVE EPISODE ()	132
HENOCH SCHONLEIN PURPURA ()	138
KAWASAKI DISEASE ()	148
INTUSSUSCEPTION ()	155
INJECTION SITE ABSCESS ()	159
FOOT POSITIONAL DEFORMATION ()	162
HOSPITAL CHECK-UP (AFTER DISCHARGE) ()	164
OCCURRENCE OF ADVERSE EVENTS TO BE REPORTED IN THE EXPEDITED ADVERSE EVENT REPORT ()	165
EXPEDITED ADVERSE EVENTS () - Repeating Form	166
COVID-19 CORONAVIRUS INFECTION DIAGNOSIS (COVID-19 Diagnosis)	175
COVID-19 CORONAVIRUS INFECTION ASSESSMENT (COVID-19 Assessment) - Repeating Form	176
PROTOCOL DEVIATION (Protocol Deviations) - Repeating Form	178
STUDY CONCLUSION ()	181
MANUAL CLEANING STATUS ()	183
SAMPLE RETENTION PERIOD () - Repeating Form	184
CLUSTER INFORMATION ()	185
HOSPITAL STUDY LOGBOOK () - Repeating Form	186
STUDY DSS DENOMINATOR LOGBOOK ()	187
INVESTIGATOR SIGNATURE ()	188

Annotated Study Book for Study Design: EPI-MALARIA-003 VS AME (115056)

Study Design Version: 5.0

Sponsor: GlaxoSmithKline

Protocol: EPI-MALARIA-003 VS AME (115056)

Generic Drug Name: RTS,S antigen and AS01E adjuvant

A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01E vaccine in young children in sub-Saharan Africa.

Generated by Central Designer™

March 22, 2022 7:11PM

EPI-MALARIA-003 VS AME (115056): SCREENING () [NOT SUBMITTED]		
SCREENING		
1.	Initials: <i>[hidden]</i> [Initials]	A3
2. *	Please tick box to confirm CRF creation:	[A:Y] ☐
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): ENROLLMENT ()	
ENROLLMENT	
1. *	Type of data [NOT SUBMITTED] [A:S] ☐ [DM.SUBJID] Subject Number N10 [A:C] ☐ Center Data
2.	Study participant: [hidden] [Subj Nr] [NOT SUBMITTED] N10
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): DEMOGRAPHY ()			
DEMOGRAPHY			
1.* ✓	Date of birth: [DOB]	[DM.BRTHDTC] Req ☐ / Req ☐ / Req ☐ (2012-2029)	
2.* ✓	Sex: [Sex]	[DM.SEX] [A:F] ☐ Female [A:M] ☐ Male	
3.	Weight for Safety DB (Do not delete) [hidden]	[NOT SUBMITTED] XXXXX	
4.* ✓	Does the study participant live in a RTS,S exposed or unexposed cluster? [Does the study participant live in a RTS,S exposed or unexposed cluster?]	[SC.SCCAT = "CLUSTER INFORMATION"] [A:1] [SC.SCORRES] [SC.SCTEST = "Type Of Residence"] ☐ [NOT SUBMITTED] ☐ [cDISTGHANAEX] ☐ Exposed Cluster Please select district/sub-county/cluster: ☐ [NOT SUBMITTED] Unexposed Cluster Please select district/sub-county/cluster: ☐ [cDISTGHANAUNEX] ☐	
PARTICIPATION IN OTHER TRIAL			
5.*	Does the study participant currently participate in any clinical trial assessing any investigational medication or vaccination? [Does the Study participant currently participate in any clinical trial assessing any investigational medication or vaccination?]	[SUPPDM.QVAL when QNAM = "PARCLTRL"] [A:Y] ☐ [SUPPDM.QVAL when QNAM = "TRLTYPE"] [The selected value is added to the calculated value of SUPPDM.QVAL when QNAM = "TRLTYPE" separated by a comma] Yes, Please select type [A:IV] ☐ [NOT SUBMITTED] Investigational Vaccination, Please select type of disease [A:AM] ☐ Anti Malaria [A:OD] ☐ Other Disease [A:IM] ☐ [NOT SUBMITTED] Investigational Medication, Please select type of diseases [A:AM] ☐ Anti Malaria [A:OD] ☐ Other Disease [A:N] ☐ No	
6.*	Was the study participant part of the EPI-MAL-002 study? [Was the study participant part of the EPI-MAL-002 study?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPDM.QVAL when QNAM = "DMPTOTHF"] Yes, please specify the study participant number N5 [A:N] ☐ No	
HOUSEHOLD_INFO [SC.SCCAT = "HOUSEHOLD INFORMATION"] [SS.SSCAT = "HOUSEHOLD INFORMATION"]			
7.*	How many persons are living in the household (including study participant)? [How many persons are living in the household (including study participant)?]	[SC.SCORRES] [SC.SCTEST = "Number of Persons In The Household"] A2	
8.*	From those persons, how many are in the given age range [From those persons, how many are in the given age range]	[A:1] ☐ [SC.SCTEST = "No.of Persons 0-<3 Years in Household"] [SC.SCORRES] number of person 0 - < 3 years old: A2 [A:2] ☐ [SC.SCTEST = "No.of Persons 3-<6 Years in Household"] [SC.SCORRES] number of person 3 - < 6 years old: A2 [A:3] ☐ [SC.SCTEST = "No.of Persons 6-<12 Years in Household"] [SC.SCORRES] number of person 6 - < 12 years old: A2 [A:4] ☐ [SC.SCTEST = "No.of Persons 12-<18 Years in Household"] [SC.SCORRES] number of person 12 - < 18 years old: A2	
9.*	Neighbourhood of residence:	[SC.SCTEST = "Neighbourhood of Residence"] [SC.SCORRES] [A:1] ☐ urban [A:2] ☐ semi-rural [A:3] ☐ rural area	
10.*	What is the approximate distance between the study participant house and the closest health care facility? [What is the approximate distance between the study participant house and the closest health care facility?]	[SS.SSTEST = "Distance House And Health Care Facility"] [SS.SSORRES] [A:1] ☐ < 5 Km [A:2] ☐ 5 - < 10 Km [A:3] ☐ 10 - < 20 Km [A:4] ☐ 20 - < 30 Km [A:5] ☐ >= 30 Km	
11.*	What is the closest health care facility?	[SS.SSTEST = "Closest Health Care Facility"] [SS.SSORRES] [A:1] ☐ Primary health care facility [A:2] ☐ [SS.SSTEST = "Name Of Closest Hospital"] [SS.SSORRES] Hospital : please provide the hospital name A200	
PATIENT IDENTIFICATION			
Only to be used during the study conduct in case the existing subject number needs to be changed			
12.	Please enter new subject number [Changed subject number]	[DM.SUBJID] N10	
13.	Study participant: [hidden] [Subj Nr]	[NOT SUBMITTED] N10	
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.			

Codelist Values Tables: DEMOGRAPHY						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cDISTGHANAEX	String		Kintampo North	1	citmGD1	itmCOUNTRY
			Kintampo South	2	citmGD2	
			Techiman North	3	citmGD3	
			Nkoranza North	4	citmGD4	
			Kasena Nankana West	5	citmGD5	

cDISTGHANAUNEX	String	Kasena Nankana Municipal	6	citmGD6	itmCOUNTRY1
		Kombewa	7	citmKD1	
		Gem	8	citmKD2	
		Exposed Malawi 1	9	citmDME1	
		Exposed Malawi 2	10	citmDME2	
		Techiman South	1	citmDGE1	
		Nkoranza South	2	citmDGE2	
		Bulisa North	3	citmDGE3	
		Bulisa South	4	citmDGE4	
		Nyando	5	citmDKUN1	
		Bondo	6	citmDKUN2	
		Unexposed Malawi 1	7	citmMALUNE1	
		Unexposed Malawi 2	8	citmMALUNE2	

EPI-MALARIA-003 VS AME (115056): INFORMED CONSENT ()		
INFORMED CONSENT [DS.DSTERM and DS.DSDECOD = "INFORMED CONSENT OBTAINED"] [DS.DSSCAT = "INFORMED CONSENT"] [DS.DSCAT = "PROTOCOL MILESTONE"]		
I certify that Informed Consent has been obtained prior to any study procedure.		
1.* Informed Consent Date: [IC date]	[DS.DSSTDTC] [DM.RFICDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029)	
2. Tick box if verbal consent was provided [Tick box if verbal consent was provided]	[DS.DSTERM and DS.DSDECOD = "VERBAL CONSENT OBTAINED"] [A:Y] ☐ [DS.DSSTDTC] Yes Date of verbal consent ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2020-2029)	
3.* Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for future research? [Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for future research?]	[DS.DSSCAT = "INFORMED CONSENT - LABORATORY"] [DS.DSCAT = "OTHER EVENT"] [A:N][DS.DSTERM and DS.DSDECOD = "SUBJECT DID NOT AGREE THAT HER/HIS BIOLOGICAL SAMPLE(S) MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] [A:Y][DS.DSTERM and DS.DSDECOD = "SUBJECT AGREED THAT HER/HIS BIOLOGICAL SAMPLE(S) MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] ☐ No ☐ Yes ☐ Not applicable	
4. Informed consent section number [hidden] [Section number]	[NOT SUBMITTED] N10	
5. Disposition Event Category [hidden]	[NOT SUBMITTED] ☐ [cIDSCAT_DSCAT] ☐	
6. Disposition Event Subcategory [hidden]	[NOT SUBMITTED] ☐ [cIDSSCAT_DSSCAT] ☐	
7. Standardized Disposition Term [hidden]	[NOT SUBMITTED] ☐ [cINCOMPLT_DSDECOD] ☐	
8. Did subject's parent(s) / legally acceptable representatives consent to using his/her medical and personal information for further research, once the study is complete?	[DS.DSSCAT = "INFORMED CONSENT"] [DS.DSCAT = "OTHER EVENT"] [A:N][DS.DSTERM = "SUBJECT(S) PARENT(S)/LAR(S) DID NOT AGREE THAT HER/HIS MEDICAL AND PERSONAL INFORMATION MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] [DS.DSDECOD = "SUBJECT(S) PARENT(S)/LAR(S) DID NOT AGREE THAT HER/HIS MEDICAL AND PERSONAL INFORMATION MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] [A:Y][DS.DSTERM = "SUBJECT(S) PARENT(S)/LAR(S) AGREED THAT HER/HIS MEDICAL AND PERSONAL INFORMATION MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] [DS.DSDECOD = "SUBJECT(S) PARENT(S)/LAR(S) AGREED THAT HER/HIS MEDICAL AND PERSONAL INFORMATION MAY BE USED BY GSK BIOLOGICALS FOR FUTURE RESEARCH"] ☐ No ☐ Yes	
COHORT IDENTIFICATION		
9.* Will the study participant be part of active surveillance? [Will the subject be part of active surveillance?]	[DM.ARM = "ACTIVE SURVEILLANCE"] [DM.ACTARM = "ACTIVE SURVEILLANCE"] [SUPPDM.QVAL = "ACTIVE SURVEILLANCE" when QNAM = "COHORT"] [DM.ACTARMCD = "AS"] [DM.ARMCD = "AS"] [A:Y][SUPPDM.QVAL = "ENHANCED HOSPITALIZATION SURVEILLANCE" when QNAM = "COHORT"] [DM.ACTARMCD = "EHS"] [DM.ARMCD = "EHS"] [A:N] ☐ No ☐ Yes [CE.CEPRESP = "Y"] [CE.CEEVINTX = "AT TIME OF ENROLLMENT"] [CE.CECAT = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] Does subject show any significant development delay, physical disabilities at the time of enrollment? [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] Yes --> Please specify A200 [A:N][CE.CEOCCUR = "N"] ☐ No [A:NA] ☐ Not applicable	
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.		

Codelist Values Tables: INFORMED CONSENT				
Codelist RefName	Codelist Data Type	Subset	Label	Code
cIDSCAT_DSCAT	String		Disposition Event	DISPOSITION EVENT
			Other Event	OTHER EVENT
			Protocol Milestone	PROTOCOL MILESTONE
cIDSSCAT_DSSCAT	String		End of study	END OF STUDY
			Epoch continuation	EPOCH CONTINUATION
			Informed consent	INFORMED CONSENT
			Randomisation agreement	RANDOMISATION AGREEMENT
			Screening failure	SCREENING FAILURE
			Telephone contact	TELEPHONE CONTACT
			Visit continuation	VISIT CONTINUATION
			Visit continuation by phone	VISIT CONTINUATION BY PHONE
cINCOMPLT_DSDECOD	String		Completed	COMPLETED
			Consent withdrawal, not due to an adverse event	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
			Consent withdrawal, not due to a serious adverse event	CONSENT WITHDRAWAL, NOT DUE TO A SERIOUS ADVERSE EVENT
			Consent withdrawal / not willing to participate, not due to a (s)ae	CONSENT WITHDRAWAL / NOT WILLING TO PARTICIPATE, NOT DUE TO A (S)AE
			Death	DEATH
			Eligibility criteria not fulfilled (inclusion and exclusion criteria)	ELIGIBILITY CRITERIA NOT FULFILLED (INCLUSION AND EXCLUSION CRITERIA)
			Informed consent obtained	INFORMED CONSENT OBTAINED
			Lost to follow-up	LOST TO FOLLOW-UP
			Migrated / moved from the study area	MIGRATED / MOVED FROM THE STUDY AREA

		Missing confirmed	MISSING CONFIRMED	ctmMISSING_CONFIRMED_002
		Non-Serious Adverse Event onset in the course or after previous study epoch	NON-SERIOUS ADVERSE EVENT ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmNON_SERIOUS_ADVERSE_EVENT_ONSET_IN_THE_COURSE_OR_AFTER
		Non-Serious Adverse Event or non-serious pIMD onset in the course or after previous study epoch	NON-SERIOUS ADVERSE EVENT OR NON-SERIOUS PIMD ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmNON_SERIOUS_ADVERSE_EVENT_OR_NON_SERIOUS_PIMD_ONSET_IN
		Other	OTHER	ctmOTHER10
		Progressive disease	PROGRESSIVE DISEASE	ctmPROGRESSIVE_DISEASE
		Protocol violation	PROTOCOL VIOLATION	ctmPROTOCOL_VIOLATION
		Randomized	RANDOMIZED	ctmRANDOMIZED
		Same reason and decision as previous visit	SAME REASON AND DECISION AS PREVIOUS VISIT	ctmSAME_REASON_AND_DECISION_AS_PREVIOUS_VISIT
		Non-Serious Adverse Events or Serious Adverse Events	NON SERIOUS OR SERIOUS ADVERSE EVENT	ctmNON_SERIOUS_OR_SERIOUS_AE
		Serious Adverse Event or Non-Serious Related AE	SERIOUS ADVERSE EVENT AND/OR NON-SERIOUS RELATED ADVERSE EVENT	ctmSERIOUS_ADVERSE_EVENT_OR_NON_SERIOUS_RELATED_ADVERS
		Serious Adverse Event and/or pIMD	SERIOUS ADVERSE EVENT AND/OR PIMD	ctmSERIOUS_ADVERSE_EVENT_AND_OR_PIMD
		Serious Adverse Event and/ or pIMD and/or Non-Serious Related AE	SERIOUS ADVERSE EVENT AND/ OR PIMD AND/OR NON-SERIOUS RELATED ADVERSE EVENT	ctmSERIOUS_ADVERSE_EVENT_AND__OR_PIMD_AND_OR_NON_SERIOUS_R
		Serious adverse event not related to study participation or to a gsk concurrent medication	SERIOUS ADVERSE EVENT NOT RELATED TO STUDY PARTICIPATION OR TO A GSK CONCURRENT MEDICATION	ctmSERIOUS_ADVERSE_EVENT_NOT_RELATED_TO_STUDY_PARTICIPATIO
		Serious Adverse Event onset in the course or after previous study epoch	SERIOUS ADVERSE EVENT ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmSERIOUS_ADVERSE_EVENT_ONSET_IN_THE_COURSE_OR_AFTER_PREV
		Serious adverse event related to study participation or to a gsk concurrent medication	SERIOUS ADVERSE EVENT RELATED TO STUDY PARTICIPATION OR TO A GSK CONCURRENT MEDICATION	ctmSERIOUS_ADVERSE_EVENT_RELATED_TO_STUDY_PARTICIPATION_OR
		Solicited Adverse Event	SOLICITED ADVERSE EVENT	ctmSOLICITED_ADVERSE_EVENT
		Sponsor study termination	SPONSOR STUDY TERMINATION	ctmSPONSOR_STUDY_TERMINATION
		Unsolicited Non-Serious Adverse Event	UNSOLICITED NON-SERIOUS ADVERSE EVENT	ctmUNSOLICITED_NON_SERIOUS_ADVERSE_EVENT
		Safety information obtained	SAFETY INFORMATION OBTAINED	ctmSAFETY_INFORMATION_OBTAINED
		Safety information not obtained	SAFETY INFORMATION NOT OBTAINED	ctmSAFETY_INFORMATION_NOT_OBTAINED
		Study ended	STUDY ENDED	ctmSTUDY_ENDED

EPI-MALARIA-003 VS AME (115056): ELIGIBILITY CRITERIA(ACTIVE SURVEILLANCE) ()		
ELIGIBILITY CRITERIA(ACTIVE SURVEILLANCE) [IE.VISITNUM = "(visitnum attached to this form)"]		
1. ☒	Did the subject meet all the entry criteria? [Eligible]	[NOT SUBMITTED] [A:Y] ☐ [SUPPDM.QVAL when QNAM = "AGEGRP"] Yes -> What is the study group of the study participant? [A:DTP group] ☐ DTP group [A:Catch-up group] ☐ Catch-up group [A:N] ☐ No -> Tick all boxes corresponding to violations of any inclusion/exclusion criteria. Do not enter the subject into the study if he/she failed any of the inclusion or exclusion criteria below. [IE.IEORRES = "N" when IE.IECAT = "INCLUSION"] INCLUSION CRITERIA Tick the boxes corresponding to any of the inclusion criteria the subject failed. [A:INCL01] ☐ [IE.IETESTCD] [IE.IETEST] ☐ Study participants parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol. [A:INCL02] ☐ Written informed consent provided from either the parent(s) or LAR of the study participant. [A:INCL03] ☐ Study participant living in the HDSS or equivalent surveillance system area. [A:INCL04] ☐ For enrolment in the active surveillance-DTP group: children must be aged < 18 months, identified at any administration of DTP/HepB/Hib (or before 3rd dose of DTP/HepB/Hib in case of hospitalisation and vaccinated with at least one dose of DTP/HepB/Hib) [A:INCL05] ☐ For enrolment in the active surveillance-Catch-up group: children must be aged < 18 months, received at least one dose of DTP/HepB/Hib, whose age corresponds to the age after 3rd dose of DTP/HepB/Hib and identified at time of first dose of RTS,S/AS01E [IE.IEORRES = "Y" when IE.IECAT = "EXCLUSION"] EXCLUSION CRITERIA Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry. [A:EXCL01] ☐ [IE.IETESTCD] [IE.IETEST] ☐ Child in care
2.	Eligibility section number [hidden] [Section number]	[NOT SUBMITTED] N10
3.	IECAT_INCL [hidden]	[IE.IECAT = "INCLUSION"] ☐ [cIECAT_IECAT] ☐
4.	IETESTYN_INCL [hidden]	[NOT SUBMITTED] ☐ [cINY_IETESTYN] ☐
5.	IECAT_EXCL [hidden]	[IE.IECAT = "EXCLUSION"] ☐ [cIECAT_IECAT] ☐
6.	IETESTYN_EXCL [hidden]	[NOT SUBMITTED] ☐ [cINY_IETESTYN] ☐
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

Codelist Values Tables: ELIGIBILITY CRITERIA(ACTIVE SURVEILLANCE)						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIECAT_IECAT	String		Exclusion Criteria	EXCLUSION	citmEXCLUSION_CRITERIA	IECAT_INCL_Y_HID, IECAT_EXCL_Y_HID
			Inclusion Criteria	INCLUSION	citmINCLUSION_CRITERIA	
cINY_IETESTYN	String		No	N	citmNO_11	IETESTYN_INCL_Y_HID, IETESTYN_EXCL_Y_HID
			Yes	Y	citmYES_11	

EPI-MALARIA-003 VS AME (115056): ELIGIBILITY CRITERIA (ENHANCED HOSPITALISATION SURVEILLANCE) ()	
ELIGIBILITY CRITERIA (ENHANCED HOSPITALISATION SURVEILLANCE) [IE.VISITNUM = "(visitnum attached to this form)"]	
1. ☒ Did the subject meet all the entry criteria? [Eligible]	[NOT SUBMITTED] [A:Y] ☐ Yes [A:N] ☐ Tick the boxes corresponding to any of the inclusion criteria the subject failed [IE.IEORRES = "N" when IE.IECAT = "INCLUSION"] INCLUSION CRITERIA [A:INCL05] ☐ Study participants parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol. [A:INCL06] ☐ Written informed consent provided from either the parent(s) or LAR of the study participant. [A:INCL07] ☐ Study participant living in the HDSS or equivalent surveillance system area. [A:INCL08] ☐ For enrolment in the enhanced hospitalisation surveillance: children must be aged at least 6 weeks and less than 5 years of age [Per protocol Amd #2] and hospitalised at any time during the study. Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry [IE.IEORRES = "Y" when IE.IECAT = "EXCLUSION"] EXCLUSION CRITERIA [A:EXCL02] ☐ Child in care
2. Eligibility section number [hidden] [Section number]	[NOT SUBMITTED] N10
3. IECAT_INCL [hidden]	[IE.IECAT = "INCLUSION"] ☐ [cIECAT_IECAT]
4. IETESTYN_INCL [hidden]	[NOT SUBMITTED] ☐ [cINY_IETESTYN]
5. IECAT_EXCL [hidden]	[IE.IECAT = "EXCLUSION"] ☐ [cIECAT_IECAT]
6. IETESTYN_EXCL [hidden]	[NOT SUBMITTED] ☐ [cINY_IETESTYN]
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

Codelist Values Tables: ELIGIBILITY CRITERIA (ENHANCED HOSPITALISATION SURVEILLANCE)						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIECAT_IECAT	String		Exclusion Criteria	EXCLUSION	cltmEXCLUSION_CRITERIA	IECAT_INCL_Y_HID_PAS, IECAT_EXCL_Y_HID_PAS
			Inclusion Criteria	INCLUSION	cltmINCLUSION_CRITERIA	
cINY_IETESTYN	String		No	N	cltmNO_11	IETESTYN_INCL_Y_HID_PAS, IETESTYN_EXCL_Y_HID_PAS
			Yes	Y	cltmYES_11	

EPI-MALARIA-003 VS AME (115056): CHECK FOR STUDY CONTINUATION () [When "Study discontinuation" tickbox is ticked on the bottom of the page, then DSDECOD for subject disposition record (DSCAT = DISPOSITION EVENT) is completed with the major reason of discontinuation selected on this page.]		
CHECK FOR STUDY CONTINUATION [Irrespective of the study discontinuation tickbox, another event record will be generated when the question "Was the study participant seen at this visit?" is answered NO (DSCAT = "OTHER EVENT" and DSDECOD = "NOT RETURNED FOR VISIT").]		
1. * Was the study participant seen at this visit? [Was the subject seen at this visit?]	[NOT SUBMITTED] [A:Y] [A:N][DS.DSDECOD = "NOT RETURNED FOR VISIT"] [DS.DSSCAT = "VISIT CONTINUATION - VISITNUM [visitnum attached to this form]"] [DS.DSSCAT = "OTHER EVENT"]	☐ [SV.SVSTDTCT] [SV.SVENDTCT] Yes -> Date of visit: ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [SS.SSORRES] [SS.SSTEST = "Date of Return When Moved for >3 Months"] [SS.SSCAT = "STUDY CONTINUATION"] In case of migrated / moved from the study area for more than 3 months, please provide the date of return ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [SS.SSORRES] [SS.SSTEST = "Date of Migration When Moved for >3 Mths"] [SS.SSCAT = "STUDY CONTINUATION"] In case of migrated/moved from the study area for more than 3 months please provide the date of migration (if done since last visit) ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) ☐ No [DS.DSTERM] -> Please select the major reason: [A:SAE] [A:PTV] ☐ Serious Adverse Event ☐ Protocol violation, please specify: A200 ☐ [A:CWS][When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] Consent Withdrawal ->Please specify the reason (Only if the Subject's parents / Legally Acceptable Representative has / have spontaneously explained it): [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] A200 [A:MIG] Or tick box if reason not provided [A:N][NOT SUBMITTED] ☐ [SUPPDS.QVAL when QNAM = "MOVEDTC"] Migrated / moved from the study area : ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) ☐ Lost to follow-up ☐ Sponsor study termination ☐ [DM.DTHDTC] Subject died -> Date of death: ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [DD.DDORRES] -> A200 [A:HOS] Cause of death: [DD.DDTEST = "Type of Diagnosis"] [DD.DDORRES] [A:VER] Verbal autopsy [A:MED] Medical diagnoses ☐ Hospitalisation at the time of the visit -> Please make sure that hospitalisation section has been completed ☐ [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] Other, please specify A200 -> For serious adverse events (except death) and Other reasons only: Please select who made the decision: [A:I][SUPPDS.QVAL when QNAM = "PRDECMK"] ☐ Investigator ☐ Subject's parents / Legally Acceptable Representatives
2. Tick box if the visit was performed by phone call or other means of virtual contact [Tick box if the visit was performed by phone call or other means of virtual contact]	[SV.SVGRPID = "PHONE CONTACT"] [A:Y] ☐ Yes	
PERMANENT DISCONTINUATION [NOT SUBMITTED]		
3. Study discontinuation:	[A:1] ☐ Tick box only if permanent discontinuation, i.e. if the subject definitively withdraws from the study. In this case, terminate the CRF: Complete Vaccination, Outpatient, Hospitalisation, AESI and SAE sections and study conclusion as appropriate	

Key: [*] = Item is required [✓] = Source verification required
 Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

EPI-MALARIA-003 VS AME (115056): SIGNS AND SYMPTOMS ()

MEDICAL HISTORY	
1. Are there any developmental delay or physical disabilities [Are there any developmental delay or physical disability]	[CE.CEOCCUR] [CE.CEPRESP = "Y"] [CE.CETERM = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] [CE.CECAT = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] [A:Y] ☐ Yes [A:N] ☐ No [A:NA] ☐ Not applicable
2. Were any of the conditions listed below present at any time? [Were any of the conditions listed below present at any time?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "RISKFCR"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "RISKFCR" consists of all selected values, separated by a comma] Please select all that apply [A:RF001] ☐ Malnutrition [A:RF002] ☐ Tuberculosis [A:RF005] ☐ History of temperature >=37.5°C (axillary) [A:RF006] ☐ Malaria [A:RF007] ☐ Known HIV infection [A:RF008] ☐ Anaemia (Hb < 11 g/dL) [A:RF009] ☐ Drugs exposure [A:RF010] ☐ Traditional medicine exposure [A:RF011] ☐ Toxic agent exposure [A:RF099] ☐ [SUPPHO.QVAL when QNAM = "OTHRKSP"] Other, please specify A200
3. Is there haemoglobinopathy diagnosed in this study participant? [Is there haemoglobinopathy diagnosed in this study participant?]	[SUPPHO.QVAL when QNAM = "HMGLDIAG"] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HMGLSYMP"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "HMGLSYMP" consists of all selected values, separated by a comma] Please select all that apply [A:1] ☐ Thalassemia [A:2] ☐ Sickle Cell Anaemia [A:3] ☐ G6PD deficiency [A:7] ☐ [SUPPHO.QVAL when QNAM = "OTHMGLSP"] Other, please specify A200
4. Are there any known comorbidity conditions other than haemoglobinopathy? [Is there any change in the comorbidity other than haemoglobinopathy since enrollment?]	[A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "COMFCTR1" or "COMFCTR2" or "COMFCTR3" or "COMFCTR4"] [Note: The calculated value consists of all selected values, separated by a comma. If calculated value is more than 200 characters, it is split into multiple QVAL (with QNAM = "COMFCTR1", "COMFCTR2", "COMFCTR3" and "COMFCTR4")] Please select all that apply [A:MH011] ☐ Premature birth [A:MH012] ☐ Difficult birth/ hypoxia [A:MH003] ☐ Congenital birth defect [A:MH001] ☐ [SUPPHO.QVAL when QNAM = "DGNLHOSP"] Diagnosis of last hospitalization A200 [A:MH002] ☐ Developmental retardation [A:MH004] ☐ History of head trauma [A:MH005] ☐ History of joints trauma [A:MH006] ☐ [SUPPHO.QVAL when QNAM = "OTHTRAS1"] History of other trauma Please Specify A200 [A:MH007] ☐ History of serious non neurologic infectious disease (sepsis, peritonitis, internal abscesses) [A:MH008] ☐ History of meningitis /encephalitis [A:MH009] ☐ History of other neurologic or brain disease [A:MH010] ☐ Known epilepsy/ seizures [A:MH013] ☐ Previous abdominal surgery [A:MH014] ☐ Known bowel disfunction [A:MH015] ☐ Known bleeding disorder in the family [A:MH017] ☐ Diabetes mellitus [A:MH019] ☐ Congenital disease of the spine [A:MH021] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDS1"] Other Chronic Disease A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDSP", separated by a comma] [A:1] ☐ If congenital, please select the box [A:MH022] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDS1"] Other Congenital Disease A200 [A:MH023] ☐ [SUPPHO.QVAL when QNAM = "OTHCOFS1"] Other comorbidity factor A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDS1", separated by a comma] [A:1] ☐ If congenital, please select the box

5.* ✓	Does the child have any of the following symptoms at the time of the visit or in the past 48 hours? [Does the child have any of the following symptoms at the time of the visit or in the past 48 hours?]	[A:N][NOT SUBMITTED] ☐ No [A:Y][CE.CESTDTC] ☐ Yes -> Onset of first signs & symptoms: ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) -> Are the following signs and symptoms present at the time of the visit or in the past 48 hours? [FA.FASCAT = "TEMPERATURE"] [FA.FAOBJ = "TEMPERATURE >=37.5C"] [FA.FAEVINTX = "-P48H TO VISIT"] Temperature >= 37.5°C (axillary) during visit or in past 48 hours [A:Y][CE.CEOCCUR] [CE.CESCAT = "TEMPERATURE"] [CE.CETERM = "TEMPERATURE >=37.5C"] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Yes --> please record axillary temperature in °C XX.X [A:N] [A:ND][CE.CESTAT = "NOT DONE"] [CE.CEREASND = "NOT CHECKED"] [CE.CESCAT = "FEVER"] [CE.CETERM = "FEVER"] Was fever reported by the parents / LAR ? [N:1][CE.CEOCCUR] ☐ Yes [N:0] ☐ No [CE.CESCAT = "SKIN AND MUCOSA"] Skin and Mucosa [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CEOCCUR = "N"] [CE.CETERM = "SKIN AND MUCOSA" when CE.CEOCCUR is not "Y"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "NEUROLOGIC"] Neurologic [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CETERM = "NEUROLOGIC" when CE.CEOCCUR is not "Y"] [CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "RESPIRATORY"] Respiratory [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "EYES"] Eyes [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "BONES AND JOINTS"] Bones and joints [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "INJECTION SITE"] Injection site [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply [A:N][CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "DIGESTION"] Digestion [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] Yes --> Tick all that apply	[A:LSN] ☐ Lesions [A:HMT] ☐ Hematoma [A:ODA] ☐ Oedema [A:BDG] ☐ Bleeding [A:NSS] ☐ Neck stiffness [A:WKS] ☐ Muscle weakness [A:BCS] ☐ Behaviour changes [A:SZS] ☐ Seizures [A:RVS] ☐ Regress in verbal, seeing, hearing or moving capacity [A:LOC] ☐ Loss of consciousness [A:LTH] ☐ Lethargy [A:CC] ☐ Continuous crying [A:FBG] ☐ abnormal breathing [A:NBG] ☐ Cyanosis [A:YLN] ☐ Yellow [A:RED] ☐ Red or discharge [A:DNL] ☐ Sensitivity to light [A:DIJ] ☐ Difficulty in moving joints [A:FDM] ☐ Foot deformation [A:SWJ] ☐ Swelling of joints [A:HOJ] ☐ Hotness of joints [A:PAN] ☐ Pain [A:SWE] ☐ Swelling [A:HOT] ☐ Hot [A:VMG] ☐ Vomiting [A:VME] ☐ Vomiting everything [A:DWB] ☐ Diarrhea [A:DRE] ☐ refusal / difficulty to eat or to drink - Change in food / milk intake [A:UBF] ☐ Dehydration

EPI-MALARIA-003 VS AME (115056): USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR () [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "USUAL PREVENTIVE MEASURES"]	
MALARIA PREVENTIVE MEASURES	
1.* Usually, how many days per week does the study participant sleep under the mosquito net? [Usually, how many days per week does the study participant sleep under the mosquito net?]	[ER.ERTERM = "Usually sleep under a mosquito net"] [ER.EROCCUR] [A:1] ☐ Always [A:2][SUPPER.QVAL when QNAM = "SLMNFREQ"] ☐ Most of time (4 to 6 days per week) [A:3] ☐ Sometimes (1 to 3 days per week) [A:4] ☐ Never
2.* What are the characteristics of the usually used mosquito net?	[SUPPER.QVAL when QNAM = "MNETUSE"] [A:1] ☐ No use of bednet [SUPPER.QVAL when QNAM = "BNL1Y"] -> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:1] ☐ Last impregnation less than 1 year ago [A:2] ☐ Last impregnation more than 1 year ago [A:3] ☐ Never impregnated [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:1] ☐ No [A:2] ☐ < 5 holes [A:3] ☐ >= 5 holes
3.* Was indoor residual spray used in past 12 months to spray interior walls of this part of the house? [Was indoor residual spray used in past 12 months to spray interior walls of this part of the house?]	[ER.EREVLINT = "-P12M"] [ER.ERTERM = "Use of indoor residual spray"] [ER.EROCCUR] [A:Y] ☐ [SUPPER.QVAL when QNAM = "HOUSPRAY"] Yes, --> if yes, please specify how many months ago was house sprayed [A:Z] [A:N] ☐ No
4.* Are other malaria preventive measures usually applied in the study participant's house? [Are other malaria preventive measures usually applied in the study participant's house?]	[ER.ERTERM = "Apply other malaria preventive measures"] [ER.EROCCUR] [N:1] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] [Note: The calculated value of SUPPER.QVAL when QNAM = "PRMSRTYP" consists of all selected values, separated by a comma] Yes, Please select which are applicable [A:1] ☐ Mosquito coil [A:2] ☐ Commercial spray (e.g. DOOM) [A:3] ☐ Herbs [A:4] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] Other, please specify [A:200] [N:0] ☐ No
5.* Did the study participant ever receive malaria preventive treatment (Seasonal Malaria Chemoprophylaxis & Intermittent Preventive Therapy)? [Did the study participant ever receive malaria preventive treatment (Seasonal Malaria Chemoprophylaxis & Intermittent Preventive Therapy)?]	[ER.ERTERM = "Ever received malaria preventive treatment (Seasonal Malaria Chemoprophylaxis - Intermittent Preventive Therapy)"] [A:Y][ER.EROCCUR = "Y"] ☐ [SUPPER.QVAL when QNAM = "TRTENR"] Yes, Was the treatment received after enrolment? [A:Y] ☐ Yes (please complete medication form) [A:N][ER.EROCCUR = "N"] ☐ [SUPPER.QVAL when QNAM = "PTRTTTPT"] No, when was the treatment administered? [A:1] ☐ less than 1 month before enrollment [A:2] ☐ 1 to <6 months before enrollment [A:3] ☐ 6 to <12 months before enrollment [A:4] ☐ 1 year or more before enrollment [A:N] ☐ No
HEALTH CARE SEEKING BEHAVIOR [SS.SSCAT = "HEALTH CARE SEEKING BEHAVIOR"]	
6.* Where do you usually seek for health care when your child is ill?	[SS.SSTEST = "Health Care Provider Usually Contacted"] [SS.SSORRES] [A:1] ☐ Community health worker [A:2] ☐ Primary health care facility [A:3] ☐ Hospital [A:4] ☐ Private clinic [A:5] ☐ Drug seller / pharmacy (without prescription) [A:6] ☐ Traditional medicine [A:7] ☐ [SS.SSORRES] Other health care [A:200] [SS.SSTEST = "Distance House and Health Care Provider"] [SS.SSORRES] what is the distance between this usually used health care provider and your home? [A:1] ☐ < 5 Km [A:2] ☐ 5 - < 10 Km [A:3] ☐ 10 - < 20 Km [A:4] ☐ 20 - < 30 Km [A:5] ☐ >= 30 Km
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): MALARIA PREVENTION & HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD () [ER.ERPRES = "Y"]	
MALARIA PREVENTIVE MEASURES [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "ACTUAL PREVENTIVE MEASURES"]	
1. * Did the study participant sleep last night under a mosquito net?	[ER.EROCCUR] [ER.ERTERM = "Sleep under a mosquito net last night"] [ER.EREVINTX = "LAST NIGHT"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNL1Y"] Yes ---> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNHOLES"] Yes, --->How many holes of that size ? [A:1] ☐ < 5 [A:2] ☐ >= 5
HEALTH SEEKING BEHAVIOUR [ER.ERCAT = "HEALTH SEEKING BEHAVIOR"]	
2. * Was the study participant treated for fever or malaria in the last 14 days? [Was the subject treated for fever or malaria in the last 14 days?]	[A:Y] [ER.EROCCUR = "Y"] [ER.ERTERM = "Treated for fever or Malaria"] [ER.EREVLINT = "-P14D"] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Yes, Where was the study participant taken for treatment? [A:1] ☐ Home [A:2] ☐ Drug Seller [A:3] ☐ Pharmacy [A:4] ☐ Private Clinic [A:5] ☐ Health Centre [A:6] ☐ Hospital [A:7] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Other, please specify A250 [SUPPER.QVAL when QNAM = "TRTWHEN"] When was the study participant taken for treatment? [A:1] ☐ Onset [A:2] ☐ Subject Did Not Improve [A:3] ☐ Subject Got Worse [A:4] ☐ [SUPPER.QVAL when QNAM = "TRTWHEN"] Other, please specify A200 [SUPPER.QVAL when QNAM = "TRTTPT"] What time was the study participant taken for treatment? [A:1] ☐ Same Day [A:2] ☐ Next Day [A:3] ☐ Two Days Later [A:4] ☐ More Than Two Days Later [A:N] [ER.EROCCUR = "N"] ☐ No
EXPOSURE TO ENVIRONMENTAL HAZARDS [ER.ERCAT = "EXPOSURE TO ENVIRONMENTAL HAZARDS"]	
3. * Was the study participant exposed to environmental hazards during last year?	[ER.EROCCUR] [ER.ERTERM = "Exposed to environmental hazards"] [ER.EREVLINT = "-P1Y"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPEST"] ☐ Yes, Please select which are applicable [A:1] ☐ [SUPPER.QVAL when QNAM = "FREPEST"] Pesticide [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:2] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPCHEM"] Chemicals (other than pesticide) [A:1] ☐ [SUPPER.QVAL when QNAM = "FREQCHEM"] [A:2] ☐ permanently [A:3] ☐ frequently [A:4] ☐ sometimes [A:4] ☐ rarely [A:3] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPRAD"] Radiations [A:1] ☐ [SUPPER.QVAL when QNAM = "FREQRAD"] [A:2] ☐ permanently [A:3] ☐ frequently [A:4] ☐ sometimes [A:4] ☐ rarely [A:4] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPOTHZ"] [SUPPER.QVAL when QNAM = "OTHZSPEC"] Other, please specify A225 [SUPPER.QVAL when QNAM = "FREQOTHZ"] [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): SIGNS AND SYMPTOMS ()

MEDICAL HISTORY	
1. Is there any change in the conditions listed below since previous visit? [Is there any change in the conditions listed below since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:RF001] ☐ Malnutrition [A:RF002] ☐ Tuberculosis [A:RF005] ☐ History of temperature >=37.5°C (axillary) [A:RF006] ☐ Malaria [A:RF007] ☐ Known HIV infection [A:RF008] ☐ Anaemia (Hb < 11 g/dL) [A:RF009] ☐ Drugs exposure [A:RF010] ☐ Traditional medicine exposure [A:RF011] ☐ Toxic agent exposure [A:RF099] ☐ [SUPPHO.QVAL when QNAM = "OTHRSKSP"] Other, please specify A200
2. Is there any change in the diagnosis of haemoglobinopathy since previous visit? [Is there any change in the diagnosis of haemoglobinopathy since previous visit?]	[SUPPHO.QVAL when QNAM = "HMGDIAG"] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:1] ☐ Thalassemia [A:2] ☐ Sickle Cell Anaemia [A:3] ☐ G6PD deficiency [A:7] ☐ [SUPPHO.QVAL when QNAM = "OTHMGLSP"] Other, please specify A200
3. Is there any change in the comorbidity other than haemoglobinopathy since previous visit? [Is there any change in the comorbidity other than haemoglobinopathy since previous visit?]	[A:N] [NOT SUBMITTED] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:MH011] ☐ Premature birth [A:MH012] ☐ Difficult birth/ hypoxia [A:MH003] ☐ Congenital birth defect [A:MH001] ☐ [SUPPHO.QVAL when QNAM = "DGNLHOSP"] Diagnosis of last hospitalization A200 [A:MH002] ☐ Developmental retardation [A:MH004] ☐ History of head trauma [A:MH005] ☐ History of joints trauma [A:MH006] ☐ [SUPPHO.QVAL when QNAM = "OTHTRAS1"] History of other trauma Please Specify A200 [A:MH007] ☐ History of serious non neurologic infectious disease (sepsis, peritonitis, internal abscesses) [A:MH008] ☐ History of meningitis /encephalitis [A:MH009] ☐ History of other neurologic or brain disease [A:MH010] ☐ Known epilepsy/ seizures [A:MH013] ☐ Previous abdominal surgery [A:MH014] ☐ Known bowel disfunction [A:MH015] ☐ Known bleeding disorder in the family [A:MH017] ☐ Diabetes mellitus [A:MH019] ☐ Congenital disease of the spine [A:MH021] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDS1"] Other Chronic Disease A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDS1", separated by a comma] [A:1] ☐ If congenital,please select the box [A:MH022] ☐ [SUPPHO.QVAL when QNAM = "OTHCODS1"] Other Congenital Disease A200 [A:MH023] ☐ [SUPPHO.QVAL when QNAM = "OTHCOFS1"] Other comorbidity factor A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCODS1", separated by a comma] [A:1] ☐ If congenital,please select the box
CHILD ILL FLAG AND SYMPTOMS [CE.CECAT = "SIGNS AND SYMPTOMS"] [CE.CEEVINTX = "-P48H TO VISIT"] [FA.FACAT = "SIGNS AND SYMPTOMS"]	
4.* Does the child have any of the following symptoms at the time of the visit or in the past 48 hours? ✓ [Does the child have any of the following symptoms at the time of the visit or in the past 48 hours?]	[A:N] [NOT SUBMITTED] ☐ No [A:Y] ☐ [CE.CESTDTC] Yes -> Onset of first signs & symptoms: Req / Req / Req (2018-2029) -> Are the following signs and symptoms present at the time of the visit or in the past 48 hours? [FA.FASCAT = "TEMPERATURE"] [FA.FA0B] = "TEMPERATURE >=37.5°C" [FA.FAEVINTX = "-P48H TO VISIT"] [CE.CESCAT = "TEMPERATURE"] [CE.CETERM = "TEMPERATURE >=37.5°C"]

Temperature $\geq 37.5^{\circ}\text{C}$ (axillary) during visit or in past 48 hours
 [A:Y][CE.CEOCCUR = "Y"] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"]
 Yes --> please record axillary temperature in $^{\circ}\text{C}$
 [A:N] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CEOCCUR] [CE.CESCAT = "FEVER"] [CE.CETERM = "FEVER"]

Was fever reported by the parents / LAR ?
 [N:1] ☐ Yes
 [N:0] ☐ No
 [CE.CESCAT = "SKIN AND MUCOSA"]

Skin and Mucosa
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:LSN] ☐ Lesions
 [A:HMT] ☐ Hematoma
 [A:ODA] ☐ Oedema
 [A:BDG] ☐ Bleeding
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "NEUROLOGIC"]

Neurologic
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:NSS] ☐ Neck stiffness
 [A:WKS] ☐ Muscle weakness
 [A:BCS] ☐ Behaviour changes
 [A:SZS] ☐ Seizures
 [A:RVS] ☐ Regress in verbal, seeing, hearing or moving capacity
 [A:LOC] ☐ Loss of consciousness
 [A:LTH] ☐ Lethargy
 [A:CC] ☐ Continuous crying
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "RESPIRATORY"]

Respiratory
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:FBG] ☐ abnormal breathing
 [A:NBG] ☐ Cyanosis
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "EYES"]

Eyes
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:YLW] ☐ Yellow
 [A:RED] ☐ Red or discharge
 [A:DNL] ☐ Sensitivity to light
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "BONES AND JOINTS"]

Bones and joints
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:DLJ] ☐ Difficulty in moving joints
 [A:FDM] ☐ Foot deformation
 [A:SWJ] ☐ Swelling of joints
 [A:HOJ] ☐ Hotness of joints
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "INJECTION SITE"]

Injection site
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:PAN] ☐ Pain
 [A:SWE] ☐ Swelling
 [A:HOT] ☐ Hot
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "DIGESTION"]

Digestion
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:VMG] ☐ Vomiting
 [A:VME] ☐ Vomiting everything
 [A:DWB] ☐ Diarrhea
 [A:DRE] ☐ refusal / difficulty to eat or to drink - Change in food / milk intake
 [A:UBF] ☐ Dehydration
 [A:BIS] ☐ Blood in stools
 [A:STP] ☐ Stomach / Abdominal pain
 [A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "OTHER SYSTEM"]

Other system
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"]
 Yes --> Please Specify

		[A:N] [A:ND][CE.CESTAT = "NOT DONE"] ☐ No ☐ Not checked
HEALTH CARE FACILITY		
5.*	Did the study participant visit an Outpatient (consultation) since previous visit? [Did the study participant visit an Outpatient (consultation) since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
6.*	Was the study participant hospitalized since previous visit? [Was the study participant hospitalized since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
7.*	Is the study participant referred to any health care facility after this visit? [Is the subject referred to any health care facility after this visit?]	[SUPPCE.QVAL when QNAM = "REFHCF"] [A:N] ☐ No [A:Y] ☐ [SUPPCE.QVAL when QNAM = "HCFTYPE"] Yes -> Please specify type of health care facility [A:LE1] ☐ Primary health care facility [A:HOS] ☐ Hospital Please update vaccination status and provide schedule for next follow up visit
Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR () [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "USUAL PREVENTIVE MEASURES"] [ER.EREVINTX = "SINCE LAST VISIT"]	
MALARIA PREVENTIVE MEASURES	
1.* Is there a change in the number of days per week the study participant usually sleeps under a mosquito net since last visit? [Is there a change in the number of days per week the study participant usually sleeps under a mosquito net since last visit?]	[ER.EROCUR] [ER.ETERM = "Change in frequency of sleeping under a mosquito net"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "SLMNFREQ"] Yes, what's the new frequency? [A:1] ☐ Always [A:2] ☐ Most of time (4 to 6 days per week) [A:3] ☐ Sometimes (1 to 3 days per week) [A:4] ☐ Never
2.* Is there a change in the characteristics of the usually used mosquito net since last visit? [Is there a change in the characteristics of the usually used mosquito net since last visit?]	[ER.EROCUR] [ER.ETERM = "Change in characteristics of the mosquito net"] [A:N] ☐ No [A:Y] ☐ Yes, what are the new characteristics? [SUPPER.QVAL when QNAM = "MNETUSE"] [A:1] ☐ No use of bednet [SUPPER.QVAL when QNAM = "BNL1Y"] -> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:1] ☐ Last impregnation less than 1 year ago [A:2] ☐ Last impregnation more than 1 year ago [A:3] ☐ Never impregnated [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:1] ☐ No [A:2] ☐ < 5 holes [A:3] ☐ >= 5 holes
3.* Was indoor residual spray used since last visit to spray interior walls of study participant's house? [Was indoor residual spray used since last visit to spray interior walls of study participant's house?]	[ER.EROCUR] [ER.ETERM = "Use of indoor residual spray"] [A:Y] ☐ Yes [A:N] ☐ No
4.* Is there a change in other malaria preventive measures applied to study participant's house since last visit? [Is there a change in other malaria preventive measures applied to study participant's house since last visit?]	[ER.ETERM = "Change in other malaria preventive measures applied"] [ER.EROCUR] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] [Note: The calculated value of SUPPER.QVAL when QNAM = "PRMSRTYP" consists of all selected values, separated by a comma] Yes, Please select which are applicable [A:1] ☐ Mosquito coil [A:2] ☐ Commercial spray (e.g. DOOM) [A:3] ☐ Herbs [A:4] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] Other, please specify A200
5.* Did the study participant receive malaria preventive treatment since last visit? (SMC-IPT) [Did the study participant receive malaria preventive treatment since last visit? (SMC-IPT)]	[ER.EROCUR] [ER.ETERM = "Received malaria preventive treatment (Seasonal Malaria Chemoprophylaxis - Intermittent Preventive Therapy)"] [A:1] ☐ No [A:2] ☐ Yes, -> please complete medication form
HEALTH CARE SEEKING BEHAVIOR [SS.SSCAT = "HEALTH CARE SEEKING BEHAVIOR"] [SS.SSEVINTX = "SINCE LAST VISIT"]	
6.* Is there a change in the place you usually seek for health care when study participant is ill? [Is there a change in the place you usually seek for health care when study participant is ill?]	[SS.SSORRES] [SS.SSTEST = "Change in Health Care Provider"] [A:N] ☐ No [A:Y] ☐ [SS.SSTEST = "New Health Care Provider"] [SS.SSORRES] Yes, what is the new health care provider you usually contact? [A:1] ☐ Community health worker [A:2] ☐ Primary health care facility [A:3] ☐ Hospital [A:4] ☐ Private clinic [A:5] ☐ Drug seller / pharmacy (without prescription) [A:6] ☐ Traditional medicine [A:7] ☐ [SS.SSORRES] Other health care A200 [SS.SSORRES] [SS.SSTEST = "Distance House and Health Care Provider"] what is the distance between this usually used health care provider and your home? [A:1] ☐ < 5 Km [A:2] ☐ 5 - < 10 Km [A:3] ☐ 10 - < 20 Km [A:4] ☐ 20 - < 30 Km [A:5] ☐ >= 30 Km
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): SIGNS AND SYMPTOMS ()

MEDICAL HISTORY	
1. Is there any change in the conditions listed below since previous visit? [Is there any change in the conditions listed below since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:RF001] ☐ Malnutrition [A:RF002] ☐ Tuberculosis [A:RF005] ☐ History of temperature >=37.5°C (axillary) [A:RF006] ☐ Malaria [A:RF007] ☐ Known HIV infection [A:RF008] ☐ Anaemia (Hb < 11 g/dL) [A:RF009] ☐ Drugs exposure [A:RF010] ☐ Traditional medicine exposure [A:RF011] ☐ Toxic agent exposure [A:RF099] ☐ [SUPPHO.QVAL when QNAM = "OTHRKSP"] Other, please specify A200
2. Is there any change in the diagnosis of haemoglobinopathy since previous visit? [Is there any change in the diagnosis of haemoglobinopathy since previous visit?]	[SUPPHO.QVAL when QNAM = "HMGLDIAG"] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:1] ☐ Thalassemia [A:2] ☐ Sickle Cell Anaemia [A:3] ☐ G6PD deficiency [A:7] ☐ [SUPPHO.QVAL when QNAM = "OTHMGLSP"] Other, please specify A200
3. Is there any change in the comorbidity other than haemoglobinopathy since previous visit? [Is there any change in the comorbidity other than haemoglobinopathy since previous visit?]	[A:N] [NOT SUBMITTED] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HOCONDTN"] Please select all that apply [A:MH011] ☐ Premature birth [A:MH012] ☐ Difficult birth/ hypoxia [A:MH003] ☐ Congenital birth defect [A:MH001] ☐ [SUPPHO.QVAL when QNAM = "DGNLHOSP"] Diagnosis of last hospitalization A200 [A:MH002] ☐ Developmental retardation [A:MH004] ☐ History of head trauma [A:MH005] ☐ History of joints trauma [A:MH006] ☐ [SUPPHO.QVAL when QNAM = "OTHTRAS1"] History of other trauma Please Specify A200 [A:MH007] ☐ History of serious non neurologic infectious disease (sepsis, peritonitis, internal abscesses) [A:MH008] ☐ History of meningitis /encephalitis [A:MH009] ☐ History of other neurologic or brain disease [A:MH010] ☐ Known epilepsy/ seizures [A:MH013] ☐ Previous abdominal surgery [A:MH014] ☐ Known bowel disfunction [A:MH015] ☐ Known bleeding disorder in the family [A:MH017] ☐ Diabetes mellitus [A:MH019] ☐ Congenital disease of the spine [A:MH021] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDS1"] [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDS1", separated by a comma] Other Chronic Disease A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDS1", separated by a comma] [A:1] ☐ If congenital, please select the box [A:MH022] ☐ [SUPPHO.QVAL when QNAM = "OTHCODS1"] Other Congenital Disease A200 [A:MH023] ☐ [SUPPHO.QVAL when QNAM = "OTHCOFS1"] Other comorbidity factor A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCODS1", separated by a comma] [A:1] ☐ If congenital, please select the box
CHILD ILL FLAG AND SYMPTOMS [CE.CECAT = "SIGNS AND SYMPTOMS"] [CE.CEEVINTX = "-P48H TO VISIT"] [FA.FACAT = "SIGNS AND SYMPTOMS"]	
4. Does the child have any of the following symptoms at the time of the visit or in the past 48 hours? [Does the child have any of the following symptoms at the time of the visit or in the past 48 hours?]	[A:N] [NOT SUBMITTED] ☐ No [A:Y] ☐ [CE.CESTDTC] Yes -> Onset of first signs & symptoms: ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) -> Please select all signs /symptoms that apply

[FA.FASCAT = "TEMPERATURE"] [FA.FA0B] = "TEMPERATURE >=37.5C" [FA.FAEVINTX = "-P48H TO VISIT"] [CE.CESCAT = "TEMPERATURE"] [CE.CETERM = "TEMPERATURE >=37.5C"]

Temperature >= 37.5°C (axillary) during visit or in past 48 hours

[A:Y][CE.CEOCCUR] ☐ [FA.FA0RES] [FA.FATEST = "Temperature"] [FA.FA0RESU = "C"] [FA.FALOC = "AXILLA"]

Yes --> please record axillary temperature in °C

[A:N] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CEOCCUR] [CE.CESCAT = "FEVER"] [CE.CETERM = "FEVER"]

Was fever reported by the parents / LAR ?

[N:1] ☐ Yes

[N:0] ☐ No

[CE.CESCAT = "SKIN AND MUCOSA"]

Skin and Mucosa

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:LSN] ☐ Lesions

[A:HMT] ☐ Hematoma

[A:ODA] ☐ Oedema

[A:BDG] ☐ Bleeding

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "NEUROLOGIC"]

Neurologic

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:NSS] ☐ Neck stiffness

[A:WKS] ☐ Muscle weakness

[A:BCS] ☐ Behaviour changes

[A:SSS] ☐ Seizures

[A:RVS] ☐ Regress in verbal, seeing, hearing or moving capacity

[A:LOC] ☐ Loss of consciousness

[A:LTH] ☐ Lethargy

[A:CC] ☐ Continuous crying

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "RESPIRATORY"]

Respiratory

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:FBG] ☐ abnormal breathing

[A:NBG] ☐ Cyanosis

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "EYES"]

Eyes

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:YLW] ☐ Yellow

[A:RED] ☐ Red or discharge

[A:DNL] ☐ Sensitivity to light

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "BONES AND JOINTS"]

Bones and joints

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:DIJ] ☐ Difficulty in moving joints

[A:FDM] ☐ Foot deformation

[A:SWJ] ☐ Swelling of joints

[A:HOJ] ☐ Hotness of joints

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "INJECTION SITE"]

Injection site

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:PAN] ☐ Pain

[A:SWE] ☐ Swelling

[A:HOT] ☐ Hot

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "DIGESTION"]

Digestion

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]

Yes --> Tick all that apply

[A:VMG] ☐ Vomiting

[A:VME] ☐ Vomiting everything

[A:DWB] ☐ Diarrhea

[A:DRE] ☐ refusal / difficulty to eat or to drink - Change in food / milk intake

[A:UBF] ☐ Dehydration

[A:BIS] ☐ Blood in stools

[A:STP] ☐ Stomach / Abdominal pain

[A:N][CE.CEOCCUR = "N"] ☐ No

[A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked

[CE.CESCAT = "OTHER SYSTEM"]

Other system

[A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"]

		Yes --> Please Specify A200
		[A:N] [A:ND][CE.CESTAT = "NOT DONE"] ☐ No ☐ Not checked
DEVELOPMENT / DISABILITY STATUS [CE.CECAT = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] [CE.CEPRESP = "Y"] [CE.CEEVINTX = "AT TIME OF VISIT"]		
5.*	Was the development /disability status checked at this visit? (please refer to protocol/SPM guidance).	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [CE.CEOCCUR] Yes -> Does subject show any developmental delay, physical disabilities at the time of this visit? [A:N] ☐ [CE.CETERM = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] ☐ No [A:Y] ☐ [SUPPCE.QVAL when QNAM = "REFFURAS"] Yes -> Was the child referred for further assessment? [A:N] ☐ No [A:Y] ☐ Yes
HEALTH CARE FACILITY		
6.*	Did the study participant visit an Outpatient (consultation) since previous visit? [Did the study participant visit an Outpatient (consultation) since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
7.*	Was the study participant hospitalized since previous visit? [Was the study participant hospitalized since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
8.*	Is the study participant referred to any health care facility after this visit? [Is the subject referred to any health care facility after this visit?]	[SUPPCE.QVAL when QNAM = "REFHCF"] [A:N] ☐ No [A:Y] ☐ [SUPPCE.QVAL when QNAM = "HCFTYPE"] Yes, Please specify type of health care facility [A:LE1] ☐ Primary health care facility [A:HOS] ☐ Hospital
Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): CHECK FOR STUDY CONTINUATION ()	
DOV	
1. * Date of Visit	[NOT SUBMITTED] Req ☐ / Req ☐ / Req ☐ (2018-2029)
VISIT NO	
2. Visit Number [read-only]	[XX(Domain).VISITNUM] N4
3. * This visit number is related to [This visit number is related to]	[NOT SUBMITTED] [ciVISITNUM] ☐
CHECK FOR STUDY CONTINUATION	
4. * Was the study participant seen at this visit? [Was the subject seen at this visit?]	[NOT SUBMITTED] [A:Y] ☐ [SV.SVSTDTCT] [SV.SVENDTCT] Yes -> Date of visit: Req ☐ / Req ☐ / Req ☐ (2018-2029) [SS.SSORRES] [SS.SSTEST = "Date of Return When Moved for >3 Months"] [SS.SSCAT = "STUDY CONTINUATION"] In case of migrated / moved from the study area for more than 3 months, please provide the date of return Req ☐ / Req ☐ / Req ☐ (2018-2029) [SS.SSORRES] [SS.SSTEST = "Date of Migration When Moved for >3 Mths"] [SS.SSCAT = "STUDY CONTINUATION"] In case of migrated/moved from the study area for more than 3 months please provide the date of migration (if done since last visit) Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:N] ☐ [DS.DSDECOD = "NOT RETURNED FOR VISIT"] [DS.DSSCAT = "VISIT CONTINUATION - VISITNUM [visitnum attached to this form]"] [DS.DSCAT = "OTHER EVENT"] No [DS.DSTERM] -> Please select the major reason: [A:SAE] ☐ Serious Adverse Event [A:PTV] ☐ [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] Protocol violation, please specify: A50 [A:CWS] ☐ Consent Withdrawal ->Please specify the reason (Only if the Subject's parents / Legally Acceptable Representative has / have spontaneously explained it): [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] A200 [NOT SUBMITTED] Or tick box if reason not provided [A:N] ☐ [A:MIG] ☐ [SUPPDS.QVAL when QNAM = "MOVEDTC"] Migrated / moved from the study area : Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:LFU] ☐ Lost to follow-up [A:SST] ☐ Sponsor study termination [A:DED] ☐ [DM.DTHDTC] Subject died -> Date of death: Req ☐ / Req ☐ / Req ☐ (2018-2029) [DD.DDORRES] [DD.DDCAT = "STUDY CONTINUATION"] [DD.DDTEST = "Cause of Death"] -> Cause of death: A200 [DD.DDORRES] [DD.DDTEST = "Type of Diagnosis"] [A:VER] ☐ Verbal autopsy [A:MED] ☐ Medical diagnoses Hospitalisation at the time of the visit -> Please make sure that the hospitalisation section has been completed [A:HOS] ☐ [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] [A:OTH] ☐ Other, please specify A200 [SUPPDS.QVAL when QNAM = "PRDECMAX"] -> For serious adverse events (except death) and Other reasons only: Please select who made the decision: [A:I] ☐ Investigator [A:P] ☐ Subject's parents / Legally Acceptable Representatives
5. Tick box if the visit was performed by phone call or other means of virtual contact [Tick box if the visit was performed by phone call or other means of virtual contact]	[SV.SVGRPID = "PHONE CONTACT"] [A:Y] ☐ Yes
PERMANENT DISCONTINUATION [NOT SUBMITTED]	
6. Study discontinuation:	[A:I] ☐ Tick box only if permanent discontinuation, i.e. if the subject definitively withdraws from the study. In this case, terminate the CRF: Complete Vaccination, Outpatient, Hospitalisation, AESI and SAE sections and study conclusion as appropriate
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

Codelist Values Tables: CHECK FOR STUDY CONTINUATION						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciVISITNUM	String		1	1	citmVIS1	itmVISREL
			2	2	citmVIS2	
			3	3	citmVIS3	
			4	4	citmVIS4	

			5	5	citmVIS5	
			6	6	citmVIS6	
			7	7	citmVIS7	
			8	8	citmVIS8	
			9	9	citmVIS9	

EPI-MALARIA-003 VS AME (115056): SIGNS AND SYMPTOMS ()

VISITNO1	
1. Visit Number [read-only]	[XX(Domain).VISITNUM] N4
MEDICAL HISTORY	
2. Is there any change in the conditions listed below since previous visit? [Is there any change in the conditions listed below since previous visit?]	[A:N][NOT SUBMITTED] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "RISKFCR"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "RISKFCR" consists of all selected values, separated by a comma] Please select all that apply [A:RF001] ☐ Malnutrition [A:RF002] ☐ Tuberculosis [A:RF005] ☐ History of temperature >=37.5°C (axillary) [A:RF006] ☐ Malaria [A:RF007] ☐ Known HIV infection [A:RF008] ☐ Anaemia (Hb < 11 g/dL) [A:RF009] ☐ Drugs exposure [A:RF010] ☐ Traditional medicine exposure [A:RF011] ☐ Toxic agent exposure [A:RF099] ☐ [SUPPHO.QVAL when QNAM = "OTHRKSP"] Other, please specify A200
3. Is there any change in the diagnosis of haemoglobinopathy since previous visit? [Is there any change in the diagnosis of haemoglobinopathy since previous visit?]	[SUPPHO.QVAL when QNAM = "HMGLDIAG"] [A:N] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "HMGLSYMP"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "HMGLSYMP" consists of all selected values, separated by a comma] Please select all that apply [A:1] ☐ Thalassemia [A:2] ☐ Sickle Cell Anaemia [A:3] ☐ G6PD deficiency [A:7] ☐ [SUPPHO.QVAL when QNAM = "OTHMGLSP"] Other, please specify A200
4. Is there any change in the comorbidity other than haemoglobinopathy since previous visit? [Is there any change in the comorbidity other than haemoglobinopathy since previous visit?]	[A:N][NOT SUBMITTED] ☐ No [A:Y] ☐ [SUPPHO.QVAL when QNAM = "COMFCR1" or "COMFCR2" or "COMFCR3" or "COMFCR4"] [Note: The calculated value consists of all selected values, separated by a comma. If calculated value is more than 200 characters, it is split into multiple QVAL (with QNAM = "COMFCR1", "COMFCR2", "COMFCR3" and "COMFCR4")] Please select all that apply [A:MH011] ☐ Premature birth [A:MH012] ☐ Difficult birth/ hypoxia [A:MH003] ☐ Congenital birth defect [A:MH001] ☐ [SUPPHO.QVAL when QNAM = "DGNLHOSP"] Diagnosis of last hospitalization A200 [A:MH002] ☐ Developmental retardation [A:MH004] ☐ History of head trauma [A:MH005] ☐ History of joints trauma [A:MH006] ☐ [SUPPHO.QVAL when QNAM = "OTHTRAS1"] History of other trauma Please Specify A200 [A:MH007] ☐ History of serious non neurologic infectious disease (sepsis, peritonitis, internal abscesses) [A:MH008] ☐ History of meningitis /encephalitis [A:MH009] ☐ History of other neurologic or brain disease [A:MH010] ☐ Known epilepsy/ seizures [A:MH013] ☐ Previous abdominal surgery [A:MH014] ☐ Known bowel disfunction [A:MH015] ☐ Known bleeding disorder in the family [A:MH017] ☐ Diabetes mellitus [A:MH019] ☐ Congenital disease of the spine [A:MH021] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDS1"] Other Chronic Disease A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDSP", separated by a comma] [A:1] ☐ If congenital, please select the box [A:MH022] ☐ [SUPPHO.QVAL when QNAM = "OTHCODS1"] Other Congenital Disease A200 [A:MH023] ☐ [SUPPHO.QVAL when QNAM = "OTHCOFS1"] Other comorbidity factor A200 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCODS1", separated by a comma] [A:1] ☐ If congenital, please select the box

CHILD ILL FLAG AND SYMPTOMS [CE.CECAT = "SIGNS AND SYMPTOMS"] [CE.CEEVINTX = "-P48H TO VISIT"] [FA.FACAT = "SIGNS"]

AND SYMPTOMS"]

5.* Does the child have any of the following symptoms at the time of the visit or in the past 48 hours?
 ✓ [Does the child have any of the following symptoms at the time of the visit or in the past 48 hours?]

[A:N][NOT SUBMITTED] ☐ No
 [A:Y] ☐ [CE.CESTDTC]
 Yes -> Onset of first signs & symptoms: / / (2018-2029)

-> Are the following signs and symptoms present at the time of the visit or in the past 48 hours?
 [FA.FASCAT = "TEMPERATURE"] [FA.FAOBJ = "TEMPERATURE >=37.5C"] [FA.FAEVINTX = "-P48H TO VISIT"] [CE.CESCAT = "TEMPERATURE"] [CE.CETERM = "TEMPERATURE >=37.5C"]

Temperature >= 37.5°C (axillary) during visit or in past 48 hours
 [A:Y][CE.CEOCCUR] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"]
 Yes --> please record axillary temperature in °C

[A:N] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CEOCCUR] [CE.CESCAT = "FEVER"] [CE.CETERM = "FEVER"]

Was fever reported by the parents / LAR ?
 [N:1] ☐ Yes
 [N:0] ☐ No
 [CE.CESCAT = "SKIN AND MUCOSA"]

Skin and Mucosa
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:LSN] ☐ Lesions
 [A:HMT] ☐ Hematoma
 [A:ODA] ☐ Oedema
 [A:BDG] ☐ Bleeding

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "NEUROLOGIC"]

Neurologic
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:NSS] ☐ Neck stiffness
 [A:WKS] ☐ Muscle weakness
 [A:BCS] ☐ Behaviour changes
 [A:SZS] ☐ Seizures
 [A:RVS] ☐ Regress in verbal, seeing, hearing or moving capacity
 [A:LOC] ☐ Loss of consciousness
 [A:LTH] ☐ Lethargy
 [A:CC] ☐ Continuous crying

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "RESPIRATORY"]

Respiratory
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:FBG] ☐ abnormal breathing
 [A:NBG] ☐ Cyanosis

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "EYES"]

Eyes
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:YLOW] ☐ Yellow
 [A:RED] ☐ Red or discharge
 [A:DNL] ☐ Sensitivity to light

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "BONES AND JOINTS"]

Bones and joints
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:DIJ] ☐ Difficulty in moving joints
 [A:FDM] ☐ Foot deformation
 [A:SWJ] ☐ Swelling of joints
 [A:HOJ] ☐ Hotness of joints

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "INJECTION SITE"]

Injection site
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:PAN] ☐ Pain
 [A:SWE] ☐ Swelling
 [A:HOT] ☐ Hot

[A:N][CE.CEOCCUR = "N"] ☐ No
 [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
 [CE.CESCAT = "DIGESTION"]

Digestion
 [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] [Note: A Clinical Event record will be generated for each condition selected in this codelist]
 Yes --> Tick all that apply
 [A:VMG] ☐ Vomiting
 [A:VME] ☐ Vomiting everything
 [A:DWB] ☐ Diarrhea
 [A:DRE] ☐ refusal / difficulty to eat or to drink - Change in food / milk intake
 [A:UBF] ☐ Dehydration
 [A:BIS] ☐ Blood in stools

		[A:N][CE.CEOCCUR = "N"] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked [CE.CESCAT = "OTHER SYSTEM"] [A:STP] ☐ Stomach / Abdominal pain Other system [A:Y][CE.CEOCCUR = "Y"] ☐ [CE.CETERM when CE.CEOCCUR = "Y"] Yes --> Please Specify A200 [A:N] ☐ No [A:ND][CE.CESTAT = "NOT DONE"] ☐ Not checked
HEALTH CARE FACILITY		
6.*	Did the study participant visit an Outpatient (consultation) since previous visit? [Did the study participant visit an Outpatient (consultation) since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
7.*	Was the study participant hospitalized since previous visit? [Was the study participant hospitalized since previous visit?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
8.*	Is the study participant referred to any health care facility after this visit? [Is the subject referred to any health care facility after this visit?]	[SUPPCE.QVAL when QNAM = "REFHCF"] [A:N] ☐ No [A:Y] ☐ [SUPPCE.QVAL when QNAM = "HCFTYPE"] Yes --> Please specify type of health care facility [A:LE1] ☐ Primary health care facility [A:HOS] ☐ Hospital Please update vaccination status and provide schedule for next follow up visit
Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR () [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "USUAL PREVENTIVE MEASURES"] [ER.EREVINTX = "SINCE LAST VISIT"]	
VISITNO1	
1. Visit Number <i>[read-only]</i>	[ER.VISITNUM] N4
MALARIA PREVENTIVE MEASURES	
2.* Is there a change in the number of days per week the study participant usually sleeps under a mosquito net since last visit? [Is there a change in the number of days per week the study participant usually sleeps under a mosquito net since last visit?]	[ER.EROCUR] [ER.ERTERM = "Change in frequency of sleeping under a mosquito net"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "SLMNFREQ"] Yes, what's the new frequency? [A:1] ☐ Always [A:2] ☐ Most of time (4 to 6 days per week) [A:3] ☐ Sometimes (1 to 3 days per week) [A:4] ☐ Never
3.* Is there a change in the characteristics of the usually used mosquito net since last visit? [Is there a change in the characteristics of the usually used mosquito net since last visit?]	[ER.EROCUR] [ER.ERTERM = "Change in characteristics of the mosquito net"] [A:N] ☐ No [A:Y] ☐ Yes, what are the new characteristics? [SUPPER.QVAL when QNAM = "MNETUSE"] [A:1] ☐ No use of bednet [SUPPER.QVAL when QNAM = "BNLIY"] -> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:1] ☐ Last impregnation less than 1 year ago [A:2] ☐ Last impregnation more than 1 year ago [A:3] ☐ Never impregnated [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:1] ☐ No [A:2] ☐ < 5 holes [A:3] ☐ >= 5 holes
4.* Was indoor residual spray used since last visit to spray interior walls of study participant's house? [Was indoor residual spray used since last visit to spray interior walls of study participant's house?]	[ER.EROCUR] [ER.ERTERM = "Use of indoor residual spray"] [A:Y] ☐ Yes [A:N] ☐ No
5.* Is there a change in other malaria preventive measures applied to study participant's house since last visit? [Is there a change in other malaria preventive measures applied to study participant's house since last visit?]	[ER.EROCUR] [ER.ERTERM = "Change in other malaria preventive measures applied"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] [Note: The calculated value of SUPPER.QVAL when QNAM = "PRMSRTYP" consists of all selected values, separated by a comma] Yes, Please select which are applicable [A:1] ☐ Mosquito coil [A:2] ☐ Commercial spray (e.g. DOOM) [A:3] ☐ Herbs [A:4] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] Other, please specify A200
6.* Did the study participant receive malaria preventive treatment since last visit? (SMC-IPT) [Did the study participant receive malaria preventive treatment since last visit? (SMC-IPT)]	[ER.EROCUR] [ER.ERTERM = "Received malaria preventive treatment (Seasonal Malaria Chemoprophylaxis - Intermittent Preventive Therapy)"] [A:1] ☐ No [A:2] ☐ Yes, -> please complete medication form
HEALTH CARE SEEKING BEHAVIOR [SS.SSCAT = "HEALTH CARE SEEKING BEHAVIOR"] [SS.SSEVINTX = "SINCE LAST VISIT"]	
7.* Is there a change in the place you usually seek for health care when study participant is ill? [Is there a change in the place you usually seek for health care when study participant is ill?]	[SS.SSORRES] [SS.SSTEST = "Change in Health Care Provider"] [A:N] ☐ No [A:Y] ☐ [SS.SSTEST = "New Health Care Provider"] [SS.SSORRES] Yes, what is the new health care provider you usually contact? [A:1] ☐ Community health worker [A:2] ☐ Primary health care facility [A:3] ☐ Hospital [A:4] ☐ Private clinic [A:5] ☐ Drug seller / pharmacy (without prescription) [A:6] ☐ Traditional medicine [A:7] ☐ [SS.SSORRES] Other health care A200 [SS.SSORRES] [SS.SSTEST = "Distance House and Health Care Provider"] what is the distance between this usually used health care provider and your home? [A:1] ☐ < 5 Km [A:2] ☐ 5 - < 10 Km [A:3] ☐ 10 - < 20 Km [A:4] ☐ 20 - < 30 Km [A:5] ☐ >= 30 Km
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): MALARIA PREVENTION â€ˆC" HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD () [ER.ERPRES = "Y"]	
VISITNO1	
1. Visit Number [read-only]	[ER.VISITNUM] N4
MALARIA PREVENTIVE MEASURES [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "ACTUAL PREVENTIVE MEASURES"]	
2.* Did the study participant sleep last night under a mosquito net?	[ER.EROCCUR] [ER.ERTERM = "Sleep under a mosquito net last night"] [ER.EREVTX = "LAST NIGHT"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNLIY"] Yes ---> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNHOLES"] Yes, ---->How many holes of that size ? [A:1] ☐ < 5 [A:2] ☐ >= 5
HEALTH SEEKING BEHAVIOUR [ER.ERCAT = "HEALTH SEEKING BEHAVIOR"]	
3.* Was the study participant treated for fever or malaria in the last 14 days? [Was the subject treated for fever or malaria in the last 14 days?]	[A:Y][ER.EROCCUR = "Y"] [ER.ERTERM = "Treated for fever or Malaria"] [ER.EREVLINT = "-P14D"] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Yes, Where was the study participant taken for treatment? [A:1] ☐ Home [A:2] ☐ Drug Seller [A:3] ☐ Pharmacy [A:4] ☐ Private Clinic [A:5] ☐ Health Centre [A:6] ☐ Hospital [A:7] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Other, please specify A250 [SUPPER.QVAL when QNAM = "TRTWHEN"] When was the study participant taken for treatment? [A:1] ☐ Onset [A:2] ☐ Subject Did Not Improve [A:3] ☐ Subject Got Worse [A:4] ☐ [SUPPER.QVAL when QNAM = "TRTWHEN"] Other, please specify A200 [SUPPER.QVAL when QNAM = "TRTTPT"] What time was the study participant taken for treatment? [A:1] ☐ Same Day [A:2] ☐ Next Day [A:3] ☐ Two Days Later [A:4] ☐ More Than Two Days Later [A:N][ER.EROCCUR = "N"] ☐ No
EXPOSURE TO ENVIRONMENTAL HAZARDS [ER.ERCAT = "EXPOSURE TO ENVIRONMENTAL HAZARDS"]	
4.* Was the study participant exposed to environmental hazards during last year?	[ER.EROCCUR] [ER.ERTERM = "Exposed to environmental hazards"] [ER.EREVLINT = "-P1Y"] [A:N] ☐ No [A:Y][SUPPER.QVAL = "Y" when QNAM = "EXPPEST"] ☐ Yes, Please select which are applicable [A:1] ☐ [SUPPER.QVAL when QNAM = "FREPEST"] Pesticide [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:2] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPHEM"] Chemicals (other than pesticide) [A:1][SUPPER.QVAL when QNAM = "FREQHEM"] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:3] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPRAD"] Radiations [A:1][SUPPER.QVAL when QNAM = "FREQRAD"] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:4] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPOTHZ"] [SUPPER.QVAL when QNAM = "OTHZSPEC"] Other, please specify A225 [SUPPER.QVAL when QNAM = "FREQOTHZ"] [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely

Key: [*] = Item is required [✓] = Source verification required

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EPI-MALARIA-003 VS AME (115056): LOG STATUS () [NOT SUBMITTED]

MEDICATION

1.*	Have any medications required to be reported per protocol been taken? [Have any medications required to be reported per protocol been taken?]	[A:N] ☐ No [A:Y] ☐ Yes -> Please complete the corresponding page
2.	Medication category [hidden] [Medication category]	☐ [cCMCAT_CMCAT] ☐

VACCINATION

3.* ✓	Has the subject received any vaccination? [Has the subject received any vaccination?]	[A:N] ☐ No [A:Y] ☐ Yes -> Please complete the corresponding page
4.	Vaccination Category [hidden]	☐ [cCMCAT_CMCAT] ☐

Key: [*] = Item is required [✓] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: LOG STATUS						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cCMCAT_CMCAT	String		Concomitant medication	CONCOMITANT MEDICATION	ctmCONCOMITANT_MEDICATION	CMCAT1, CMCAT
			Concomitant vaccination	CONCOMITANT VACCINATION	ctmCONCOMITANT_VACCINATION	
			Vaccination history	VACCINATION HISTORY	ctmVACCINATION_HISTORY	

EPI-MALARIA-003 VS AME (115056): MEDICATION () - Repeating Form									
#									
1									
MEDICATION [CM.CMCAT = "CONCOMITANT MEDICATION"]									
1.	No. [read-only] [No.]	[NOT SUBMITTED] N10							
2.*	Drug name: [Drug Name]	[CM.CMTRT] A100							
3.	Modified reported term [hidden] [For GSK - DM]	[CM.CMMODIFY] A100							
4.	GSK Drug synonym [hidden]	[NOT SUBMITTED] A100							
5.	GSK Drug Collection code [hidden]	[SUPPCM.QVAL when QNAM = "CMGSKCD"] A10							
6.	Failed coding [hidden]	[NOT SUBMITTED] A10							
7.*	Medical indication: [In anticipation of any vaccine reaction]	[CM.CMINDC] Medical indication: A200 [CM.CMINDC] [A:IN ANTICIPATION OF STUDY VACCINE REACTION][When this field is selected, then the text "IN ANTICIPATION OF STUDY VACCINE REACTION" is added to the calculated value of CMINDC, separated by a comma] ☐ In anticipation of any vaccine reaction [A:CHRONIC USE][When this field is selected, then the text "LONG TERM / CHRONIC USE" is added to the calculated value of CMINDC, separated by a comma] ☐ Long term / Chronic use							
8.	Tick box if related to an Expedited AE Report [Already reported in an Expedited AE Report]	[NOT SUBMITTED] [A:Y] ☐ [NOT SUBMITTED] Yes, Expedited AE form number N4							
9.*	How is this medication reported to site staff? [Prescription information reported ?]	[SUPPCM.QVAL when QNAM = "DRUGREP"] [A:1] ☐ Recorded (evidence of prescription) [A:2] ☐ [SUPPCM.QVAL when QNAM = "DRUGTYPE"] Reported [A:1] ☐ Prescribed (without any evidence) [A:2] ☐ Self-medicated							
10.*	Dose: [Dose]	[CM.CMDOSE] xxxxxxxxx.							
11.*	Unit: [Unit]	[CM.CMDOSU] ☐ [cUNIT_CMDOSU] ☐							
12.*	Frequency: [Frequency]	[CM.CMDOFRQ] ☐ [cIFREQ_CMDOFRQ] ☐							
13.*	Route: [Route]	[CM.CMRROUTE] [A:INHALATION] ☐ Inhalation [A:INTRA-ARTICULAR] ☐ Intra-articular [A:INTRADERMAL] ☐ Intradermal [A:INTRAMUSCULAR] ☐ Intramuscular [A:INTRAVENOUS] ☐ Intravenous [A:NASAL] ☐ Nasal [A:PO] ☐ Oral [A:PARENTERAL] ☐ Parenteral [A:RECTAL] ☐ Rectal [A:SUBCUTANEOUS] ☐ Subcutaneous [A:SUBLINGUAL] ☐ Sublingual [A:TOPICAL] ☐ Topical [A:OTHER] ☐ [CM.CMRROUTE] Other, please specify A200 [A:UNKNOWN] ☐ Unknown							
14.*	Start date: [Start date]	[CM.CMSTDTC] ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2012-2029)							
15.*	End date: or tick box if continuing at end of study [End date]	[CM.CMENDDTC] End date: ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2012-2029) [CM.CMENRPT = "ONGOING"] [CM.CMENTPT = "END OF STUDY"] Continuing at end of study? [A:Y] ☐							
16.	Drug name: Generic name is preferred but trade name is preferred in case of multi-component drugs [hidden] [Drug name]	[NOT SUBMITTED] A100							
17.	Drug name: Generic name is preferred but trade name is preferred in case of multi-component drugs [hidden] [Drug name]	[NOT SUBMITTED] A100							
18.	Vaccination Category [hidden]	[NOT SUBMITTED]							

			
19.	Code for CM [hidden] [Code for CM]	[NOT SUBMITTED] 	
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.			

Codelist Values Tables: MEDICATION						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cUNIT_CMDOSU	String		Application	AP	ctmAPPLICATION	itmMED_UNIT
			Blister	BLS	ctmBLISTER_002	
			Caplet	CAPL	ctmCAPLET	
			Capsule Dosing Unit	CAPSULE	ctmCAPSULE_DOSING_UNIT__CAP	
			Centigram	cg	ctmCENTIGRAM	
			Drop	gtt	ctmDROP	
			Enzyme-Linked Immunosorbent Assay Unit	ELISA unit	ctmENZYME_LINKED_IMMUNOSORBENT_ASSAY_UNIT	
			Grain	GR	ctmGRAIN	
			Gram	G	ctmGRAM	
			Gram per Kilogram	g/kg	ctmGRAM_PER_KILOGRAM	
			Gram per Square Meter	g/m2	ctmGRAM_PER_SQUARE_METER	
			g/L	g/L	ctmGRAM_PER_LITER	
			Inch	IN	ctmINCH	
			Injection	INJ	ctmINJECTION	
			Iu x 10^3	IU3	ctmIU_X_10_3	
			Iu x 10^6	IU6	ctmIU_X_10_6	
			Liter	L	ctmLITER	
			Lozenge Dosing Unit	LOZENGE	ctmLOZENGE_DOSING_UNIT	
			Mcg/mg	MCG/MG	ctmMCG_MG	
			Megabecquerel	MBq	ctmMEGABECQUEREL	
			Mg/ml	MGML	ctmMG_ML	
			Micromole	umol	ctmMICROMOLE	
			Micro unit	MCU	ctmMICRO_UNIT	
			Milliequivalent	mEq	ctmMILLIEQUIVALENT	
			Milligram	mg	ctmMILLIGRAM	
			Milligram per Kilogram	mg/kg	ctmMILLIGRAM_PER_KILOGRAM	
			Milligram per Minute	mg/min	ctmMILLIGRAM_PER_MINUTE	
			Milligram per Square Meter	mg/m2	ctmMILLIGRAM_PER_SQUARE_METER	
			Milliliters per Hour	mL/h	ctmMILLILITERS_PER_HOUR	
			Milliliter	mL	ctmMILLILITER	
			Millimeter	mm	ctmMILLIMETER	
			Millimole	mmol	ctmMILLIMOLE	
			Nanogram	ng	ctmNANOGRAM	
			Nebule	NEBULE	ctmNEBULE	
			Ng/kg	NGK	ctmNG_KG	
			Ounce	oz	ctmOUNCE	
			Patch Dosing Unit	PATCH	ctmPATCH_DOSING_UNIT	
			Percentage	%	ctmPERCENTAGE	
			Puff	PUFF	ctmPUFF	
			Sachet dosing unit	SACHET	ctmSACHET_DOSING_UNIT	
			Spray Dosing Unit	SPRAY	ctmSPRAY_DOSING_UNIT	
			Suppository Dosing Unit	SUPPOSITORY	ctmSUPPOSITORY_DOSING_UNIT	
			Tablespoon Dosing Unit	Tbsp	ctmTABLESPOON_DOSING_UNIT	
			Tablet Dosing Unit	TABLET	ctmTABLET_DOSING_UNIT	
			Teaspoon Dosing Unit	tsp	ctmTEASPOON_DOSING_UNIT	
			Ubecquerel	UBQ	ctmUBECQUEREL	
			Ugk	UGK	ctmUGK	
			Unit	U	ctmUNIT	
			Unknown	UNKNOWN	ctmUNKNOWN_002	
			Variable dose	VA	ctmVARIABLE_DOSE	
			Vial Dosing Unit	VIAL	ctmVIAL_DOSING_UNIT	
cIFREQ_CMDOSFRQ	String		3 times per day	TID	ctm3_TIMES_PER_DAY	itmFREQUENCY
			4 times per day	QID	ctm4_TIMES_PER_DAY	
			4 times per week	4 TIMES PER WEEK	ctm4_TIMES_PER_WEEK__QIS	
			5 Times Daily	5 TIMES PER DAY	ctm5_TIMES_DAILY	

			5 Times Per Week	5 TIMES PER WEEK	cltm5_TIMES_PER_WEEK	
			After meal	PC	cltmAFTER_MEAL	
			As needed	PRN	cltmAS_NEEDED	
			Before meal	AC	cltmBEFORE_MEAL	
			Continuous	CONTINUOUS	cltmCONTINUOUS	
			Daily	QD	cltmDAILY	
			Every 2 hours	Q2H	cltmEVERY_2_HOURS	
			Every 2 weeks	EVERY 2 WEEKS	cltmEVERY_2_WEEKS_Q2S	
			Every 3 days	Q3D	cltmEVERY_3_DAYS	
			Every 3 months	Q3M	cltmEVERY_3_MONTHS	
			Every 3 weeks	EVERY 3 WEEKS	cltmEVERY_3_WEEKS_Q3S	
			Every 4 days	Q4D	cltmEVERY_4_DAYS	
			Every 4 hours	Q4H	cltmEVERY_4_HOURS	
			Every evening	QPM	cltmEVERY_EVENING	
			Every hour	QH	cltmEVERY_HOUR	
			Every Month	QM	cltmEVERY_MONTH_PER_MONTH	
			Every morning	QAM	cltmEVERY_MORNING	
			Every other day	QOD	cltmEVERY_OTHER_DAY	
			Every week	EVERY WEEK	cltmEVERY_WEEK_PER_WEEK_QS	
			Once	ONCE	cltmONCE	
			Three times a week	3 TIMES PER WEEK	cltmTHREE_TIMES_A_WEEK_TIS	
			Twice per day	BID	cltmTWICE_PER_DAY	
			Twice per week	2 TIMES PER WEEK	cltmTWICE_PER_WEEK_BIS	
cICMCAT_CMCAT	String		Concomitant medication	CONCOMITANT MEDICATION	cltmCONCOMITANT_MEDICATION	CMCAT
			Concomitant vaccination	CONCOMITANT VACCINATION	cltmCONCOMITANT_VACCINATION	
			Vaccination history	VACCINATION HISTORY	cltmVACCINATION_HISTORY	

EPI-MALARIA-003 VS AME (115056): VACCINATION () - Repeating Form [CM.CMCAT = "CONCOMITANT VACCINATION"]					
#					
1					
VACCINATION					
1.* ✓	Select the Vaccination Category	[CM.CMSCAT] [A:DTP] ☐ DTP type [A:RTS] ☐ RTS,S [A:OTH] ☐ [CM.CMSCAT] Other -> Please specify A200			
2.* ✓	Specify the Vaccine name Trade / Generic name [Vaccine name]	[CM.CMTRT] A60			
3.* ✓	Dose No	[SUPPCM.QVAL when QNAM = "CMDOSNUM"] N4			
4.*	Route: [Route]	[CM.CMROUTE] [A:INHALATION] ☐ Inhalation [A:INTRADERMAL] ☐ Intradermal [A:INTRAMUSCULAR] ☐ Intramuscular [A:INTRAVENOUS] ☐ Intravenous [A:NASAL] ☐ Nasal [A:PO] ☐ Oral [A:PARENTERAL] ☐ Parenteral [A:SUBCUTANEOUS] ☐ Subcutaneous [A:SUBLINGUAL] ☐ Sublingual [A:TRANSDERMAL] ☐ Transdermal [A:OTHER] ☐ Other, please specify A200 [A:UNKNOWN] ☐ Unknown			
5.*	Administration date: [Administration date]	[CM.CMSTDTC] [CM.CMENDTC] ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2012-2029)			
6.	Vaccination Category [hidden]	[NOT SUBMITTED] ☐ [c CMCAT_CMCAT]			
7.	Code for CM [hidden] [Code for CM]	[NOT SUBMITTED] A1			
8.*	Is there a source document confirming information about vaccination	[SUPPCM.QVAL when QNAM = "SRCVACYN"] [A:N] ☐ No [A:Y] ☐ [SUPPCM.QVAL when QNAM = "SRCTYPE"] [Note: The calculated value of SUPPCM.QVAL when QNAM = "SRCTYPE" consists of all selected values, separated by a comma] Yes -> please select all which are applicable [A:1] ☐ Individual Vaccination card [A:2] ☐ Vaccination register from health care facility [A:3] ☐ Vaccination data collected during census round			
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.					

Codelist Values Tables: VACCINATION						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
c CMCAT_CMCAT	String		Concomitant medication	CONCOMITANT MEDICATION	cltmCONCOMITANT_MEDICATION	CMCAT
			Concomitant vaccination	CONCOMITANT VACCINATION	cltmCONCOMITANT_VACCINATION	
			Vaccination history	VACCINATION HISTORY	cltmVACCINATION_HISTORY	

EPI-MALARIA-003 VS AME (115056): OUTPATIENT VISIT STATUS ()		
OUTPATIENT VISIT FLG [NOT SUBMITTED]		
1. *	Are there clinical records of outpatient visits at any health care facility? [Is there record of any visits (without hospitalization) to health care facility?]	[A:Y] ☐ Yes [A:N] ☐ No
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): OUTPATIENT VISIT () - Repeating Form									
#	SLIDE READING DETAILS AND SUPPORTIVE LABORATORY RESULTS								
1									
OUTPATIENT VISIT [HO.HOTERM = "OUTPATIENT VISIT"] [HO.HOCAT = "OUTPATIENT VISIT"] [FA.FACAT = "OUTPATIENT VISIT"]									
1.	Outpatient visit (consultation) number [read-only]				[HO.HOREFID] [HO.HOOCUR = "Y"] N3				
2.*	Outpatient visit date				[HO.HOSTDTC] [HO.HOENDTC] Req/Unk / / Req/Unk / / Req (2018-2029)				
MALARIA [FA.FASCAT = "MALARIA"] [SUPPPR.QVAL = "MALARIA" when QNAM = "RELDIS"] [SUPPLB.QVAL = "MALARIA" when QNAM = "RELDIS"] [SUPPMB.QVAL = "MALARIA" when QNAM = "RELDIS"]									
3.*	Are any signs of uncomplicated Malaria present? [Malaria Uncomplicated]				[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF UNCOMPLICATED MALARIA"] [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] Yes --> (select all that apply) [A:TEM] Temperature >=37.5°C (axillary) [A:ANA] Child unwell [A:OTE] No evidence of vital organ dysfunction				
4.*	Are there any signs of severe malaria present? [Malaria severe]				[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF SEVERE MALARIA"] [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] Yes --> (select all that apply) [A:ACD] Acidosis (a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate >= 5 mmol/L) [A:ANN] Severe malarial anaemia (haemoglobin concentration <= 5 g/dL or a haematocrit of <= 15% in children < 12 years of age with a parasite count > 10,000/micro L) [A:PRO] Prostration (generalised weakness so that the person is unable to sit, stand or walk without assistance) [A:RES] Respiratory distress (rapid, deep, laboured breathing) [A:SEI] Multiple convulsions (more than two episodes within 24 h) [A:CHA] Impaired consciousness (a Glasgow coma score < 11 in children >= 2 years of age or a Blantyre coma score < 3 in children < 2 years of age) [A:HYP] Hypoglycaemia (blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)) [A:SBP] Decompensated shock [Systolic blood pressure (< 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill))] [A:JDC] Jaundice (plasma or serum bilirubin > 50 micro mol/L (3 mg/dL) with a parasite count > 100,000/micro L) [A:PLO] Pulmonary oedema (radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation) [A:RFL] Renal impairment (plasma or serum creatinine > 265 micro mol/L (3 mg/dL) or blood urea > 20 mmol/L) [A:ABL] Significant bleeding (including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena) [A:HPP] Hyperparasitaemia [P. falciparum parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/micro L)] [A:SHO] Compensated shock (capillary refill >= 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension) [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200				
[NOT SUBMITTED] As per Study Protocol, does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE04"] Yes, please specify Expedited AE Number: N4									
5.*	Are there any signs of cerebral malaria in this severe malaria? [Is it a cerebral malaria]				[FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA"] [FA.FAORRES = "N"] [A:Y] Yes, please provide all information [FA.FAORRES] [FA.FATEST = "Type"] Coma Score type [A:1] Glasgow Coma (child >= 2 years) [A:2] Blantyre Coma (child < 2 year) [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA SCORE"] Coma Score result [cICOMA_SCORE] [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA AFTER SEIZURES"] Was there a coma after seizures? [A:Y] Yes [A:NA] NA [FA.FAORRES] [FA.FATEST = "Duration"] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA"] If Yes, please provide Duration of coma A3 [FA.FAORRESU] Duration Unit [cIDURATION_TP]				
6.*	Was Retinoscopy performed ? [retinoscopy was done ?]				[PR.PRPRES = "Y"] [PR.PRCAT = "RETINOSCOPY"] [PR.PRTRT = "RETINOSCOPY"] [PR.PROCUR] [A:Y] [FA.FAOBJ = "RETINOSCOPY"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] Yes, Was retinopathy diagnosed? [A:Y] Yes [A:N] No [A:N] No				
7.*	Was the malaria diagnosis confirmed by Test? [malaria confirmatory test]				[FA.FAOBJ = "MALARIA DIAGNOSIS: CONFIRMATION BY TEST"] [A:Y] [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] Yes --> Test done? [A:RDT] [FA.FAORRES = "RDT"] [FA.FATEST = "Test Type"] [FA.FAOBJ = "MALARIA RAPID DIAGNOSTIC TEST: PLASMODIUM SUBTYPES DIFFERENTIATED"] RDT --> Test able to differentiate the [A:Y] [MB.MBCAT = "MALARIA DIAGNOSTICS"] [MB.MBTST = "Organism Present"] [MB.MBSPEC = "BLOOD"] Plasmodium subtypes: [MB.MBMETHOD = "IMMUNOASSAY"] [MB.MBORRES] Yes, please specify: [A:PO] P. Ovale [A:PV] P. Vivax [A:PM] P. Malaria [A:PF] P. Falciparum [A:N] No [SUPPMB.QVAL when QNAM = "TSTDTC"] Date of RDT testing Req/Unk / / Req/Unk / / Req (2018-2029) [DI.DIVAL when DIPARM = "TRADE NAME"] [DI.DIVAL = "MALARIA RAPID DIAGNOSTIC TEST" when DIPARM = "DEVICE TYPE"] Name of the RDT A200				

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		[A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "PULMONARY TUBERCULOSIS DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "GASTROINTESTINAL DISEASE"] Gastrointestinal disease [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "GASTROINTESTINAL DISEASE DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "URINARY TRACT INFECTIONS"] Urinary tract infections [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "URINARY TRACT INFECTIONS DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "MALNUTRITION"] Malnutrition [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "MALNUTRITION DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "INJURY / POISONING (ACCIDENT)"] Injury / poisoning (accident) [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "INJURY / POISONING (ACCIDENT) DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "HIV"] HIV [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SKIN DISEASE"] Skin disease [A:1][FA.FATEST = "Diagnosis Type"] [FA.FAORRES] [A:2] [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "SKIN DISEASE DIAGNOSIS: CONFIRMATION BY TEST"] Diagnosis confirmed by a test, please specify A200 [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "OTHER DISEASE"] [FA.FAORRES] [FA.FATEST = "Specification"] Other A200
		[A:GAS] [A:URI] [A:MAN] [A:INJ] [A:HIV] [A:SKI] [A:OTO]
SUSPECTED AESI [FA.FAOBJ = "SUSPECTED AESI"] [FA.FASCAT = "DIAGNOSIS RECORDED"]		
10.* ✓	Suspected AESI [Suspected AESI]	[FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Suspected AESI [A:ACU] ☐ Acute disseminated encephalomyelitis (ADEM) [A:ENC] ☐ Encephalitis [A:GUI] ☐ Guillain barre syndrome [A:SEI] ☐ Generalized convulsive seizures [A:DIA] ☐ Diabetes mellitus type 1 [A:HEP] ☐ Hepatic Insufficiency [A:REN] ☐ Renal Insufficiency [A:JUV] ☐ Juvenile Chronic Arthritis [A:STE] ☐ Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [A:ANP] ☐ Anaphylaxis [A:THR] ☐ Thrombocytopenia [A:INC] ☐ Intussusception [A:HSP] ☐ Henoch Schonlein Purpura [A:HHE] ☐ Hypotonic Hyporesponsive Episode (HHE) [A:KD] ☐ Kawasaki Disease [A:ABS] ☐ Injection site abscess [A:FOO] ☐ Foot positional deformation [A:NON] ☐ None [NOT SUBMITTED] As per Study Protocol, does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAE02"]

Yes, please specify Expedited AE Number:

N4

SUSPECTED MENINGITIS

11.* Suspected Meningitis
✓ [Suspected Meningitis]

[FA.FAOBJ = "SUSPECTED MENINGITIS"] [FA.FASCAT = "DIAGNOSIS RECORDED"]
[FA.FAORRES] [FA.FATEST = "Occurrence"]
Suspected Meningitis [A:N] No
[A:Y] Yes

[NOT SUBMITTED]
As per Study Protocol, does this event need to be recorded in the Expedited AE screen? [A:N] No
[A:Y] [SUPPAE.QVAL when QNAM = "AESAEN03"]
Yes, please specify Expedited AE Number:

N4

OTHER AE [FA.FAOBJ = "OTHER AE"] [FA.FASCAT = "DIAGNOSIS RECORDED"]

12.* Other AE (other AE than AESI or meningitis)
✓ [Other AE (other AE than AESI or meningitis)]

[FA.FAORRES] [FA.FATEST = "Occurrence"]
[A:N] No
[A:Y] [FA.FAORRES] [FA.FATEST = "Diagnosis"]
Yes --> Please Specify

A200

STUDY PARTICIPANT REFERRED

13.* Has the study participant been referred to the hospital after this visit?

[SUPPHO.QVAL when QNAM = "REFHOSP"]
[A:N] No
[A:Y] Yes

Key: [*] = Item is required [✓] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: OUTPATIENT VISIT						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciCOMA_SCORE	String		0	1	citmSCORE1	itmCOMA_SCORE
			1	2	citmSCORE2	
			2	3	citmSCORE3	
			3	4	citmSCORE4	
			4	5	citmSCORE5	
			5	6	citmSCORE6	
			6	7	citmSCORE7	
			7	8	citmSCORE8	
			8	9	citmSCORE9	
			9	10	citmSCORE10	
			10	11	citmSCORE11	
			11	12	citmSCORE12	
			12	13	citmSCORE13	
			13	14	citmSCORE14	
			14	15	citmSCORE15	
			15	16	citmSCORE16	
ciDURATION_TP	String		Minutes	1	citmMIN	itmDURATION_MAL_TP
			Hours	2	citmHRS	
			Days	3	citmDAY	

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Annotated Study Book - EPI-MALARIA-003 VS AME (115056)

40/188

EPI-MALARIA-003 VS AME (115056): HOSPITALIZATION: GENERAL INFO () [HO.HOCAT = "HOSPITALIZATION"] [AE.AECAT = "HOSPITALIZATION"] [FA.FACAT = "HOSPITALIZATION"]		
DOV		
1.*	Date of Visit	[SV.SVSTDTCT] [SV.SVENDTCT] Req ☐ / Req ☐ / Req ☐ (2018-2029)
VISIT NO		
2.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
HOSPITALIZATION DETAILS [HO.HOTERM = "HOSPITALIZATION"]		
3.	Date of admission [Date of admission]	[HO.HOSTDTCT] [HO.HOCCUR = "Y"] Req ☐ / Req ☐ / Req ☐ (2018-2029)
4.*	Please complete date of onset of symptoms for primary diagnosis: [Please complete date of onset of symptoms for primary diagnosis]	[SUPPHO.QVAL when QNAM = "PDSTDTCT"] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) NReq ☐ : NReq ☐ 24-hour clock
5.*	In which type of health care facility does the hospitalisation take place [In which type of health care facility does the hospitalisation take place]	[SUPPHO.QVAL when QNAM = "HCFCTYPE"] [A:1] ☐ Primary health care facility [A:2] ☐ [SUPPHO.QVAL when QNAM = "HCFNAME"] Hospital, -> Name of the hospital(s) A500
TEMPERATURE [FA.FASCAT = "TEMPERATURE"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "DURING HOSPITALIZATION"]		
6.*	What was the highest temperature measured during hospitalization? [What was the highest temperature measured during hospitalization?]	[FA.FALOC] [A:RECTAL] ☐ Rectal [A:AX] ☐ Axillary [A:ORL] ☐ Oral [A:ND] ☐ Not Done [FA.FATEST = "Temperature"] [FA.FAORRES] [FA.FAORRESU = "C"] XX.X °C
AESI - meningitis - SAE		
7.*	Is there any AESI, meningitis or SAE (related to study procedure) diagnosed (either suspected or confirmed) at this hospitalization? [Is there any AESI, meningitis or SAE (related to study procedure) diagnosed (either suspected or confirmed) at this hospitalization?]	[NOT SUBMITTED] [A:Y] ☐ Yes --> Please complete related form [A:N] ☐ No
MALARIA [FA.FASCAT = "MALARIA"]		
8.*	Is there any Malaria diagnosed (either suspected or confirmed) at this hospitalization? [Is there any Malaria diagnosed (either suspected or confirmed) at this hospitalization?]	[FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "MALARIA DIAGNOSIS (SUSPECTED OR CONFIRMED)"] Yes --> Please complete the related form [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [A:N] ☐ No
HAEMOGLOBIN MEASUREMENT [FA.FASCAT = "HAEMOGLOBIN MEASUREMENT"] [AE.AESCAT = "HAEMOGLOBIN MEASUREMENT"] [LB.LBSCAT = "HAEMOGLOBIN MEASUREMENT"]		
9.*	Was the haemoglobin test done? (ALL STUDY PARTICIPANT) [Was the haemoglobin test done? (ALL SUBJECTS)]	[A:Y] [FA.FAORRES = "Y"] [FA.FAOBJ = "HAEMOGLOBIN TEST"] [FA.FATEST = "Occurrence"] [LB.LBORRES] [LB.LBTST = "Hemoglobin"] [LB.LBCAT = "HEMATOLOGY"] Yes --> Level of Haemoglobin XXX.XX [AE.AETERM = "ANAEMIA (HAEMOGLOBIN < 11g/dL)"] [AE.AEPRESP = "Y"] [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "ANAEMIA (HAEMOGLOBIN < 11g/dL)"] Is haemoglobin value < 11g/dL? [A:Y] ☐ Yes (Anemia) Yes --> Please complete the related form [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [A:N] [FA.FAORRES] ☐ No = "N" As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENO"] SAE Number N4
OTHER DISEASES [NOT SUBMITTED]		
10.*	Can you record signs and symptoms of any other diseases? [Can you record signs and symptoms of any other diseases?]	[A:Y] ☐ Yes --> Please complete the related form [A:N] ☐ No
OTHER DISEASES DIAGNOSIS [NOT SUBMITTED]		
11.*	Are there any other infectious diseases, malnutrition or injuries diagnosed at this hospitalization? [Are there any other infectious diseases, malnutrition or injuries diagnosed at this hospitalization?]	[A:Y] ☐ Yes --> Please complete the related form [A:N] ☐ No
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): USUAL MALARIA PREVENTIVE MEASURES AND HEALTH SEEKING BEHAVIOUR () [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "USUAL PREVENTIVE MEASURES"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
MALARIA PREVENTIVE MEASURES		
2.*	Usually, how many days per week does the study participant sleep under the mosquito net? [Usually, how many days per week does the study participant sleep under the mosquito net?]	[ER.ERTERM = "Usually sleep under a mosquito net"] [ER.EROCCUR] [A:1] ☐ Always [A:2] ☐ Most of time (4 to 6 days per week) [A:3] ☐ Sometimes (1 to 3 days per week) [A:4] ☐ Never [SUPPER.QVAL when QNAM = "SLMNFREQ"]
3.	What are the characteristics of the usually used mosquito net?	[SUPPER.QVAL when QNAM = "MNETUSE"] [A:1] ☐ No use of bednet [SUPPER.QVAL when QNAM = "BNL1Y"] -> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:1] ☐ Last impregnation less than 1 year ago [A:2] ☐ Last impregnation more than 1 year ago [A:3] ☐ Never impregnated [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:1] ☐ No [A:2] ☐ < 5 holes [A:3] ☐ >= 5 holes
4.	Was indoor residual spray used in past 12 months to spray interior walls of this part of the house? [Was indoor residual spray used in past 12 months to spray interior walls of this part of the house?]	[ER.EREVLINT = "-P12M"] [ER.ERTERM = "Use of indoor residual spray"] [ER.EROCCUR] [A:Y] ☐ [SUPPER.QVAL when QNAM = "HOUSPRAY"] Yes, --> if yes, please specify how many months ago was house sprayed A2 [A:N] ☐ No
5.*	Are other malaria preventive measures usually applied in the study participant's house? [Are other malaria preventive measures usually applied in the study participant's house?]	[ER.ERTERM = "Apply other malaria preventive measures"] [ER.EROCCUR] [N:1] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] [Note: The calculated value of SUPPER.QVAL when QNAM = "PRMSRTYP" consists of all selected values, separated by a comma] Yes, Please select which are applicable [A:1] ☐ Mosquito coil [A:2] ☐ Commercial spray (e.g. DOOM) [A:3] ☐ Herbs [A:4] ☐ [SUPPER.QVAL when QNAM = "PRMSRTYP"] Other, please specify A200 [N:0] ☐ No
6.	Did the study participant ever receive malaria preventive treatment (Seasonal Malaria Chemoprophylaxis &€" intermittent Preventive Therapy)? [Did the study participant ever receive malaria preventive treatment (Seasonal Malaria Chemoprophylaxis &€" intermittent Preventive Therapy)?]	[ER.ERTERM = "Ever received malaria preventive treatment (Seasonal Malaria Chemoprophylaxis - Intermittent Preventive Therapy)"] [A:Y] ☐ [ER.EROCCUR = "Y"] ☐ [SUPPER.QVAL when QNAM = "TRTENR"] Yes, Was the treatment received after enrolment? [A:Y] ☐ Yes (please complete medication form) [A:N] ☐ [ER.EROCCUR = "N"] ☐ [SUPPER.QVAL when QNAM = "PRTTTPT"] No, when was the treatment administered? [A:1] ☐ less than 1 month before enrollment [A:2] ☐ 1 to <6 months before enrollment [A:3] ☐ 6 to <12 months before enrollment [A:4] ☐ 1 year or more before enrollment [A:N] ☐ No
HEALTH CARE SEEKING BEHAVIOR [SS.SSCAT = "HEALTH CARE SEEKING BEHAVIOR"]		
7.*	Where do you usually seek for health care when your child is ill?	[SS.SSTEST = "Health Care Provider Usually Contacted"] [SS.SSORRES] [A:1] ☐ Community health worker [A:2] ☐ Primary health care facility [A:3] ☐ Hospital [A:4] ☐ Private clinic [A:5] ☐ Drug seller / pharmacy (without prescription) [A:6] ☐ Traditional medicine [A:7] ☐ [SS.SSORRES] Other health care A200 [SS.SSTEST = "Distance House and Health Care Provider"] [SS.SSORRES] what is the distance between this usually used health care provider and your home? [A:1] ☐ < 5 Km [A:2] ☐ 5 - < 10 Km [A:3] ☐ 10 - < 20 Km [A:4] ☐ 20 - < 30 Km [A:5] ☐ >= 30 Km
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): MALARIA PREVENTION â€” HEALTH SEEKING BEHAVIOUR - EXPOSURE TO ENVIRONMENTAL HAZARD () [ER.ERPRES = "Y"]	
VISIT NO	
1. Hospitalisation number [read-only]	[ER.VISITNUM] N4
MALARIA PREVENTIVE MEASURES [ER.ERCAT = "MALARIA PREVENTIVE MEASURES"] [ER.ERSCAT = "ACTUAL PREVENTIVE MEASURES"]	
2.* Did the study participant sleep last night under a mosquito net?	[ER.EROCCUR] [ER.ERTERM = "Sleep under a mosquito net last night"] [ER.EREVTX = "LAST NIGHT"] [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNLIY"] Yes ---> Bednet -> New (less than 1 year) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNIMPREG"] -> Bednet -> Impregnated (dipped in liquid to repel mosquitos after purchase) [A:N] ☐ No [A:Y] ☐ Yes [SUPPER.QVAL when QNAM = "BNHOLES"] -> Bednet -> Pierced/torn (holes big enough to let one finger go through) [A:N] ☐ No [A:Y] ☐ [SUPPER.QVAL when QNAM = "BNHOLES"] Yes, ---->How many holes of that size ? [A:1] ☐ < 5 [A:2] ☐ >= 5
HEALTH SEEKING BEHAVIOUR [ER.ERCAT = "HEALTH SEEKING BEHAVIOR"]	
3.* Was the study participant treated for fever or malaria in the last 14 days? [Was the subject treated for fever or malaria in the last 14 days?]	[A:Y][ER.EROCCUR = "Y"] [ER.ERTERM = "Treated for fever or Malaria"] [ER.EREVLINT = "-P14D"] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Yes, Where was the study participant taken for treatment? [A:1] ☐ Home [A:2] ☐ Drug Seller [A:3] ☐ Pharmacy [A:4] ☐ Private Clinic [A:5] ☐ Health Centre [A:6] ☐ Hospital [A:7] ☐ [SUPPER.QVAL when QNAM = "TRTWHERE"] Other, please specify A250 [SUPPER.QVAL when QNAM = "TRTWHEN"] When was the study participant taken for treatment? [A:1] ☐ Onset [A:2] ☐ Subject Did Not Improve [A:3] ☐ Subject Got Worse [A:4] ☐ [SUPPER.QVAL when QNAM = "TRTWHEN"] Other, please specify A200 [SUPPER.QVAL when QNAM = "TRTTPT"] What time was the study participant taken for treatment? [A:1] ☐ Same Day [A:2] ☐ Next Day [A:3] ☐ Two Days Later [A:4] ☐ More Than Two Days Later [A:N][ER.EROCCUR = "N"] ☐ No
EXPOSURE TO ENVIRONMENTAL HAZARDS [ER.ERCAT = "EXPOSURE TO ENVIRONMENTAL HAZARDS"]	
4.* Was the study participant exposed to environmental hazards during last year?	[ER.EROCCUR] [ER.ERTERM = "Exposed to environmental hazards"] [ER.EREVLINT = "-P1Y"] [A:N] ☐ No [A:Y][SUPPER.QVAL = "Y" when QNAM = "EXPPEST"] ☐ Yes, Please select which are applicable [A:1] ☐ [SUPPER.QVAL when QNAM = "FREPEST"] Pesticide [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:2] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPHEM"] Chemicals (other than pesticide) [A:1][SUPPER.QVAL when QNAM = "FREQHEM"] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:3] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPRAD"] Radiations [A:1][SUPPER.QVAL when QNAM = "FREQRAD"] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely [A:4] ☐ [SUPPER.QVAL = "Y" when QNAM = "EXPOTHZ"] [SUPPER.QVAL when QNAM = "OTHZSPEC"] Other, please specify A225 [SUPPER.QVAL when QNAM = "FREQOTHZ"] [A:1] ☐ permanently [A:2] ☐ frequently [A:3] ☐ sometimes [A:4] ☐ rarely
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.	

EPI-MALARIA-003 VS AME (115056): HOSPITALISATION MEDICAL HISTORY ()	
VISIT NO	
1. Hospitalisation number <i>[read-only]</i>	[HO.VISITNUM] N4
RISK FACTORS	
2.* Were any of the conditions listed below present at any time since last month? [Were any of the conditions listed below present at any time since last month?]	[NOT SUBMITTED] [A:N] [NOT SUBMITTED] ☐ No [A:Y] [SUPPHO.QVAL when QNAM = "RISKFCTR"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "RISKFCTR" consists of all selected values, separated by a comma] Yes --> Please select all that apply [A:RF001] ☐ [A:RF002] ☐ [A:RF005] ☐ [A:RF006] ☐ [A:RF007] ☐ [A:RF008] ☐ [A:RF009] ☐ [A:RF010] ☐ [A:RF011] ☐ [A:RF099] ☐ Malnutrition Tuberculosis History of temperature >=37.5°C (axillary) Malaria Known HIV infection Anaemia (Hb < 11 g/dL) Drugs exposure Traditional medicine exposure Toxic agent exposure [SUPPHO.QVAL when QNAM = "OTHRSKSP"] Other --> Please Specify A200
COMORBIDITY FACTORS	
3.* Is there haemoglobinopathy diagnosed in this study participant? [haemoglobinopathy diagnosed in study]	[SUPPHO.QVAL when QNAM = "HMGLDIAG"] [A:N] ☐ No [A:Y] [SUPPHO.QVAL when QNAM = "HMGLSYMP"] [Note: The calculated value of SUPPHO.QVAL when QNAM = "HMGLSYMP" consists of all selected values, separated by a comma] Yes, please select all which are all applicable [A:1] ☐ Thalassemia [A:2] ☐ Sickle Cell Anaemia [A:3] ☐ G6PD deficiency [A:7] ☐ [SUPPHO.QVAL when QNAM = "OTHMGLSP"] Other, please specify A20
4.* Are there any known pre-existing conditions other than haemoglobinopathy? [Are there any known pre-existing conditions?]	[A:N] ☐ No [A:Y] [SUPPHO.QVAL when QNAM = "COMFCTR1" or "COMFCTR2" or "COMFCTR3" or "COMFCTR4"] [Note: The calculated value consists of all selected values, separated by a comma. If calculated value is more than 200 characters, it is split into multiple QVAL (with QNAM = "COMFCTR1", "COMFCTR2", "COMFCTR3" and "COMFCTR4")] Yes --> Select all that apply [A:MH011] ☐ Premature birth [A:MH012] ☐ Difficult birth/ hypoxia [A:MH003] ☐ Congenital birth defect [A:MH001] ☐ [SUPPHO.QVAL when QNAM = "DGNLHOSP"] Past hospitalization --> Diagnosis of last hospitalization A20 [A:MH002] ☐ Developmental retardation [A:MH004] ☐ History of head trauma [A:MH005] ☐ History of joints trauma [A:MH006] ☐ [SUPPHO.QVAL when QNAM = "OTHRASP"] History of other trauma --> Please Specify A200 [A:MH007] ☐ History of serious non neurologic infectious disease (sepsis, peritonitis, internal abscesses) [A:MH008] ☐ History of meningitis /encephalitis [A:MH009] ☐ History of other neurologic or brain disease [A:MH010] ☐ Known epilepsy/ seizures [A:MH013] ☐ Previous abdominal surgery [A:MH014] ☐ Known bowel disfunction [A:MH015] ☐ Known bleeding disorder in the family [A:MH017] ☐ Diabetes mellitus [A:MH019] ☐ Congenital disease of the spine [A:MH021] ☐ [SUPPHO.QVAL when QNAM = "OTHCHDSP"] Other Chronic Disease: A30 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCHDSP", separated by a comma] [A:1] ☐ If congenital, please select the box [A:MH022] ☐ [SUPPHO.QVAL when QNAM = "OTHCODSP"] Other Congenital Disease (Including Known Family Disorders): A30 [A:MH023] ☐ [SUPPHO.QVAL when QNAM = "OTHCOFSP"] Other Comorbidity Factor: A30 [When this field is selected, then the text "CONGENITAL" is added to the calculated value of SUPPHO.QVAL when QNAM = "OTHCOFSP", separated by a comma] [A:1] ☐ If congenital, please select the box
BIOLOGICAL SAMPLES	
5.* Was a blood sample taken? [Was a blood sample taken?]	[NOT SUBMITTED] [A:Y] [LB.LBSPEC = "SERUM" or "BLOOD"] ☐ [LB.LBDTC] Yes --> Date Of Collection: ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [NOT SUBMITTED] please specify number of available tubes with serum N3 [NOT SUBMITTED] please specify number of available tubes with serum in mL XXX.X [A:N] ☐ No

6. *	Is there a portion of CSF sample for long term storage? [Has a blood sample for storage / possible further testing been taken?]	[NOT SUBMITTED] [A:Y][LB.LBSPEC = "CEREBROSPINAL FLUID"] [LB.LBDTC] Yes --> Date Of Collection: ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [NOT SUBMITTED] please specify number of available tubes with CSF N3 [NOT SUBMITTED] please specify number of available tubes with CSF in mL XX.X ☐ No [A:N]
Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): AESI - MENINGITIS â€” SAE () [FA.FASCAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	XX[Domain].VISITNUM N4
AESI - MENINGITIS â€” SAE [FA.FASCAT and FA.FAOBJ = "SAE"]		
2.	SAE related to study procedure (blood draw for any suspected AESI or meningitis case) (if selected, Please complete adequate section) [SAE related to study procedure (blood draw for any suspected AESI or meningitis case) (if selected, Please complete adequate section)]	[FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [FA.FAORRES] [FA.FATEST = "ICD10 Code"] ICD10 Code A200
3.	Encephalitis or Acute Disseminated Encephalomyelitis (ADEM) (if selected, Please complete adequate section) [Encephalitis or Acute Disseminated Encephalomyelitis (ADEM) (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "ENCEPHALITIS OR ACUTE DISSEMINATED ENCEPHALOMYELITIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
4.	Guillain barre syndrome (if selected, Please complete adequate section) [Guillain barrÃ© syndrome (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "GUILLAIN BARRE SYNDROME"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
5.	Generalized convulsive seizures (if selected, Please complete adequate section) [Generalized convulsive seizures (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "GENERALIZED CONVULSIVE SEIZURES"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
6.	Diabetes mellitus type 1 (if selected, Please complete adequate section) [Diabetes mellitus type 1 (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "DIABETES MELLITUS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
7.	Hepatic Insufficiency (if selected, Please complete adequate section) [Hepatic Failure (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "HEPATIC INSUFFICIENCY"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
8.	Renal Insufficiency (if selected, Please complete adequate section) [Renal Failure (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "RENAL INSUFFICIENCY"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
9.	Juvenile Chronic Arthritis (if selected, Please complete adequate section) [Chronic Juvenile Arthritis (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "JUVENILE CHRONIC ARTHRITIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
10.	Stevens Johnson Syndrome (SJS) And Toxic Epidermal Necrolysis (TEN) (if selected, Please complete adequate section) [Stevens Johnsons Syndrom: (SJS) And Toxic Epidermal Necrolysis (TEN) (if selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "STEVENS JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis

		[SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
11. ✓	Anaphylaxis (If selected, Please complete adequate section) [Anaphylaxis (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "ANAPHYLAXIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
12. ✓	Thrombocytopenia (If selected, Please complete adequate section) [Thrombocytopenia (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "THROMBOCYTOPENIA"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
13. ✓	Intussusception (If selected, Please complete adequate section) [Intussusception (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "INTUSSUSCEPTION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
14. ✓	Henoch Schonlein Purpura (If selected, Please complete adequate section) [Henoch Schönlein Purpura (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "HENOCH SCHOLEIN PURPURA"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
15. ✓	Hypotonic Hyporesponsive Episode (HHE) (If selected, Please complete adequate section) [Hypotonic Hyporesponsive Episode (HHE) (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "HYPOTONIC HYPORESPONSIVE EPISODE"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
16. ✓	Kawasaki Disease (If selected, Please complete adequate section) [Kawasaki Disease (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "KAWASAKI DISEASE"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
17. ✓	Injection Site Abscess (If selected, Please complete adequate section) [Abscess At/Near Injection Site (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "INJECTION SITE ABSCESS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
18. ✓	Foot Positional Deformation (If selected, Please complete adequate section) [Foot Positional Deformation (If selected, Please complete adequate section)]	[FA.FASCAT and FA.FAOBJ = "FOOT POSITIONAL DEFORMATION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis [SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
MENINGITIS [FA.FASCAT and FA.FAOBJ = "MENINGITIS"]		
19.* ✓	Is there any meningitis diagnosed at this hospitalisation? [Is there any meningitis diagnosed at this hospitalisation?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [A:Y]... Yes, please complete the corresponding section [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG]... Primary diagnosis [A:2DG]... Secondary diagnosis

			[SUPPAE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200
[A:N] ☐ No			
Key: [*] = Item is required [✔] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.			

EPI-MALARIA-003 VS AME (115056): MALARIA () [AE.AECAT = "HOSPITALIZATION"] [FA.FACAT = "HOSPITALIZATION"]	
VISIT NO	
1.	Hospitalisation number [read-only] XX(Domain).VISITNUM N4
MALARIA [AE.AETERM = "MALARIA"] [AE.AESCAT = "MALARIA"] [FA.FASCAT = "MALARIA"]	
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☒ [SUPPAE.QVAL when QNAM = "AESAE02"] [As per Study Protocol does this event need to be recorded in the Expedited AE screen?] Yes -> Please specify Expedited AE Number N4
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms] [AE.AESTDTC] [SUPPPR.QVAL = "MALARIA" when QNAM = "RELDIS"] [SUPPLB.QVAL = "MALARIA" when QNAM = "RELDIS"] [SUPPMB.QVAL = "MALARIA" when QNAM = "RELDIS"] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029)
4.* ✓	End date of symptoms [AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐
5.* ✓	Are any signs of uncomplicated Malaria present? [Malaria Uncomplicated] [FA.FAOBJ = "SIGNS OF UNCOMPLICATED MALARIA"] [FA.FAORRES] [A:N] ☐ No [A:Y][FA.FATEST = "Occurrence"] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (select all that apply) [A:TEM] ☐ Temperature >= 37.5 °C (axillary) [A:ANA] ☐ Child Unwell [A:OTE] ☐ No evidence of vital organ dysfunction
6.* ✓	Are there any signs of severe malaria present? [Malaria severe] [FA.FAOBJ = "SIGNS OF SEVERE MALARIA"] [FA.FAORRES] [A:N] ☐ No [A:Y][FA.FATEST = "Occurrence"] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (select all that apply) [A:ACD] ☐ Acidosis (a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate >= 5 mmol/L) [A:ANN] ☐ Severe malarial anaemia (haemoglobin concentration <= 5 g/dL or a haematocrit of <= 15% in children < 12 years of age with a parasite count > 10,000/micro L) [A:PRO] ☐ Prostration (generalised weakness so that the person is unable to sit, stand or walk without assistance) [A:RES] ☐ Respiratory distress (rapid, deep, laboured breathing) [A:SEI] ☐ Multiple convulsions (more than two episodes within 24 h) [A:CHA] ☐ Impaired consciousness (a Glasgow coma score < 11 in children >= 2 years of age or a Blantyre coma score < 3 in children < 2 years of age) [A:HYP] ☐ Hypoglycaemia (blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)) [A:SBP] ☐ Decompensated shock [Systolic blood pressure (< 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill))] [A:JDC] ☐ Jaundice (plasma or serum bilirubin > 50 micro mol/L (3 mg/dL) with a parasite count > 100,000/micro L) [A:PLO] ☐ Pulmonary oedema (radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation) [A:RFL] ☐ Renal impairment (plasma or serum creatinine > 265 micro mol/L (3 mg/dL) or blood urea > 20 mmol/L) [A:ABL] ☐ Significant bleeding (including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena) [A:HPP] ☐ Hyperparasitaemia (P. falciparum parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/micro L)) [A:SHO] ☐ Compensated shock (capillary refill >= 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension) [A:OTH] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other A200 Please Specify As per Study Protocol, does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ Yes
7.* ✓	Are there any signs of cerebral malaria in this severe malaria? [Is it a cerebral malaria] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA"] [A:Y] ☐ [FA.FAORRES = "Y"] [FA.FATEST = "Occurrence"] Yes, please provide all information [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA SCORE"] [FA.FAORRES] [FA.FATEST = "Type"] Coma Score type [A:1] ☐ Glasgow Coma (child >= 2 years) [A:2] ☐ Blantyre Coma (child < 2 year) [FA.FAORRES] [FA.FATEST = "Score"] Coma Score result ☐ [cdCOMA_SCORE] [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA AFTER SEIZURES"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Was there a coma after seizures? [A:Y] ☐ Yes [A:NA] ☐ NA [FA.FAOBJ = "SIGNS OF CEREBRAL MALARIA: COMA"] [FA.FAORRES] [FA.FATEST = "Duration"] If Yes, please provide Duration of coma A3 [FA.FAORRESU] Duration Unit ☐ [cdDURATION_TP] [A:N] ☐ No
8.* ✓	Was Retinoscopy performed ? [retinoscopy was done ?] [PR.PRCAT = "RETINOSCOPY"] [PR.PRTRT = "RETINOSCOPY"] [PR.PROCCUR] [A:Y][PR.PRPRESP = "Y"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "RETINOSCOPY"] Yes, was retinopathy diagnosed or not? [A:Y] ☐ Yes [A:N] ☐ No [A:N] ☐ No
9.* ✓	Was the malaria diagnosis confirmed by Test? [malaria confirmatory test] [A:Y][FA.FAORRES = "Y"] ☐ Yes --> Test done? [A:RDT][FA.FAORRES = "RDT"] [FA.FATEST = "Test Type"] [FA.FAOBJ = "MALARIA DIAGNOSIS: CONFIRMATION BY TEST"] ☐ [FA.FAOBJ = "MALARIA RAPID DIAGNOSTIC TEST: PLASMODIUM SUBTYPES DIFFERENTIATED"] [FA.FAORRES] [FA.FATEST = "Result"] RDT --> Test able to differentiate the Plasmodium subtypes: [A:Y] ☐ [MB.MBORRES] [MB.MBCAT = "MALARIA DIAGNOSTICS"] [MB.MBTST = "Organism Present"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "IMMUNOASSAY"] Yes, please specify: [A:PO][Note: The calculated value of MB.MBORRES consists of all selected values, separated by a comma] [A:PV] [A:PM] [A:PF] ☐ P. Ovale ☐ P. Vivax ☐ P. Malaria ☐ P.

[A:SLID] [FA.FAORRES = "SLIDE"] [FA.FATEST = "Test Type"] ☐ Slide --> Please complete the slide reading details
 [FA.FAOBJ] = "MALARIA DIAGNOSIS: CONFIRMATION
 BY TEST")

[A:N] [FA.FATEST = "Occurrence"] [FA.FAORRES = "N"] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "MALARIA DIAGNOSIS NOT CONFIRMED BY TEST"]

No --> Please Specify

[FA.FAORRES] [FA.FATEST = "Result"]

--> [A:RDT] ☐ RDT negative
 [A:SLIDE] ☐ Slide negative
 [A:DIAG] ☐ Test not done

10.									
SLIDE READING DETAILS AND SUPPORTIVE LABORATORY RESULTS Entry [MB.MBCAT = "MALARIA MICROSCOPY"] [MB.MBMETHOD = "SMEAR"] [MB.MBSPEC = "BLOOD"]									
10.1	Date of slide reading [Date of slide reading]	[SUPPMB.QVAL when QNAM = "TSTDTC"] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029)							
10.2	ID of the slide reader [ID of the slide reader]	[SUPPMB.QVAL when QNAM = "TECHID"] A20							
10.3	P.Ovale Result [P.Ovale Result]	[MB.MBTST = "Plasmodium Ovale"] [MB.MBORRES when MBTSTDTL = "IDENTIFICATION"] [A:Ng] ☐ Negative [A:Po] ☐ [MB.MBORRES when MBTSTDTL = "QUANTIFICATION, EXACT"] [MB.MBORRESU = "parasites/uL"] Positive --> Parasites/micro L A7							
10.4	P.Vivax Result [P.Vivax Result]	[MB.MBTST = "Plasmodium Vivax"] [MB.MBORRES when MBTSTDTL = "IDENTIFICATION"] [A:Ng] ☐ Negative [A:Po] ☐ [MB.MBORRES when MBTSTDTL = "QUANTIFICATION, EXACT"] [MB.MBORRESU = "parasites/uL"] Positive --> Parasites/micro L A7							
10.5	P.Malaria Result [P.Malaria Result]	[MB.MBTST = "Plasmodium Malaria"] [MB.MBORRES when MBTSTDTL = "IDENTIFICATION"] [A:Ng] ☐ Negative [A:Po] ☐ [MB.MBORRES when MBTSTDTL = "QUANTIFICATION, EXACT"] [MB.MBORRESU = "parasites/uL"] Positive --> Parasites/micro L A7							
10.6	P.Falciparum [P.Falciparum]	[MB.MBTST = "Plasmodium Falciparum"] [MB.MBORRES when MBTSTDTL = "IDENTIFICATION"] [A:Ng] ☐ Negative [A:Po] ☐ [MB.MBORRES when MBTSTDTL = "QUANTIFICATION, EXACT"] [MB.MBORRESU = "parasites/uL"] Positive --> Parasites/micro L A7							
10.7	Test Done	[LB.LBSCAT = "SUPPORTIVE LABORATORY RESULTS"] [LB.LBTST] [A:LAB1] ☐ Base Deficit [A:LAB2] ☐ Bicarbonate [A:LAB3] ☐ Lactate [A:LAB4] ☐ Glucose [A:LAB5] ☐ Haemoglobin [A:LAB6] ☐ Haematocrit [A:LAB7] ☐ Creatinine [A:LAB8] ☐ Urea [A:LAB9] ☐ Bilirubin [A:LAB0] ☐ [SUPPLB.QVAL when QNAM = "TSOTHR"] Other, please specify A200							
10.8	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)							
10.9	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxxx.xxx							
10.10	Units [Units]	[LB.LBORRESU] A12							

Key: [*] = Item is required [✓] = Source verification required

Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: MALARIA						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciCOMA_SCORE	String		0	1	citmSCORE1	itmCOMA_SCORE
			1	2	citmSCORE2	
			2	3	citmSCORE3	
			3	4	citmSCORE4	
			4	5	citmSCORE5	
			5	6	citmSCORE6	
			6	7	citmSCORE7	
			7	8	citmSCORE8	

			8	9	citmSCORE9	
			9	10	citmSCORE10	
			10	11	citmSCORE11	
			11	12	citmSCORE12	
			12	13	citmSCORE13	
			13	14	citmSCORE14	
			14	15	citmSCORE15	
			15	16	citmSCORE16	
cIDURATION_TP	String		Minutes	1	citmMIN	itmDURATION_MAL_TP
			Hours	2	citmHRS	
			Days	3	citmDAY	

EPI-MALARIA-003 VS AME (115056): OTHER DISEASES SIGNS AND SYMPTOMS ()

VISIT NO		
1.	Hospitalisation number <i>[read-only]</i>	XX(Domain).VISITNUM N4
OTHER DISEASES SIGNS AND SYMPTOMS [CE.CECAT = "HOSPITALIZATION: OTHER DISEASES SIGNS AND SYMPTOMS"] [CE.CEOCCUR = "Y"]		
2.	General [General]	[CE.CETERM] [CE.CESCAT = "GENERAL"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1a] ☐ Temperature >=37.5°C (axillary) [A:2a] ☐ Fatigue [A:3a] ☐ Oedema [A:6a] ☐ Weight less than - 2 SD (and more than - 3 SD) [A:7a] ☐ Weight less than -3 SD [A:8a] ☐ Hyperglycaemia [A:9a] ☐ Hypoglycaemia < 3.3 mmol/L [A:10a] ☐ Weakness [A:11a] ☐ General malaise [A:12a] ☐ Dehydration [A:13a] ☐ Cyanosis [A:14a] ☐ Acute Pain [A:15a] ☐ Chronic pain [A:16a] ☐ Acidosis (plasma bicarbonate < 15 mmol/L) [A:17a] ☐ [CE.CETERM] Other Please Specify A200
3.	Cardiovascular [Cardiovascular]	[CE.CETERM] [CE.CESCAT = "CARDIOVASCULAR"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1b] ☐ Heart failure [A:2b] ☐ Tachycardia [A:3b] ☐ Faint pulse [A:4b] ☐ Low blood pressure [A:5b] ☐ [CE.CETERM] Other Please Specify A200
4.	Respiratory [Respiratory]	[CE.CETERM] [CE.CESCAT = "RESPIRATORY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1c] ☐ Cough [A:2c] ☐ Respiratory distress [A:3c] ☐ [CE.CETERM] Other Please Specify A200
5.	Neurology [Neurology]	[CE.CETERM] [CE.CESCAT = "NEUROLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1d] ☐ Altered consciousness [A:2d] ☐ Coma [A:3d] ☐ Neck stiffness [A:4d] ☐ Opisthotonus [A:5d] ☐ Kernig sign [A:6d] ☐ Prostration [A:7d] ☐ Sensitivity to light [A:8d] ☐ Seizures [A:9d] ☐ Muscular weakness [A:10d] ☐ Muscular spasm [A:11d] ☐ Paralysis [A:13d] ☐ [CE.CETERM] Other Please Specify A200
6.	Skin and mucosa [Skin and mucosa]	[CE.CETERM] [CE.CESCAT = "SKIN AND MUCOSA"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1e] ☐ Redness [A:2e] ☐ Rash [A:3e] ☐ Lesions [A:4e] ☐ Itching [A:5e] ☐ Lymphadenopathy [A:6e] ☐ Ulcer [A:8e] ☐ Loss of hair / nails [A:9e] ☐ [CE.CETERM] Other Please Specify A200
7.	Hematology [Hematology]	[CE.CETERM] [CE.CESCAT = "HEMATOLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1f] ☐ Pallor [A:2f] ☐ Petechia [A:3f] ☐ Bleeding [A:4f] ☐ Bruising [A:5f] ☐ [CE.CETERM] Other Please Specify A200

8.	Gastroenterology [Gastroenterology]	[CE.CETERM] [CE.CESCAT = "GASTROENTEROLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1g] ☐ Dysphagia [A:2g] ☐ Jaundice [A:3g] ☐ Diarrhoea [A:4g] ☐ Vomiting [A:5g] ☐ Abdominal mass [A:6g] ☐ Blood in stool [A:7g] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
9.	Urology [Urology]	[CE.CETERM] [CE.CESCAT = "UROLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1h] ☐ Dysuria [A:2h] ☐ Frequent miction [A:3h] ☐ Purulent urine [A:4h] ☐ Blood in urine [A:5h] ☐ Mass in renal area [A:6h] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
10.	Musculo sceletal / Orthopedics [Musculo sceletal / Orthopedics]	[CE.CETERM] [CE.CESCAT = "MUSCULOSKELETAL / ORTHOPEDICS"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1i] ☐ Broken bone [A:2i] ☐ Pus in joint [A:3i] ☐ Pus in bone [A:4i] ☐ Redness of joints [A:5i] ☐ Joints stiffness [A:6i] ☐ Limping [A:7i] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
11.	Reproductive organs [Reproductive organs]	[CE.CETERM] [CE.CESCAT = "REPRODUCTIVE ORGANS"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1j] ☐ Ulcer on reproductive organs [A:3j] ☐ Discharge [A:4j] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
12.	Psychiatry [Psychiatry]	[CE.CETERM] [CE.CESCAT = "PSYCHIATRY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1k] ☐ Abnormal behaviour [A:2k] ☐ Irritability [A:3k] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
13.	Ophthalmology [Ophthalmology]	[CE.CETERM] [CE.CESCAT = "OPHTHALMOLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1l] ☐ Blurred vision [A:2l] ☐ Redness of eye [A:3l] ☐ Pus in the eye [A:4l] ☐ Wound in the eye [A:5l] ☐ Swelling of the eye [A:6l] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
14.	Otorhinolaryngology [Otorhinolaryngology]	[CE.CETERM] [CE.CESCAT = "OTORHINOLARYNGOLOGY"] [Note: A Clinical Event record will be generated for each condition selected in this codelist] [A:1m] ☐ Throat redness [A:2m] ☐ Running nose [A:3m] ☐ Wound or ulcer in mouth [A:4m] ☐ Pus in the ear [A:5m] ☐ [CE.CETERM] Other ☐ A200 Please Specify	
15.	SAE Number ☒ [SAE Number]	[SUPPAE.QVAL when QNAM = "AESAENO"] Yes -> Please specify Expedited AE Number N4	
Key: [*] = Item is required [☒] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.			

VISIT NO	
1.	Hospitalisation number [read-only] XX(Domain).VISITNUM N4
OTHER DISEASES: DIAGNOSIS	
2. ✓	Respiratory tract infection (other than tuberculosis) [Respiratory tract infection] [CE.CETERM = "RESPIRATORY TRACT INFECTION OTHER THAN TUBERCULOSIS"] [FA.FASCAT = "RESPIRATORY TRACT INFECTION OTHER THAN TUBERCULOSIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "RESPIRATORY TRACT INFECTION OTHER THAN TUBERCULOSIS"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [FA.FAORRES] [FA.FATEST = "Diagnosis Type"] [FA.FAOBJ = "RESPIRATORY TRACT INFECTION OTHER THAN TUBERCULOSIS"] [A:1CD] Clinical diagnosis only [A:2CD] If available, please indicate performed confirmatory diagnostic tests (select all that apply): [A:1DT] [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [FA.FAOBJ = "X RAY"] X ray --> Consistant with Diagnosis? [A:Y] Yes [A:N] No [A:2DT] [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "CULTURE TEST"] Culture Test [A:POS] Positive [A:NEG] Negative As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE01"] Yes -> Please specify Expedited AE Number N4
3. ✓	Gastrointestinal infection [Gastrointestinal infection] [CE.CETERM = "GASTROINTESTINAL INFECTION"] [FA.FASCAT = "GASTROINTESTINAL INFECTION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "GASTROINTESTINAL INFECTION"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [FA.FAORRES] [FA.FATEST = "Diagnosis Type"] [FA.FAOBJ = "GASTROINTESTINAL INFECTION"] [A:1CD] Clinical diagnosis only [A:2CD] If available, please indicate performed confirmatory diagnostic tests (select all that apply): [A:1] [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "STOOL DIRECT EXAM"] Stool direct exam [A:POS] Positive [A:NEG] Negative [A:2] [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "STOOL CULTURE"] Stool Culture [A:POS] Positive [A:NEG] Negative As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE0G"] Yes -> Please specify Expedited AE Number N4
4. ✓	Urinary tract infection [Urinary tract infection] [CE.CETERM = "URINARY TRACT INFECTION"] [FA.FASCAT = "URINARY TRACT INFECTION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "URINARY TRACT INFECTION"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [FA.FAORRES] [FA.FATEST = "Diagnosis Type"] [FA.FAOBJ = "URINARY TRACT INFECTION"] [A:1CD] Clinical diagnosis only [A:2CD] If available, please indicate performed confirmatory diagnostic tests (select all that apply): [A:Y] [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [FA.FAOBJ = "URINE ANALYSIS"] Urine Analysis --> Consistant with Diagnosis? [A:Y] Yes [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "URINE CULTURE"] Urine Culture [A:POS] Positive [A:NEG] Negative As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE0UR"] Yes -> Please specify Expedited AE Number N4
5. ✓	Tuberculosis [Tuberculosis] [CE.CETERM = "TUBERCULOSIS"] [FA.FASCAT = "TUBERCULOSIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "TUBERCULOSIS"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [FA.FAORRES] [FA.FATEST = "Diagnosis Type"] [FA.FAOBJ = "TUBERCULOSIS"] [A:1CD] Clinical diagnosis only [A:2CD] If available, please indicate performed confirmatory diagnostic tests (select all that apply): [A:1TB] [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [FA.FAOBJ = "X RAY"] X ray --> Consistant with Diagnosis? [A:Y] Yes

		[A:2TB] ☐ [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "SPUTUM CULTURE"] [A:N] ☐ No Sputum Culture [A:POS] ☐ Positive [A:NEG] ☐ Negative [A:3TB] ☐ [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "ZIEHL NEELSEN TEST"] Ziehl Neelsen test [A:POS] ☐ Positive [A:NEG] ☐ Negative As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENOU"] Yes -> Please specify Expedited AE Number N4
6. ✓	Skin and mucosal infection [Skin and mucosal infection]	[CE.CETERM = "SKIN AND MUCOSAL INFECTION"] [FA.FASCAT = "SKIN AND MUCOSAL INFECTION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [FA.FAOBJ = "SKIN AND MUCOSAL INFECTION"] [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [FA.FAORRES] [FA.FATEST = "Diagnosis Type"] [FA.FAOBJ = "SKIN AND MUCOSAL INFECTION"] [A:1CD] ☐ Clinical diagnosis only [A:2CD] ☐ If available, please indicate performed confirmatory diagnostic test [A:1SB] ☐ [FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "SWAB CULTURE"] Swab Culture [A:POS] ☐ Positive [A:NEG] ☐ Negative As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENOB"] Yes -> Please specify Expedited AE Number N4
7. ✓	Bone and joints infection [Bone and joints infection]	[CE.CETERM = "BONE AND JOINTS INFECTION"] [FA.FASCAT and FA.FAOBJ = "BONE AND JOINTS INFECTION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [SUPPAE.QVAL when QNAM = "AESAEYNB"] As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENOB"] Yes -> Please specify Expedited AE Number N4
8. ✓	Injuries [Injuries]	[CE.CETERM = "INJURIES"] [FA.FASCAT and FA.FAOBJ = "INJURIES"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENON"] Yes -> Please specify Expedited AE Number N4
9. ✓	Malnutrition [Malnutrition]	[CE.CETERM = "MALNUTRITION"] [FA.FASCAT and FA.FAOBJ = "MALNUTRITION"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENOM"] Yes -> Please specify Expedited AE Number N4
10. ✓	Other [Other]	[FA.FASCAT = "OTHER DISEASE"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis [CE.CETERM] [FA.FAOBJ] Please Specify A30 [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [CO.COVAL when IDVAR = "CESEQ"] Comments A200 As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAEENOT"] Yes -> Please specify Expedited AE Number N4
11.	Other	[FA.FASCAT = "OTHER DISEASE"]

✓	[Other]	[FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [CE.CETERM] [FA.FA08J] Please Specify A30 [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [CO.COVAL when IDVAR = "CESEQ"] Comments A200 As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE1"] Yes -> Please specify Expedited AE Number N4
12.	Other ✓ [Other]	[FA.FASCAT = "OTHER DISEASE"] [FA.FAORRES] [FA.FATEST = "Diagnosis Level"] [A:1DG] Primary diagnosis [A:2DG] Secondary diagnosis [CE.CETERM] [FA.FA08J] Please Specify A30 [SUPPCE.QVAL when QNAM = "ICD10CD"] ICD10 Code A200 [CO.COVAL when IDVAR = "CESEQ"] Comments A200 As per Study Protocol does this event need to be recorded in the Expedited AE screen? [A:N] No [A:Y] [SUPPAE.QVAL when QNAM = "AESAE2"] Yes -> Please specify Expedited AE Number N4
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): DIAGNOSIS AT DISCHARGE ()	
VISIT NO	
1.	Hospitalisation number [read-only] [XX(Domain).VISITNUM] N4
DIAGNOSIS AT DISCHARGE [HO.HOTERM = "HOSPITALIZATION"] [HO.HOCAT = "HOSPITALIZATION"]	
2.* ✓	Please record date of discharge [Please record date of discharge] [HO.HOENDTC] Req ☐ / Req ☐ / Req ☐ (2018-2029)
3. ✓	If a disease other than an AESI meningitis or SAE has been diagnosed during the hospitalization, please evaluate the severity at discharge: [If a disease other than an AESI meningitis or SAE has been diagnosed during the hospitalization, please evaluate the severity at discharge:] [SUPPHO.QVAL when QNAM = "OTDISSEV"] [A:1SI] ☐ Mild [A:2SI] ☐ Moderate [A:3SI] ☐ Severe [A:4SI] ☐ [SUPPHO.QVAL when QNAM = "ICD10CD"] Fatal -> Please specify the ICD-10 code: A200
4. ✓	If a disease other than an AESI, meningitis or SAE has been diagnosed during the hospitalization, please record the outcome at discharge: [If a disease other than an AESI, meningitis or SAE has been diagnosed during the hospitalization, please record the outcome at discharge:] [SUPPHO.QVAL when QNAM = "OTDISOUT"] [A:1] ☐ Fully recovered [A:2] ☐ Recovering [A:3] ☐ Sequelae/ Permanent damage [A:5] ☐ Not resolved [A:4] ☐ Death
5. ✓	Comment [CO.COVAL when IDVAR = "HOSEQ"] A1000
6.	
MedDRA CODE Entry [NOT SUBMITTED]	
6.1	MedDRA code after 1st line LAB result are available [hidden] [MedDRA code after 1st line LAB] A200
6.2	MedDRA code after 2nd line LAB results are available [hidden] [MedDRA code after 2nd line LAB] A200
6.3	MedDRA code after external expert adjudication [hidden] [MedDRA code after external expert adjudication] A200
EPI TEAM [NOT SUBMITTED]	
7.	Last data review date [hidden] [Last data review date] Req ☐ / Req ☐ / Req ☐ (2018-2029)
8.	MDR Name [hidden] A50
9.	Is the data review completed? (all EPI queries closed, no outstanding queries) [hidden] [Is the data review completed? (all EPI queries closed, no outstanding queries)] [A:Y] ☐ Yes --> [A:SR1] ☐ Safety review can start (AESI - meningitis - other if necessary) [A:N] ☐ No [A:SR2] ☐ No safety review needed
10. ✓	What is the preferred term associated to this event? [hidden] What is the preferred term associated to this event? A200 Other, Please specify: A200
11. ✓	What is the preferred term associated to this event? [hidden] What is the preferred term associated to this event? A200 Other, Please specify: A200

12. ✓	What is the preferred term associated to this event? <i>[hidden]</i>	What is the preferred term associated to this event? <i>A200</i> Other, Please specify: <i>A200</i>
13. ✓	What is the preferred term associated to this event? <i>[hidden]</i>	What is the preferred term associated to this event? <i>A200</i> Other, Please specify: <i>A200</i>
14. ✓	What is the preferred term associated to this event? <i>[hidden]</i>	What is the preferred term associated to this event? <i>A200</i> Other, Please specify: <i>A200</i>
15.	Comment <i>[hidden]</i> [Comment]	<i>A1000</i>
SAFETY TEAM <i>[NOT SUBMITTED]</i>		
16.	Last data review date <i>[hidden]</i> [Last data review date]	☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029)
17.	Is the data review completed? <i>[hidden]</i> [Is the data review completed?]	<i>[A:Y]</i> ☐ Yes <i>[A:N]</i> ☐ No
18.	Comment <i>[hidden]</i> [Comment]	<i>A1000</i>
19.		
ADJUDICATION DETAILS Entry <i>[NOT SUBMITTED]</i>		
19.1	PI diagnosis (1st line lab) <i>[hidden]</i> [PI diagnosis]	☐ <i>[cIPIDIAG]</i> ☐
19.2	If PI diagnosis (1st line lab) is other then please specify <i>[hidden]</i>	<i>A2000</i>

	[If other, please specify]	
19.3	Please select type of diagnosis for 1st line lab <i>[hidden]</i>	[A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis
19.4	PI diagnosis (2nd line lab) <i>[hidden]</i>	A200
19.5	Please select type of diagnosis for 2nd line lab <i>[hidden]</i>	[A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis
19.6	GSK internal adjudication <i>[hidden]</i> [GSK internal adjudication]	[A:IA1] ☐ Rejected (study participant does not suffer from the disease) [A:IA2] ☐ inconclusive (study participant probably suffers from the disease, confirmatory tests are not conclusive) [A:IA3] ☐ Confirmed (study participant certainly suffers from the disease)
19.7	Does the case needs to be reviewed by external expert panel <i>[hidden]</i> [does the case needs to be reviewed by external expert panelâ€™s]	[A:Y] ☐ Yes, --> Date case is send for review ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) Case Type : [A:1] ☐ AESI ☐ [cdSUSPECTEDAESI] ☐ [A:2] ☐ Meningitis [A:3] ☐ Doubtful Case [A:4] ☐ Malaria Case No. A10 [A:N] ☐ No
19.8	GSK additional information on diagnosis <i>[hidden]</i> [GSK additional information on diagnosis]	A60
19.9	GSK assessment for meningitis (based on 2nd line lab testing) <i>[hidden]</i> [GSK assessment for meningitis]	☐ [cdMENINGITIS1] ☐
19.10	GSK comment <i>[hidden]</i> [GSK comment]	A60
19.11	External expert adjudication <i>[hidden]</i> [External expert adjudication]	[A:EA1] ☐ Rejected (study participant does not suffer from the disease) [A:EA2] ☐ inconclusive (study participant probably suffers from the disease, confirmatory tests are not conclusive) [A:EA3] ☐ Confirmed (study participant certainly suffers from the disease)
19.12	External expert additional information on diagnosis <i>[hidden]</i> [GSK additional information on diagnosis]	A60
19.13	External expert final assessment for meningitis: <i>[hidden]</i> [External expert final assessment for meningitis]	[A:1] ☐ Aetiology confirmed meningitis [A:1] ☐ Bacterial [A:2] ☐ Viral [A:2] ☐ Probable meningitis [A:3] ☐ Aseptic meningitis [A:4] ☐ Other probable meningitis [A:3] ☐ Clinically suspected meningitis [A:4] ☐ No meningitis
19.14	What is the preferred term associated to this event? <i>[hidden]</i>	☐ [cdADJUDICATIONDETAILS] ☐ Other, Please specify: A200
19.15	Please select type of diagnosis for Preferred term. <i>[hidden]</i>	[A:1DG] ☐ Primary diagnosis [A:2DG] ☐ Secondary diagnosis

Key: [*] = Item is required [✓] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: DIAGNOSIS AT DISCHARGE						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIPIDIAG	String		Clinically diagnosed malaria	PI21	citmPI21	itmPIDIAG
			Uncomplicated malaria, P. falciparum	PI22	citmPI22	
			Severe malaria, P. falciparum	PI23	citmPI23	
			Severe malaria, no Plasmodium species	PI24	citmPI24	
			Cerebral malaria, P. falciparum	PI25	citmPI25	
			Other	PI26	citmPI26	
			Encephalitis or Acute Disseminated Encephalomyelitis (ADEM)	PI1	citmPI1	
			Guillain barre syndrome	PI2	citmPI2	
			Generalized convulsive seizures	PI3	citmPI3	
			Diabetes mellitus type 1	PI4	citmPI4	
			Hepatic Insufficiency	PI5	citmPI5	
			Renal Insufficiency	PI6	citmPI6	
			Juvenile Chronic Arthritis	PI7	citmPI7	
			Stevens Johnson Syndrome And Toxic Epidermal Necrolysis	PI8	citmPI8	
			Anaphylaxis	PI9	citmPI9	
			Thrombocytopenia	PI10	citmPI10	
			Intussusception	PI11	citmPI11	
			Henoch Schonlein Purpura	PI12	citmPI12	

		Hypotonic Hyporesponsive Episode (HHE)	PI13	citmPI13	
		Kawasaki Disease	PI14	citmPI14	
		Injection Site Abscess	PI15	citmPI15	
		Foot Positional Deformation	PI16	citmPI16	
		Malaria	PI18	citmPI18	
		Suspected Meningitis	PI17	citmPI17	
		Bacterial confirmed meningitis	PI19	citmPI19	
		Probable meningitis	PI20	citmP120	
ciSUSPECTEDAESI	String	Acute disseminated encephalomyelitis (ADEM)	ACU	citmACUTEDISSEMINATEDENCEPHALOMYELITIS	itmAESI
		Encephalitis	ENC	citmENCEPHALITIS	
		Guillain barre syndrome	GUI	citmGUILLAINBARRSYNDROME	
		Generalized Seizures	SEI	citmSEIZUR	
		Diabetes mellitus type 1	DIA	citmDIABETESMELLITUSTYPE1	
		Hepatic Insufficiency	HEP	citmHEPATICFAILURE	
		Renal Insufficiency	REN	citmRENALFAILURE	
		Juvenile Chronic Arthritis	JUV	citmJUVENILECHRONICARTHRITIS	
		Stevens johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	STE	citmSTEVENSJOHNSONSYNDROME_SJS_ANDTOXICEPIDERMAL	
		Anaphylaxis	ANP	citmANAPHYLAXIS	
		Thrombocytopenia	THR	citmTHROMBOCYTOPENIA	
		Intussusception	INC	citmINCEP	
		Henoch Schonlein Purpura	HSP	citmHSP	
		Hypotonic Hyporesponsive Episode (HHE)	HHE	citmHHE	
		Kawasaki Disease	KD	citmKD	
		Injection site abscess	ABS	citmABSCESSEINVACCINATIONSITE	
		Foot positional deformation	FOO	citmFOOTPOSITIONALDEFORMATION	
		None	NON	citmNONE1	
ciMENINGITIS1	String	Lymphocytic choriomeningitis	Lymphocytic choriomeningitis	citmLympho	itmGSK_MENINGITIS
		Congenital syphilitic meningitis	Congenital syphilitic meningitis	citmCongenitalsyphiliticmeningitis	
		Herpes simplex meningitis	Herpes simplex meningitis	citmHerpesimplexmeningitis	
		Herpes zoster meningitis	Herpes zoster meningitis	citmHerpeszostermeningitis	
		Melanomatous meningitis	Melanomatous meningitis	citmMelanomatousmeningitis	
		Meningitis	Meningitis	citmMeningitis	
		Aseptic meningitis	Aseptic meningitis	citmAsepticmeningitis	
		Meningitis aspergillus	Meningitis aspergillus	citmMeningitisaspergillus	
		Bacterial meningitis	Bacterial meningitis	citmBacterialmeningitis	
		Meningitis borrelia	Meningitis borrelia	citmMeningitisborrelia	
		Meningitis candida	Meningitis candida	citmMeningitiscandida	
		Meningitis chemical	Meningitis chemical	citmMeningitischemical	
		Meningitis coccidioides	Meningitis coccidioides	citmMeningitisoccidioides	
		Meningitis coxsackie viral	Meningitis coxsackie viral	citmMeningitiscoxsackieviral	
		Meningitis cronobacter	Meningitis cronobacter	citmMeningitiscronobacter	
		Cryptococcal meningitis	Cryptococcal meningitis	citmCryptococcalmeningitis	
		Meningitis echo viral	Meningitis echo viral	citmMeningitiséchoviral	
		Enterococcal meningitis	Enterococcal meningitis	citmEnterococcalmeningitis	
		Meningitis enteroviral	Meningitis enteroviral	citmMeningitisenteroviral	
		Eosinophilic meningitis	Eosinophilic meningitis	citmEosinophilicmeningitis	
		Meningitis exserohilum	Meningitis exserohilum	citmMeningitisexserohilum	
		Fungal meningitis	Fungal meningitis	citmFungalmeningitis	
		Gonococcal meningitis	Gonococcal meningitis	citmGonococcalmeningitis	
		Meningitis haemophilus	Meningitis haemophilus	citmMeningitishemophilus	
		Meningitis herpes	Meningitis herpes	citmMeningitisherpes	
		Meningitis histoplasma	Meningitis histoplasma	citmMeningitishistoplasma	
		Meningitis leptospiral	Meningitis leptospiral	citmMeningitisleptospiral	
		Meningitis listeria	Meningitis listeria	citmMeningitislisteria	
		Meningitis meningococcal	Meningococcal meningitis	citmMeningococcalmeningitis	
		Mumps meningitis	Mumps meningitis	citmMumpsmeningitis	
		Neonatal meningitis	Neonatal meningitis	citmNeonatalmeningitis	
		Meningitis noninfective	Meningitis noninfective	citmMeningitisnoninfective	
		Pneumococcal meningitis	Pneumococcal meningitis	citmPneumococcalmeningitis	
		Salmonella meningitis	Salmonella meningitis	citmSalmonellameningitis	
		Staphylococcal meningitis	Staphylococcal meningitis	citmStaphylococcalmeningitis	
		Streptococcal meningitis	Streptococcal meningitis	citmStreptococcalmeningitis	
		Meningitis toxoplasma	Meningitis toxoplasma	citmMeningitistoxoplasma	

cIADJUDICATIONDETAILS	String	Meningitis trypanosomal	Meningitis trypanosomal	citmMeningitistrypanosomal	itmPREFER_TERM_ADJT
		Tuberculous meningitis	Tuberculous meningitis	citmTuberculousmeningitis	
		Viral meningitis	Viral meningitis	citmViralmeningitis	
		Pachymeningitis	Pachymeningitis	citmPachymeningitis	
		Pseudomonas aeruginosa meningitis	Pseudomonas aeruginosa meningitis	citmPseudomonas	
		Other	99	citmOTHER_99	
		Acute disseminated encephalomyelitis	Acute disseminated encephalomyelitis	citmAcutedis	
		Anaphylaxis	Anaphylaxis	citmAnaphylaxis	
		Aseptic meningitis	Aseptic meningitis	citmAsepticmeningitis	
		Bacterial meningitis	Bacterial meningitis	citmBacterialmeningitis	
		Cleft foot	Cleft foot	citmCLEFTFOOT	
		Congenital clubfoot	Congenital clubfoot	citmCONGENITA	
		Congenital foot malformation	Congenital foot malformation	citmCONGENITALF	
		Congenital syphilitic meningitis	Congenital syphilitic meningitis	citmCongenitalsyphiliticmeningitis	
		Congenital valgus foot deformity	Congenital valgus foot deformity	citmCONGENITALVAL	
		Congenital varus deformity of foot NOS	Congenital varus deformity of foot NOS	citmCONGENITAL	
		Convulsions generalized	Convulsions generalized	citmConvulsionsgeneralized	
		Cryptococcal meningitis	Cryptococcal meningitis	citmCryptococcalmeningitis	
		Eosinophilic meningitis	Eosinophilic meningitis	citmEosinophilicmeningitis	
		Encephalitis	Encephalitis	citmEncephalitis	
		Enterococcal meningitis	Enterococcal meningitis	citmEnterococcalmeningitis	
		Foot agenesis	Foot agenesis	citmFOOTAGENESIS	
		Fungal meningitis	Fungal meningitis	citmFungalmeningitis	
		Gonococcal meningitis	Gonococcal meningitis	citmGonococcalmeningitis	
		Guillain Barre syndrome	Guillain Barre syndrome	citmGuillainBarresyndrome	
		Henoch-Schonlein purpura	henochschonl	citmhenochschonl	
		Hepatic insufficiency	Hepatic insufficiency	citmHepaticinsufficiency	
		Herpes simplex meningitis	Herpes simplex meningitis	citmHerpesimplexmeningitis	
		Herpes zoster meningitis	Herpes zoster meningitis	citmHerpeszostermeningitis	
		Hypotonic-hyporesponsive episode	hypotonic	citmhypotonic	
		Injection site abscess	injection	citminjection	
		Intussusception	1	citmINTUSSUS	
		Juvenile rheumatoid arthritis	Juvenile rheumatoid arthritis	citmJUVENILER	
		Kawasaki's disease	Kawasaki's disease	citmKAWASAKID	
		Lymphocytic choriomeningitis	Lymphocytic choriomeningitis	citmLympho	
		Malformation foot	Malformation foot	citmMALFORMATIONFOOT	
		Melanomatous meningitis	Melanomatous meningitis	citmMelanomatousmeningitis	
		Meningitis	Meningitis	citmMeningitis	
		Meningitis aspergillus	Meningitis aspergillus	citmMeningitisaspergillus	
		Meningitis borrelia	Meningitis borrelia	citmMeningitisborrelia	
		Meningitis candida	Meningitis candida	citmMeningitiscandida	
		Meningitis chemical	Meningitis chemical	citmMeningitischemical	
		Meningitis coccidioides	Meningitis coccidioides	citmMeningitiscoccidioides	
		Meningitis coxsackie viral	Meningitis coxsackie viral	citmMeningitiscoxsackieviral	
		Meningitis cronobacter	Meningitis cronobacter	citmMeningitiscronobacter	
		Meningitis echo viral	Meningitis echo viral	citmMeningitisechoviral	
		Meningitis enteroviral	Meningitis enteroviral	citmMeningitisenteroviral	
		Meningitis exserohilum	Meningitis exserohilum	citmMeningitisexserohilum	
		Meningitis haemophilus	Meningitis haemophilus	citmMeningitishemophilus	
		Meningitis herpes	Meningitis herpes	citmMeningitisherpes	
		Meningitis histoplasma	Meningitis histoplasma	citmMeningitishistoplasma	
		Meningitis leptospiral	Meningitis leptospiral	citmMeningitisleptospiral	
		Meningitis listeria	Meningitis listeria	citmMeningitislisteria	
		Meningitis meningococcal	Meningococcal meningitis	citmMeningococcalmeningitis	
		Meningitis noninfective	Meningitis noninfective	citmMeningitisnoninfective	
		Meningitis toxoplasmal	Meningitis toxoplasmal	citmMeningitistoxoplasmal	
		Meningitis trypanosomal	Meningitis trypanosomal	citmMeningitistrypanosomal	
		Mumps meningitis	Mumps meningitis	citmMumpsmeningitis	
		Neonatal meningitis	Neonatal meningitis	citmNeonatalmeningitis	
		Pachymeningitis	Pachymeningitis	citmPachymeningitis	
		Pneumococcal meningitis	Pneumococcal meningitis	citmPneumococcalmeningitis	
		Pseudomonas aeruginosa meningitis	Pseudomonas aeruginosa meningitis	citmPseudomonas	
		Renal insufficiency	Renal insufficiency	citmRenalinsufficiency	

		Salmonella meningitis	Salmonella meningitis	citmSalmonellameningitis
		Staphylococcal meningitis	Staphylococcal meningitis	citmStaphylococcalmeningitis
		Stevens Johnson syndrome	Stevens Johnson syndrome	citmStevensJohnsonsyrndrome
		Streptococcal meningitis	Streptococcal meningitis	citmStreptococcalmeningitis
		Thrombocytopenia	Thrombotopenia	citmTHROMBOTOPENIA
		Toxic epidermal necrolysis	Toxic epidermal necrolysis	citmToxicepidermalnecrolysis
		Tuberculous meningitis	Tuberculous meningitis	citmTuberculousmeningitis
		Type I diabetes mellitus	Type I diabetes mellitus	citmTypeIdiabetesmellitus
		Viral meningitis	Viral meningitis	citmViralmeningitis
		Other	99	citmOTHER_99

EPI-MALARIA-003 VS AME (115056): ENCEPHALITIS /ADEM () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
ENCEPHALITIS OR ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) [AE.AESCAT = "ENCEPHALITIS OR ACUTE DISSEMINATED ENCEPHALOMYELITIS"] [FA.FASCAT = "ENCEPHALITIS OR ACUTE DISSEMINATED ENCEPHALOMYELITIS"]		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [SUPPAE.QVAL when QNAM = "AESAENO"] Yes -> Please specify Expedited AE Number N4
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] [Note: See CRF Page 96 for corresponding AETERM annotation] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029)
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] Ongoing at Discharge [A:1DC] ☐
5.* ✓	Please record type of onset (tick only one of the options) [Please record type of onset (tick only one of the options)]	[SUPPAE.QVAL when QNAM = "ONSETTYP"] [A:1TP] ☐ Acute onset (evolving over minutes to hours) [A:2TP] ☐ Sub-acute onset (evolving over hours to days)
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
6.* ✓	Are there any general signs present? [Are there any major signs and symptoms?]	[FA.FAOBJ = "GENERAL SIGNS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> Select all that apply [A:009][FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:101] ☐ [A:066] ☐ [A:102] ☐ [A:038] ☐ [A:040] ☐ [A:103] ☐ [A:025] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5 °C (axillary) If ticked record highest Axillary temperature from onset until discharge XX.X ☐ Headache ☐ Vomiting ☐ Bulging fontanelle ☐ Neck stiffness ☐ Kernigâ€™s signs ☐ Purpura [FA.FAORRES] [FA.FATEST = "Specification"] Other --> A200 Please Specify
7.* ✓	Are there signs of Encephalopathy? [Encephalopathy]	[FA.FAOBJ = "SIGNS OF ENCEPHALOPATHY"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (Select all that apply) [A:033] ☐ Decreased or altered level of consciousness [A:104] ☐ Lethargy [A:105] ☐ Personality changes >24 h [A:106] ☐ Decreased or absent eye contact [A:107] ☐ Decreased or absent response to stimuli (pain, heat, noise) [A:108] ☐ Decreased arousability [A:109] ☐ [FA.FAORRES] [FA.FATEST = "Type"] [FA.FAOBJ = "SEIZURES ASSOCIATED WITH LOSS OF CONSCIOUSNESS"] Seizures associated with loss of consciousness [A:FOC] ☐ Focal [A:GEN] ☐ Generalized [A:SEN] ☐ Sensitive [A:CONV] ☐ Convulsive [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Number of Episodes"] Number of seizures episodes between onset until discharge N2 [A:037] ☐ [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "COMA: LOWEST OBSERVED SCORE"] Coma --> indicate lowest observed score N3 [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "COMA: SCORE USED"] and Score used [A:COMA_SCORE] ☐ [A:XXX] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200
8.* ✓	Are there focal or multifocal neurological findings? [multifocal neurological findings]	[FA.FAOBJ = "(MULTI)FOCAL NEUROLOGICAL FINDINGS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (Select all that apply) [A:110] ☐ Aphasia , alexia, agraphia, cortical blindness [A:111] ☐ Cranial nerve abnormality/abnormalities [A:112] ☐ Visual field defect [A:113] ☐ Presence of primitive reflexes (Babinskiâ€™s sign, Glabellar, Snout/Sucking reflex) [A:115] ☐ [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "MOTOR WEAKNESS"] Motor weakness [A:DIF] ☐ Diffuse [A:FOC] ☐ Focal [A:116] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "SENSORY ABNORMALITIES"] Sensory abnormalities [A:POS] ☐ Positive [A:NEG] ☐ Negative [A:SENSO] ☐ Sensory level [A:ASYM] ☐ Asymmetric [A:117] ☐ [FA.FAORRES] [FA.FATEST = "Type"] [FA.FAOBJ = "ALTERED DEEP TENDON REFLEXES UPPER EXTREMITIES"] Altered deep tendon reflexes upper extremities [A:HYPO_RFLX] ☐ Hyporeflexia [A:HYPER_RFLX] ☐ Hyperreflexia

		Units A12	
		[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
17.2	Bleeding time [Bleeding time]	[LB.LBTTEST = "Bleeding Time"] [LB.LBORRES] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) Result [A:N] ☐ Normal [A:A] ☐ Abnormal	
BLOOD CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "BLOOD CULTURE"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "MICROBIAL CULTURE"]			
18.*	Was Blood culture done? [Was Blood culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
19.*	Blood culture [Blood culture]	[MB.MBTTEST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) [MB.MBORRES] Result [A:POS] ☐ [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOHR1"] Positive, Please Specify A200 [A:NEG] ☐ Negative	
20.*	Other, Please specify:	[MB.MBORRES] [When this field is completed, then the submitted text is added to the calculated value of MB.MBORRES, separated by a comma] A200	
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
21.*	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) [A:N] ☐ No	
22.*	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes -> Date of antibiotic started Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done	
23.*	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other -> Please specify A200 [A:5] ☐ Not documented	
24.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab	
25.*	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:N] ☐ No	
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
26.*	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
27.	CSF leukocytes [CSF leukocytes]	[LB.LBTTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
28.*	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
29.	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
30.	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
CSF EXAMINATION/STAINING [NOT SUBMITTED]			
31.*	Were CSF Examination/Staining tests done?	[A:N] ☐ No	

✓	[Were CSF Examination/Staining tests done?]	[A:Y] ☐ Yes
32. ✓		
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
32.1* ✓	CSF test Done [CSF test Done]	[LB.LBTTEST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)
32.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
32.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]		
33.* ✓	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
34. ✓	CSF Culture [CSF Culture]	[MB.MBTTEST = "Organism Present"] [SUPPMB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [MB.MBORRES] Result [A:POS] ☐ [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 Positive, Please Specify [A:NEG] ☐ Negative
CSF SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
35.* ✓	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
36. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
37. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
38. ✓		
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
38.1* ✓	Serology Test Done [Serology Test Done]	[LB.LBTTEST] ☐ [c]SEROTEST ☐
38.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
38.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
39.* ✓	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
40. ✓	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:NEG] ☐ Negative [A:POS] ☐ [LB.LBTTEST when LBORRES = "POSITIVE"] ☐ Negative ☐ [LB.LBORRES] Positive --> Specify Pathogen [A:ADENO] ☐ Adenovirus [A:CMV] ☐ CMV [A:EBV] ☐ EBV [A:ENTERO] ☐ Enterovirus [A:HIV01] ☐ HIV [A:HSV01] ☐ HSV1 [A:HHV-6] ☐ HHV-6 [A:HSV02] ☐ HSV2 [A:MUM] ☐ Mumps [A:RABIS] ☐ Rabies virus [A:VZV] ☐ VZV [A:INFLU] ☐ H. influenzae type b [A:CSF_LIST] ☐ Listeria [A:MEN01] ☐ Meningococcus

			[A:PNEU01] ☐ Pneumococcus [A:RICK] ☐ Rickettsia [A:SALSP] ☐ Salmonella sp [A:CSF_PFAL] ☐ P. falciparum [A:TUBR] ☐ M. tuberculosis [A:CSF_OTH] ☐ [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] CSF Other, Please specify A100
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
41.* ✓	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
42. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
43. ✓			
IMMUNO ELECTROPHORESIS TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTROPHORESIS TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
43.1* ✓	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTEST] ☐ [cIMMUNOELECTRO] ☐	
43.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
43.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
44.* ✓	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
45. ✓	Toxin Investigation [Toxin Investigation]	[LB.LBTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
46. ✓	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal	
47. ✓	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal	
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			
48.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
49. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other --> Please Specify A200 [PR.PRSTDTC] [PR.PRENDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No	
50. ✓			
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPREP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			

50.1* ✓	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] [c RADIOEXAM]
50.2 ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] NReq / NReq / NReq (2018-2029)
50.3* ✓	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] Yes [A:N] No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
51.* ✓	Was there a consultation with a specialist? [Was there a consultation with a neurologist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] No [A:Y] [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> was the consultation with RAFT [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] No [A:Y] Yes
52.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for Encephalitis? [Is the disease fulfilling the protocol case definition (Job Aid) for Encephalitis?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR ENCEPHALITIS"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, --> What is the final diagnosis for this disease A200 [A:Y] [FA.FATEST = "Level of Diagnostic Certainty"] [FA.FAORRES] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] 1 [A:2DGC] 2 [A:3DGC] 3
53.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for ADEM? [Is the disease fulfilling the protocol case definition (Job Aid) for ADEM?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR ADEM"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] No [A:Y] [FA.FATEST = "Level of Diagnostic Certainty"] [FA.FAORRES] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] 1 [A:2DGC] 2 [A:3DGC] 3
54.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] No [A:Y] [AE.AESEV] Yes --> [A:MIL] Mild [A:MOD] Moderate [A:SEV] Severe [A:FAT] Fatal
55.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] Fully recovered [A:RECOV] Recovering [A:SEQ] Sequelae [A:NRES] Not resolved [A:DEA] Death
56. ✓	Was ADEM confirmed by the medical exam 3 months after the nadir of symptoms? [Was ADEM confirmed by the medical exam 3 months after the nadir of symptoms?]	[FA.FAOBJ = "ADEM CONFIRMED BY MEDICAL EXAM 3 MONTHS AFTER NADIR OF SYMPTOMS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] No [A:Y] Yes
57.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Acute disseminated encephalomyelitis] Acute disseminated encephalomyelitis [A:Encephalitis] Encephalitis [A:99][NOT SUBMITTED] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"] [SUPPPR.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
58. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:Acute disseminated encephalomyelitis] Acute disseminated encephalomyelitis [A:Encephalitis] Encephalitis [A:99][NOT SUBMITTED] [FA.FAORRES] [FA.FATEST = "Diagnosis"] (Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results) Other, Please specify: A200
59. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: ENCEPHALITIS / ADEM						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cCOMA_SCOREE	String		GLASGOW	GLAS	citmGLAS	itmSCORE
			BLANTYRE	BLANT	citmBLANT	
cBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST

		Platelets	2BL	citmPLT	
		White blood cells	3BL	citmWBC	
		Neutrophils	4BL	citmNEUT	
		Lymphocytes	5BL	citmLYMP	
		Monocytes	6BL	citmMONO	
		Basophils	7BL	citmBASO	
		Eosinophils	8BL	citmEOS	
cIBIO_CHEM	String	Total bilirubin	1	citmBIO1	itmBIOCHEMTEST_ADEM
		Conjugated bilirubin	2	citmBIO2	
		Alanine amino transferase (ALT)	3	citmBIO3	
		Aspartate amino transferase (AST)	4	citmBIO4	
		Alkaline Phosphatase (ALP)	5	citmBIO5	
		Total protein	6	citmBIO6	
		Albumin	7	citmBIO7	
		Serum urea nitrogen	8	citmBIO8	
		Serum creatinine	9	citmBIO9	
		Serum sodium	10	citmBIO10	
		Serum potassium	11	citmBIO11	
		Serum chloride	12	citmBIO12	
		Serum calcium	14	citmBIO14	
		Serum magnesium	15	citmBIO15	
		Vitamin B12	16	citmBIO16	
		Folate	17	citmBIO17	
		Blood glucose	18	citmBIO18	
		Oral glucose tolerance test	19	citmBIO19	
		Fasting blood sugar	20	citmBIO20	
		Hemoglobin A1C	21	citmBIO21	
		Lipids	22	citmBIO22	
cICOAGTEST	String	Prothrombine time (PT)	1CT	citmPT	itmCOAGTST
		International normalized ratio (INR)	2CT	citmINTERNORM	
		Activated coagulation time (ACT)	3CT	citmACTCOAG	
		Activated partial thromboplastine time (APTT)	4CT	citmACTPART	
cISEROTEST	String	CMV	1ST	citmCMV	itmSEROTEST
		EBV	2ST	citmEBV	
		Enterovirus	3ST	citmENTVIR	
		HIV	4ST	citmHIVIR	
		HSV	5ST	citmHSV	
		Mumps	6ST	citmMUMPS	
		VZV	7ST	citmVZV	
		H. influenzae type b	8ST	citmHINFb	
		Listeria	9ST	citmLIST	
		Meningococcus	10ST	citmMENGS	
		Pneumococcus	11ST	citmPNEUM	
		Rickettsia	12ST	citmRICK	
		Salmonella	13ST	citmSALM	
		M. tuberculosis	14ST	citmMTUB	
		Autoantibodies	15ST	citmAUTO	
cIMMUNOELECTRO	String	H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
		Meningococcus	2IM	citmMENG	
		Pneumococcus	3IM	citmPNEU	
		Not resolved	4IM	citmNOTRES	
cIRADIOEXAM	String	CT scan	1RE	citmRE1	itmRADIOEXAM
		Electrocardiogram	2RE	citmRE2	
		Electroencephalogram	3RE	citmRE3	
		Electromyogram	4RE	citmRE4	
		MRI	5RE	citmRE5	
		Non-barium or air-contrast enema	6RE	citmRE6	
		X-ray	7RE	citmRE7	
		X-ray abdomen	8RE	citmRE8	
		Ultrasound	9RE	citmRE9	
		Ultrasound &C° cardiac	10RE	citmRE10	

EPI-MALARIA-003 VS AME (115056): GUILLAIN BARRE SYNDROME () [AE.AECAT = "HOSPITALIZATION"]			
VISIT NO			
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4	
GUILLAIN BARRE SYNDROME [AE.AESCAT = "GUILLAIN BARRE SYNDROME"] [FA.FASCAT = "GUILLAIN BARRE SYNDROME"]			
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4	
3.* ✓	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] [Note: See CRF Page 108 for corresponding AETERM annotation] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐	
SIGN AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]			
5.* ✓	Are any signs present? [Are any signs present?]	[FA.FAOBJ = "SIGNS AND SYMPTOMS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> Select all that apply [A:009][FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:001] [A:002] [A:003] [A:004] [A:005] [A:006] [A:007] [A:008] [A:010] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) ☐ If ticked record highest Axillary temperature from onset until discharge ☐ Bilateral weakness with flaccid extremities ☐ Decreased or absent deep tendon reflexes in weak limbs ☐ Absent sensitivity in legs ☐ Dysphagia (difficult swallowing) ☐ Facial paralysis ☐ Inability to close eyelids ☐ Inability to move eyes ☐ Respiratory distress ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other A200 Please Specify	
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]			
6.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No	
7.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab	
8.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No	
BLOOD COUNT [NOT SUBMITTED]			
9.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[A:N] ☐ No [A:Y] ☐ Yes	
10. ✓			
BLOOD TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD TEST"] [LB.LBSPEC = "BLOOD"]			
10.1.* ✓	Blood Test Done [Blood Test Done]	[LB.LBTST] ☐ [cIBLDTST] ☐	
10.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
10.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jD0I6VG2C? domain=xxx.xxx	
10.4 ✓	Units [Units]	[LB.LBORRESU] A12	
10.5.* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
BLOOD SMEAR [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"] [LB.LBMETHOD = "SMEAR"]			
11.* ✓	Was blood smear done? [Was blood smear done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
12. ✓	Haemolysis [Haemolysis]	[LB.LBTST = "Hemolytic Index"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
13. ✓	Sickle cells anemia test [Sickle cells anemia test]	[LB.LBTST = "Sickle Cell Anaemia"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES]	

		Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
BLOOD CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "BLOOD CULTURE"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "MICROBIAL CULTURE"]			
14.* ✓	Was Blood culture done? [Was Blood culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
15.* ✓	Blood culture [Blood culture]	[MB.MBTTEST = "Organism Present"] [SUPPMB.QVAL when QNAM = "TSTDTC"] [MB.MBORRES] Test Date / / (2018-2029) Result [A:POS] Positive, Specify [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [A:NEG] ☐ Negative	
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]			
16.* ✓	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
17.* ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
18.* ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
19.* ✓			
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]			
19.1.* ✓	Viral Serology Tests [Viral Serology Tests]	[LB.LBTTEST] ☐ [c]SEROTESTVIRAL ☐	
19.2.* ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] / / (2018-2029)	
19.3.* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
20.* ✓	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
21.* ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
22.* ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
23.* ✓			
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
23.1.* ✓	Bacterial Serology [Bacterial Serology]	[LB.LBTTEST] ☐ [c]TESTCATE ☐	
23.2.* ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] / / (2018-2029)	
23.3.* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]			
24.* ✓	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply	
25.* ✓	Autoantibodies [Autoantibodies]	[LB.LBTTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
26.* ✓	Rheumatoid factor [Rheumatoid factor]	[LB.LBTTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date / / (2018-2029) Result [A:POS] Positive [A:NEG] Negative	
27.* ✓	Medications	[LB.LBTTEST = "Medications"]	

✓		[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
28. ✓	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
29. ✓	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
30. ✓	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
31. * ✓	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] [LB.LBDTC] Yes --> specify lumbar puncture date [NReq] / [NReq] / [NReq] (2018-2029) [A:N] No
32. * ✓	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes --> Date of antibiotic started [Req] / [Req] / [Req] (2018-2029) [A:N] No [A:ND] CSF Not done
33. * ✓	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] Clear [A:2] Turbid [A:3] Yellowish [A:4] [SUPPLB.QVAL when QNAM = "ASPECT"] Other --> Please specify A200 [A:5] Not documented
34.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3 - Lost in second line lab
35. * ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date [Req] / [Req] / [Req] (2018-2029) [A:N] No
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
36. * ✓	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
37. ✓	CSF leukocytes [CSF leukocytes]	[LB.LBTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) [LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
38. * ✓	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
39. ✓	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range
40. ✓	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range
CSF EXAMINATION/STAINING [NOT SUBMITTED]		
41. * ✓	Were CSF Examination/Staining tests done? [Were CSF Examination/Staining tests done?]	[A:N] No [A:Y] Yes
42.		

✓			
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
42.1*	CSF test Done [CSF test Done]	[LB.LBTST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)	
42.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
42.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF Culture [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]			
43.*	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
44.	CSF Culture [CSF Culture]	[MB.MBTST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [MB.MBORRES] [LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive, Please Specify A200 [A:NEG] ☐ Negative	
CSFSEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
45.*	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
46.	Other, Specify [Other, Specify]	[LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
47.	Other, Specify [Other, Specify]	[LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
48.			
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
48.1*	Serology Test Done [Serology Test Done]	[LB.LBTST] ☐ [ciSEROTEST] ☐	
48.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
48.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
49.*	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
50.	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:NEG] ☐ Negative [A:POS] ☐ [LB.LBTST when LBORRES = "POSITIVE"] ☐ [LB.LBORRES] Positive --> specify pathogen [A:ADENO] ☐ Adenovirus [A:CMV] ☐ CMV [A:EBV] ☐ EBV [A:ENTERO] ☐ Enterovirus [A:HIV01] ☐ HIV [A:HSV01] ☐ HSV1 [A:HHV-6] ☐ HHV-6 [A:HSV02] ☐ HSV2 [A:MUM] ☐ Mumps [A:RABIS] ☐ Rabies virus [A:VZV] ☐ VZV [A:INFLU] ☐ H. influenzae type b [A:CSF_LIST] ☐ Listeria [A:MEN01] ☐ Meningococcus [A:PNEU01] ☐ Pneumococcus [A:RICK] ☐ Rickettsia [A:SALSP] ☐ Salmonella sp [A:CSF_PFAL] ☐ P. falciparum [A:TUBR] ☐ M. tuberculosis [A:CSF_OTH] ☐ [LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] CSF Other, please A100	

		specify	
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
51.* ✓	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
52. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
53. ✓			
IMMUNO ELECTRO Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTRO"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
53.1* ✓	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTEST] ☐ [c IMMUNOELECTRO] ☐	
53.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
53.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
54.* ✓	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
55. ✓	Toxin Investigation [Toxin Investigation]	[LB.LBTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
56. ✓	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
57. ✓	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
STOOLS [LB.LBSPEC = "STOOL"]			
58.* ✓	Was a stool sample taken? [Stool sample]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No	
59. ✓	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab	
60. ✓			
STOOL TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "STOOL TEST"] [LB.LBSPEC = "STOOL"]			
60.1* ✓	Stool Test [Stool Test]	[LB.LBTEST] ☐ [c STLTST] ☐	
60.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
60.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER STOOL TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER STOOL TEST"] [LB.LBSPEC = "STOOL"]			
61. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
62. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
63. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative

RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			
64.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
65. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other Please Specify A200	[PR.PRSTDTCT] [PR.PRENDTCT] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
66. ✓			
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			
66.1* ✓	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [cRADIOEXAM] ☐	
66.2 ✓	Test Date [Test Date]	[PR.PRSTDTCT] [PR.PRENDTCT] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
66.3* ✓	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No	
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]			
67.* ✓	Was the disease pattern monophasic? (onset àC" nadir-plateau àC" recovery) [Was the disease pattern monophasic? (onset àC" nadir-plateau àC" recovery)]	[FA.FAOBJ = "DISEASE PATTERN IS MONOPHASIC"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ No [A:Y] ☐ Yes	
68.* ✓	Was there a consultation with a specialist [Was there a consultation with a neurologist]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes	
69.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for Guillain Barre Syndrome? [Is the disease fulfilling the protocol case definition (Job Aid) for Guillain Barre Syndrome?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR GUILLAIN BARRE SYNDROME"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, --> what is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FATEST = "Level of Diagnostic Certainty"] [FA.FAORRES] Yes --> please record the level of diagnostic certainty as defined in job aid [A:1DGC] ☐ 1 [A:2DGC] ☐ 2 [A:3DGC] ☐ 3	
70.* ✓	Can the severity of the event be evaluated according to Guillain Barre Syndrome scale? [Can the severity of the event be evaluated according Guillain Barre Syndrome scale?]	[FA.FAOBJ = "SEVERITY EVALUATED ACCORDING TO GUILLAIN BARRE SYNDROME SCALE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> Please specify ☐ [cSEVENTLIST] ☐	
71.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death	
72.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Guillain Barre syndrome] ☐ Guillain Barre syndrome [A:99] [NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"] [SUPPPR.QVAL when QNAM = "RELDIS"] Other, Please specify: A200	
73. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:Guillain Barre syndrome] ☐ Guillain Barre syndrome [A:99] [NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] Other, Please specify: A200	
74. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000	

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST
			Platelets	2BL	citmPLT	
			White blood cells	3BL	citmWBC	
			Neutrophils	4BL	citmNEUT	
			Lymphocytes	5BL	citmLYMP	
			Monocytes	6BL	citmMONO	
			Basophils	7BL	citmBASO	
			Eosinophils	8BL	citmEOS	
ciSEROTESTVIRAL	String		Chickenpox (Varicella)	1STV	citmSEROTESTVIRAL1	itmSEROTESTVIRAL
			Chlamydia	2STV	citmSEROTESTVIRAL2	
			Chlamydia pneumonia	3STV	citmSEROTESTVIRAL3	
			Coronavirus	4STV	citmSEROTESTVIRAL4	
			Coxsackie	5STV	citmSEROTESTVIRAL5	
			CMV	6STV	citmSEROTESTVIRAL6	
			EBV	7STV	citmSEROTESTVIRAL7	
			Enterovirus	8STV	citmSEROTESTVIRAL8	
			Hepatitis A	9STV	citmSEROTESTVIRAL9	
			Hepatitis B	10STV	citmSEROTESTVIRAL10	
			Hepatitis C	11STV	citmSEROTESTVIRAL11	
			Hepatitis D	12STV	citmSEROTESTVIRAL12	
			HIV	13STV	citmSEROTESTVIRAL13	
			HSV	14STV	citmSEROTESTVIRAL14	
			Measles	15STV	citmSEROTESTVIRAL15	
			Mumps	16STV	citmSEROTESTVIRAL16	
			Parvovirus	17STV	citmSEROTESTVIRAL17	
			Rabies	18STV	citmSEROTESTVIRAL18	
			Rubella	19STV	citmSEROTESTVIRAL19	
			VZV	20STV	citmSEROTESTVIRAL20	
ciTESTCATE	String		Antistreptolysine O(ASLO)	1TC	citmTESTCATE1	itmTESTINFO
			Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
			Borrelia	3TC	citmTESTCATE3	
			H. influenzae type b	4TC	citmTESTCATE4	
			Leptospira	5TC	citmTESTCATE5	
			Mycoplasma	6TC	citmTESTCATE6	
			Mycoplasma pneumonia	7TC	citmTESTCATE7	
			Meningococcus	8TC	citmTESTCATE8	
			Pneumococcus	9TC	citmTESTCATE9	
			Rickettsia	10TC	citmTESTCATE10	
			Salmonella	11TC	citmTESTCATE11	
			M. tuberculosis	12TC	citmTESTCATE12	
			Typhoid fever	13TC	citmTESTCATE13	
ciSEROTEST	String		CMV	1ST	citmCMV	itmSEROTEST
			EBV	2ST	citmEBV	
			Enterovirus	3ST	citmENTVIR	
			HIV	4ST	citmHIVIR	
			HSV	5ST	citmHSV	
			Mumps	6ST	citmMUMPS	
			VZV	7ST	citmVZV	
			H. influenzae type b	8ST	citmHINFB	

		Listeria	9ST	citmLIST	
		Meningococcus	10ST	citmMENGs	
		Pneumococcus	11ST	citmPNEUM	
		Rickettsia	12ST	citmRICK	
		Salmonella	13ST	citmSALM	
		M. tuberculosis	14ST	citmMTUB	
		Autoantibodies	15ST	citmAUTO	
ciIMMUNOELECTRO	String	H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
		Meningococcus	2IM	citmMENG	
		Pneumococcus	3IM	citmPNEU	
		Not resolved	4IM	citmNOTRES	
ciSTLTST	String	Stool Blood	1ST	citmSTLTST1	itmSTLTEST
		Adenovirus	2ST	citmSTLTST2	
		Botulism Spore	3ST	citmSTLTST3	
		Campylobacter	4ST	citmSTLTST4	
		Enterovirus	5ST	citmSTLTST5	
		Poliovirus	6ST	citmSTLTST6	
		Salmonella	7ST	citmSTLTST7	
		Shigella	8ST	citmSTLTST8	
ciRADIOEXAM	String	CT scan	1RE	citmRE1	itmRADIOEXAM
		Electrocardiogram	2RE	citmRE2	
		Electroencephalogram	3RE	citmRE3	
		Electromyogram	4RE	citmRE4	
		MRI	5RE	citmRE5	
		Non-barium or air-contrast enema	6RE	citmRE6	
		X-ray	7RE	citmRE7	
		X-ray abdomen	8RE	citmRE8	
		Ultrasound	9RE	citmRE9	
		Ultrasound 36" cardiac	10RE	citmRE10	
ciSEVENTLIST	String	Healthy	HEAL	citmHEAL	itmSEVENTLIST
		Minor symptoms or signs of neuropathy but capable of usual movement/capable of running	MINOR	citmMINOR	
		Able to walk/move without support but incapable of usual movements	NOSUPP	citmNOSUPP	
		Able to walk/move only with support	WITHSUPP	citmWITHSUPP	
		Confined to bed or chair bound	NOMOVE	citmNOMOVE	
		Requiring assisted ventilation (for any part of the day or night)	VENTIL	citmVENTIL	

EPI-MALARIA-003 VS AME (115056): MENINGITIS () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
MENINGITIS [AE.AESCAT = "MENINGITIS"] [FA.FASCAT = "MENINGITIS"]		
2.*	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.*	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] [Note: See CRF Page 120 for corresponding AETERM annotation] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029)
4.*	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:IDC] ☐
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
5.*	Are there any major signs and symptoms? [Are there any major signs and symptoms?]	[FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (Select all that apply) [A:009] [FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE AND DISCHARGE"] General signs and symptoms [A:101] [A:066] [A:102] [A:038] [A:040] [A:103] [A:025] ☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge ☐ Headache ☐ Vomiting ☐ Bulging fontanelle ☐ Neck stiffness ☐ Kernig&Circumflex's signs ☐ Purpura ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Specify A200
6.*	Are there signs of Encephalopathy? [Encephalopathy]	[FA.FAOBJ = "SIGNS OF ENCEPHALOPATHY"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (Select all that apply) [A:033] ☐ Decreased or altered level of consciousness Signs of Encephalopathy [A:104] ☐ Lethargy [A:105] ☐ Personality changes >24 h [A:106] ☐ Decreased or absent eye contact [A:107] ☐ Decreased or absent response to stimuli (pain, heat, noise) [A:108] ☐ Decreased arousability [A:109] ☐ [FA.FAOBJ = "SEIZURES ASSOCIATED WITH LOSS OF CONSCIOUSNESS"] [FA.FAORRES] [FA.FATEST = "Type"] ☐ Seizures associated with loss of consciousness [A:FOC] ☐ Focal [A:GEN] ☐ Generalized [A:SEN] ☐ Sensitive [A:CONV] ☐ Convulsive [A:037] ☐ [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "COMA: LOWEST OBSERVED SCORE"] Coma --> indicate lowest observed score [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "COMA: SCORE USED"] and Score used [dCOMA_SCORE] ☐ [A:XXX] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200 [FA.FAORRES] [FA.FATEST = "Number of Episodes"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [FA.FAOBJ = "SEIZURES ASSOCIATED WITH LOSS OF CONSCIOUSNESS"] Number of seizures episodes between onset and discharge N2
7.*	Are there focal or multifocal neurological findings? [multifocal neurological findings]	[FA.FAOBJ = "(MULTI)FOCAL NEUROLOGICAL FINDINGS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> (Select all that apply) [A:110] ☐ Aphasia , alexia, agraphia, cortical blindness Focal or multifocal neurological finding [A:111] ☐ Cranial nerve abnormality/abnormalities [A:112] ☐ Visual field defect [A:113] ☐ Presence of primitive reflexes (Babinski&Circumflex's sign, Glabellar, Snout/Sucking reflex) [A:115] ☐ [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "MOTOR WEAKNESS"] Motor weakness [A:116] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "SENSORY ABNORMALITIES"] Sensory abnormalities [A:POS] ☐ Positive [A:NEG] ☐ Negative [A:SENSO] ☐ Sensory level [A:ASYM] ☐ Asymmetric [A:117] ☐ [FA.FAORRES] [FA.FATEST = "Type"] [FA.FAOBJ = "ALTERED DEEP TENDON REFLEXES UPPER EXTREMITIES"] Altered deep tendon reflexes upper extremities [A:HYPO_RFLX] ☐ Hyporeflexia [A:HYPER_RFLX] ☐ Hyperreflexia [A:ASYM_RFLX] ☐ Asymmetric reflexes [A:118] ☐ [FA.FAORRES] [FA.FATEST = "Type"] [FA.FAOBJ = "ALTERED DEEP TENDON REFLEXES LOWER EXTREMITIES"] Altered deep tendon reflexes lower extremities [A:HYPO_RFLX] ☐ Hyporeflexia [A:HYPER_RFLX] ☐ Hyperreflexia [A:ASYM_RFLX] ☐ Asymmetric reflexes

		[A:114] ☐ Cerebellar dysfunction (ataxia, dysmetria or cerebellar nystagmus) [A:099] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
8.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
9.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
10.* ✓	Was a blood sample shipped to 2nd line lab? [Was a blood sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No
BLOOD COUNT [NOT SUBMITTED]		
11.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[A:N] ☐ No [A:Y] ☐ Yes
12. ✓		
BLOOD TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD TEST"] [LB.LBSPEC = "BLOOD"]		
12.1.* ✓	Blood Test Done [Blood Test Done]	[LB.LBTST] ☐ [c]BLDTEST ☐
12.2. ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
12.3. ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx
12.4. ✓	Units [Units]	[LB.LBORRESU] A12
12.5.* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BIOCHEMISTRY [NOT SUBMITTED]		
13.* ✓	Were Biochemistry tests done? [Were Biochemistry tests done?]	[A:N] ☐ No [A:Y] ☐ Yes
14. ✓		
BIOCHEMISTRY TEST Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY TEST"] [LB.LBSPEC = "SERUM"]		
14.1.* ✓	Biochemistry Test Done [Biochemistry Test Done]	[LB.LBTST] ☐ [c]BIO_CHEM ☐
14.2. ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
14.3. ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx
14.4. ✓	Units [Units]	[LB.LBORRESU] A12
14.5.* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BLOOD CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "BLOOD CULTURE"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "MICROBIAL CULTURE"]		
15.* ✓	Was Blood culture done? [Was Blood culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
16.* ✓	Blood culture [Blood culture]	[MB.MBTST = "Organism Present"] [SUPPMB.QVAL when QNAM = "TSTDTC"] [MB.MBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ [LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Positive, Please Specify A200 [A:NEG] ☐ Negative
17.* ✓	Other, Please specify:	[MB.MBORRES] [When this field is completed, then the submitted text is added to the calculated value of MB.MBORRES, separated by a comma] A200

BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]			
18.* ✓	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
19. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
20. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
21. ✓			
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]			
21.1* ✓	Viral Serology Tests [Viral Serology Tests]	[LB.LBTEST] ☐ [cISEROTESTVIRAL] ☐	
21.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
21.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
22.* ✓	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
23. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
24. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
25. ✓			
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
25.1* ✓	Bacterial Serology [Bacterial Serology]	[LB.LBTEST] ☐ [cITESTCATE] ☐	
25.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
25.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]			
26.* ✓	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply	
27. ✓	Autoantibodies [Autoantibodies]	[LB.LBTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
28. ✓	Rheumatoid factor [Rheumatoid factor]	[LB.LBTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
29. ✓	Medications	[LB.LBTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
30. ✓	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
31. ✓	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative

32. ✓	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200		[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		[LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]							
33. ✓	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No					
34. ✓	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes -> Date of antibiotic started ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done					
35. ✓	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other -> Please specify A200 [A:5] ☐ Not documented					
36.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab					
37. ✓	Was a sample shipped to 2nd line lab? [Was the sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No					
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]							
38. ✓	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes					
39. ✓	CSF leukocytes [CSF leukocytes]	[LB.LBTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]							
40. ✓	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes					
41. ✓	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
42. ✓	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
CSF EXAMINATION/ STAINING [NOT SUBMITTED]							
43. ✓	Were CSF Examination/Staining tests done? [Were CSF Examination/Staining tests done?]	[A:N] ☐ No [A:Y] ☐ Yes					
44. ✓							
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]							
44.1. ✓	CSF test Done [CSF test Done]	[LB.LBTEST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)					
44.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)					
44.3. ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative					
CSF CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]							
45. ✓	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes					

55.1*	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTEST] [c IMMUNOELECTRO] ☐
55.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)]
55.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
56.*	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
57.	Toxin Investigation [Toxin Investigation]	[LB.LBTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
58.	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
59.	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
60.*	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
61.	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Specify A200 [PR.PRSTDTC] [PR.PRENDTC] Test Date [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)] [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
62.		
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRES = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
62.1*	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] [c RADIOEXAM] ☐
62.2	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)]
62.3*	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
63.*	Did symptomatology and diagnostic tests distinguish meningitis from Encephalitis/ADEM? [Did symptomatology and diagnostic tests distinguish meningitis from Encephalitis/ADEM?]	[FA.FAOBJ = "SYMPTOMATOLOGY AND DIAGNOSTIC TESTS DISTINGUISHED MENINGITIS FROM ENCEPHALITIS/ADEM"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Yes if so, which one A200
64.*	Was there a consultation with a specialist [Was there a consultation with a neurologist]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
65.*	Based on first line lab results, please classify the meningitis case (according to protocol definitions) [Based on first line lab results, please classify the meningitis case (according to protocol definitions)]	[FA.FAOBJ = "MENINGITIS CASE BASED ON FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:1] ☐ Bacterial confirmed meningitis [A:2] ☐ Probable meningitis [A:3] ☐ Clinically suspected meningitis [A:4] ☐ Not meningitis
66.*	What is the preferred term associated to this event after the 1st line laboratory results?	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [c MENINGITIS1] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] Other, Please specify: A200
67.*	Based on second line lab results, please classify the meningitis case (according to protocol definitions): [Second line lab results]	[FA.FAOBJ = "MENINGITIS CASE BASED ON SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:1] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"] [SUPPPR.QVAL when ☐ Aetiology confirmed meningitis]

		QNAM = "RELDIS" [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [A:2] [A:3] [A:4] ☐ Probable meningitis ☐ Clinically suspected meningitis ☐ Not meningitis
68. ✓	What is the preferred term associated to this event after the 2nd line laboratory results?	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] ☐ [c]MENINGITIS1 ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] Other, Please specify: A200
69.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:ML] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
70.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ [SUPPAE.QVAL when QNAM = "SEQUELAE"] Sequelae Please specify the sequelae ASO [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
71. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: MENINGITIS						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cICOMA_SCOREE	String		GLASGOW	GLAS	ctmGLAS	itmSCORE
			BLANTYRE	BLANT	ctmBLANT	
cIBLDTST	String		Red Blood Cells	1BL	ctmBLDTST	itmBLOODTEST
			Platelets	2BL	ctmPLT	
			White blood cells	3BL	ctmWBC	
			Neutrophils	4BL	ctmNEUT	
			Lymphocytes	5BL	ctmLYMP	
			Monocytes	6BL	ctmMONO	
			Basophils	7BL	ctmBASO	
			Eosinophils	8BL	ctmEOS	
cIBIO_CHEM	String		Total bilirubin	1	ctmBIO1	itmBIOCHEMTEST1
			Conjugated bilirubin	2	ctmBIO2	
			Alanine amino transferase (ALT)	3	ctmBIO3	
			Aspartate amino transferase (AST)	4	ctmBIO4	
			Alkaline Phosphatase (ALP)	5	ctmBIO5	
			Total protein	6	ctmBIO6	
			Albumin	7	ctmBIO7	
			Serum urea nitrogen	8	ctmBIO8	
			Serum creatinine	9	ctmBIO9	
			Serum sodium	10	ctmBIO10	

		Serum potassium	11	citmBIO11	
		Serum chloride	12	citmBIO12	
		Serum calcium	14	citmBIO14	
		Serum magnesium	15	citmBIO15	
		Vitamin B12	16	citmBIO16	
		Folate	17	citmBIO17	
		Blood glucose	18	citmBIO18	
		Oral glucose tolerance test	19	citmBIO19	
		Fasting blood sugar	20	citmBIO20	
		Hemoglobin A1C	21	citmBIO21	
		Lipids	22	citmBIO22	
ciSEROTESTVIRAL	String	Chickenpox (Varicella)	1STV	citmSEROTESTVIRAL1	itmSEROTESTVIRAL
		Chlamydia	2STV	citmSEROTESTVIRAL2	
		Chlamydia pneumonia	3STV	citmSEROTESTVIRAL3	
		Coronavirus	4STV	citmSEROTESTVIRAL4	
		Coxsackie	5STV	citmSEROTESTVIRAL5	
		CMV	6STV	citmSEROTESTVIRAL6	
		EBV	7STV	citmSEROTESTVIRAL7	
		Enterovirus	8STV	citmSEROTESTVIRAL8	
		Hepatitis A	9STV	citmSEROTESTVIRAL9	
		Hepatitis B	10STV	citmSEROTESTVIRAL10	
		Hepatitis C	11STV	citmSEROTESTVIRAL11	
		Hepatitis D	12STV	citmSEROTESTVIRAL12	
		HIV	13STV	citmSEROTESTVIRAL13	
		HSV	14STV	citmSEROTESTVIRAL14	
		Measles	15STV	citmSEROTESTVIRAL15	
		Mumps	16STV	citmSEROTESTVIRAL16	
		Parvovirus	17STV	citmSEROTESTVIRAL17	
		Rabies	18STV	citmSEROTESTVIRAL18	
		Rubella	19STV	citmSEROTESTVIRAL19	
		VZV	20STV	citmSEROTESTVIRAL20	
ciTESTCATE	String	Antistreptolysine O (ASLO)	1TC	citmTESTCATE1	itmTESTINFO
		Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
		Borrelia	3TC	citmTESTCATE3	
		H. influenzae type b	4TC	citmTESTCATE4	
		Leptospira	5TC	citmTESTCATE5	
		Mycoplasma	6TC	citmTESTCATE6	
		Mycoplasma pneumonia	7TC	citmTESTCATE7	
		Meningococcus	8TC	citmTESTCATE8	
		Pneumococcus	9TC	citmTESTCATE9	
		Rickettsia	10TC	citmTESTCATE10	
		Salmonella	11TC	citmTESTCATE11	
		M. tuberculosis	12TC	citmTESTCATE12	
		Typhoid fever	13TC	citmTESTCATE13	
ciSEROTEST	String	CMV	1ST	citmCMV	itmSEROTEST
		EBV	2ST	citmEBV	
		Enterovirus	3ST	citmENTVIR	
		HIV	4ST	citmHIVIR	
		HSV	5ST	citmHSV	
		Mumps	6ST	citmMUMPS	
		VZV	7ST	citmVZV	
		H. influenzae type b	8ST	citmHINFB	
		Listeria	9ST	citmLIST	
		Meningococcus	10ST	citmMENGS	
		Pneumococcus	11ST	citmPNEUM	
		Rickettsia	12ST	citmRICK	
		Salmonella	13ST	citmSALM	
		M. tuberculosis	14ST	citmMTUB	
		Autoantibodies	15ST	citmAUTO	
ciIMMUNOELECTRO	String	H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
		Meningococcus	2IM	citmMENG	
		Pneumococcus	3IM	citmPNEU	
		Not resolved	4IM	citmNOTRES	

cIRADIOEXAM	String		CT scan	1RE	citmRE1	itmRADIOEXAM
			Electrocardiogram	2RE	citmRE2	
			Electroencephalogram	3RE	citmRE3	
			Electromyogram	4RE	citmRE4	
			MRI	5RE	citmRE5	
			Non-barium or air-contrast enema	6RE	citmRE6	
			X-ray	7RE	citmRE7	
			X-ray abdomen	8RE	citmRE8	
			Ultrasound	9RE	citmRE9	
			Ultrasound &C" cardiac	10RE	citmRE10	
cIMENINGITIS1	String		Lymphocytic choriomeningitis	Lymphocytic choriomeningitis	citmLympho	itmPRFTerm_LAB1, itmPRFTerm_LAB2
			Congenital syphilitic meningitis	Congenital syphilitic meningitis	citmCongenitalsyphiliticmeningitis	
			Herpes simplex meningitis	Herpes simplex meningitis	citmHerpesimplexmeningitis	
			Herpes zoster meningitis	Herpes zoster meningitis	citmHerpeszostermenigitis	
			Melanomatous meningitis	Melanomatous meningitis	citmMelanomatousmeningitis	
			Meningitis	Meningitis	citmMeningitis	
			Aseptic meningitis	Aseptic meningitis	citmAsepticmeningitis	
			Meningitis aspergillus	Meningitis aspergillus	citmMeningitisaspergillus	
			Bacterial meningitis	Bacterial meningitis	citmBacterialmeningitis	
			Meningitis borrelia	Meningitis borrelia	citmMeningitisborrelia	
			Meningitis candida	Meningitis candida	citmMeningitiscandida	
			Meningitis chemical	Meningitis chemical	citmMeningitischemical	
			Meningitis coccidioides	Meningitis coccidioides	citmMeningitiscoctdioides	
			Meningitis coxsackie viral	Meningitis coxsackie viral	citmMeningitiscoxsackieviral	
			Meningitis cronobacter	Meningitis cronobacter	citmMeningitiscronobacter	
			Cryptococcal meningitis	Cryptococcal meningitis	citmCryptococcalmeningitis	
			Meningitis echo viral	Meningitis echo viral	citmMeningitisechoviral	
			Enterococcal meningitis	Enterococcal meningitis	citmEnterococcalmeningitis	
			Meningitis enteroviral	Meningitis enteroviral	citmMeningitisenteroviral	
			Eosinophilic meningitis	Eosinophilic meningitis	citmEosinophilicmeningitis	
			Meningitis exserohilum	Meningitis exserohilum	citmMeningitisexserohilum	
			Fungal meningitis	Fungal meningitis	citmFungalmeningitis	
			Gonococcal meningitis	Gonococcal meningitis	citmGonococcalmeningitis	
			Meningitis haemophilus	Meningitis haemophilus	citmMeningitishemophilus	
			Meningitis herpes	Meningitis herpes	citmMeningitisherpes	
			Meningitis histoplasma	Meningitis histoplasma	citmMeningitishistoplasma	
			Meningitis leptospiral	Meningitis leptospiral	citmMeningitisleptospiral	
			Meningitis listeria	Meningitis listeria	citmMeningitislisteria	
			Meningitis meningococcal	Meningococcal meningitis	citmMeningococcalmeningitis	
			Mumps meningitis	Mumps meningitis	citmMumpsmeningitis	
			Neonatal meningitis	Neonatal meningitis	citmNeonatalmeningitis	
			Meningitis noninfective	Meningitis noninfective	citmMeningitisnoninfective	
			Pneumococcal meningitis	Pneumococcal meningitis	citmPneumococcalmeningitis	
			Salmonella meningitis	Salmonella meningitis	citmSalmonellameningitis	
			Staphylococcal meningitis	Staphylococcal meningitis	citmStaphylococcalmeningitis	
			Streptococcal meningitis	Streptococcal meningitis	citmStreptococcalmeningitis	
			Meningitis toxoplasma	Meningitis toxoplasma	citmMeningitistoxtoplasma	
			Meningitis trypanosomal	Meningitis trypanosomal	citmMeningitistrypanosomal	
			Tuberculous meningitis	Tuberculous meningitis	citmTuberculousmeningitis	
			Viral meningitis	Viral meningitis	citmViralmeningitis	
			Pachymeningitis	Pachymeningitis	citmPachymeningitis	
			Pseudomonas aeruginosa meningitis	Pseudomonas aeruginosa meningitis	citmPseudomonas	
			Other	99	citmOTHER_99	

EPI-MALARIA-003 VS AME (115056): GENERALIZED CONVULSIVE SEIZURES () [AE.AESCAT = "GENERALIZED CONVULSIVE SEIZURES"] [FA.FASCAT = "GENERALIZED CONVULSIVE SEIZURES"] [AE.AECAT = "HOSPITALIZATION"]			
VISIT NO			
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4	
GENERALIZED CONVULSIVE SEIZURES			
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4	
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029)	
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:IDC] ☐	
5.* ✓	Are the seizures recurrent? [Are the seizures recurrent?]	[SUPPAE.QVAL when QNAM = "SZRECUR"] [A:N] ☐ No [A:Y] ☐ Yes	
6.* ✓	Were the seizures witnessed? [Were the seizures witnessed?]	[FA.FAOBJ = "SEIZURES WITNESSED"] [FA.FACAT = "HOSPITALIZATION"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Witness"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> [A:01] ☐ Health care worker [A:02] ☐ Parent/ Guardian [A:99] ☐ Other [FA.FAORRES] [FA.FATEST = "Duration"] [FA.FAORRESU = "min"] Duration of seizures? (in minutes) N3	
SIGNS AND SYMPTOMS			
Please record present signs and symptoms			
7.* ✓	Are any signs present? [Are any signs present?]	[FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"] [FA.FAOBJ = "SIGNS AND SYMPTOMS"] [FA.FAORRES] [A:N] ☐ No [A:Y] ☐ [FA.FATEST = "Signs and Symptoms"] [FA.FAORRES] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes --> Signs and symptoms [A:009] [FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAVENTX = "BETWEEN ONSET AND DISCHARGE"] [A:125] [A:119] [A:120] [A:121] [A:122] [A:123] [A:124] [A:XX] [A:126] [A:127] ☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XXX.X ☐ Reported fever (temperature > 37.5°C) at the time of seizure ☐ Sudden loss of consciousness ☐ Generalized seizures ☐ Localized seizures ☐ Tonic motor event ☐ Clonic motor event ☐ Tonic-clonic motor event ☐ Atonic motor manifestations ☐ Post ictal drowsiness [FA.FAORRES] [FA.FATEST = "Specification"] Other A200 Please Specify	
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]			
8.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No	
9.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab	
10.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No	
BLOOD GLUCOSE [NOT SUBMITTED]			
Please complete the results of tests that were performed to diagnose this event			
GLUCOSE TEST			
BIOCHEMISTRY-GLUCOSE			
11.* ✓	Were Glucose tests done? [Were Biochemistry tests done?]	[A:N] ☐ No [A:Y] ☐ Yes	
12. ✓			
BLOOD GLUCOSE TEST Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BLOOD GLUCOSE TEST"] [LB.LBSPEC = "SERUM"]			
12.1.* ✓	Blood Glucose Test Done [Blood Glucose Test Done]	[LB.LBTST] ☐ [cIBLDGLU] ☐	
12.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	

12.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDO16VG2C?domain=xxx.xxx			
12.4 ✓	Units [Units]	[LB.LBORRESU] A12			
12.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range			
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
13.* ✓	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No			
14.* ✓	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes --> Date of antibiotic started ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done			
15.* ✓	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other --> Please specify A200 [A:5] ☐ Not documented			
16.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab			
17.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No			
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
18.* ✓	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes			
19. ✓	CSF leukocytes [CSF leukocytes]	[LB.LBTST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDO16VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
20.* ✓	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes			
21. ✓	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDO16VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
22. ✓	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDO16VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF EXAMINATION/STAINING [NOT SUBMITTED]					
23.* ✓	Were CSF Examination/Staining tests done? [Were CSF Examination/Staining tests done?]	[A:N] ☐ No [A:Y] ☐ Yes			
24. ✓					
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
24.1* ✓	CSF test Done [CSF test Done]	[LB.LBTST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)			
24.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)			
24.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative			

CSF Culture [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]			
25.* ✓	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
26. ✓	CSF Culture [CSF Culture]	[MB.MBTTEST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [MB.MBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Positive, Please Specify A200 [A:NEG] ☐ Negative	
CSF SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
27.* ✓	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
28. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
29. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
30. ✓			
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
30.1* ✓	Serology Test Done [Serology Test Done]	[LB.LBTTEST] ☐ [ciSEROTEST] ☐	
30.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
30.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
31.* ✓	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
32. ✓	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) RESULT [A:NEG] ☐ Negative [A:POS] ☐ Positive --> specify pathogen [LB.LBTTEST when LBORRES = "POSITIVE"] [LB.LBORRES] ☐ Adenovirus ☐ CMV ☐ EBV ☐ Enterovirus ☐ HIV ☐ HSV1 ☐ HHV-6 ☐ HSV2 ☐ Mumps ☐ Rabies virus ☐ VZV ☐ H. influenzae type b ☐ Listeria ☐ Meningococcus ☐ Pneumococcus ☐ Rickettsia ☐ Salmonella sp ☐ P. falciparum ☐ M. tuberculosis ☐ CSF A100 Other, please specify	
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
33.* ✓	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
34. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative

35.			
IMMUNO ELECTRO Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTROPHORESIS TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
35.1*	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTEST] ☐ [c]IMMUNOELECTRO ☐	
35.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
35.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
36.*	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
37.	Toxin Investigation [Toxin Investigation]	[LB.LBTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
38.	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
39.	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]			
40.*	Please record number of seizure episodes during this hospitalization [Please record number of seizure episodes during this hospitalization]	[FA.FAORRES] [FA.FATEST = "Number of Episodes"] [FA.FAOBJ = "SEIZURE EPISODES"] [FA.FAEVINTX = "DURING HOSPITALIZATION"] N2	
41.*	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes	
42.*	Is the disease fulfilling the protocol case definition (Job Aid) for Generalised Seizures? [Is the disease fulfilling the protocol case definition (Job Aid) for Generalised Seizures?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR GENERALIZED CONVULSIVE SEIZURES"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -->what is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] ☐ 1 [A:2DGC] ☐ 2 [A:3DGC] ☐ 3 [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "FEBRILE SEIZURE"] Is it a febrile seizure? [A:N] ☐ No [A:Y] ☐ Yes --> If febrile seizure, the temperature should be >= 37.5°C [A:DNK] ☐ Do Not Know	
43.*	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal	
44.*	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death	
45.*	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Convulsions generalized] ☐ Convulsions generalized [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] Other, Please specify: A200	
46.	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:Convulsions generalized] ☐ Convulsions generalized [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:99][NOT SUBMITTED] Other, Please specify:	

A200

47.
✓

Comment

[CO.COVAL when IDVAR = "AESEQ"]
A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: GENERALIZED CONVULSIVE SEIZURES						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIBLDGLU	String		Blood Glucose	1BLG	citmBLDGLU1	itmBLOODGLU
			Oral Glucose Tolerance Test	2BLG	citmBLDGLU2	
			Fasting Blood Sugar	3BLG	citmBLDGLU3	
			Hemoglobin A1c	4BLG	citmBLDGLU4	
cISEROTEST	String		CMV	1ST	citmCMV	itmSEROTEST
			EBV	2ST	citmEBV	
			Enterovirus	3ST	citmENTVIR	
			HIV	4ST	citmHIVIR	
			HSV	5ST	citmHSV	
			Mumps	6ST	citmMUMPS	
			VZV	7ST	citmVZV	
			H. influenzae type b	8ST	citmHINFB	
			Listeria	9ST	citmLIST	
			Meningococcus	10ST	citmMENGS	
			Pneumococcus	11ST	citmPNEUM	
			Rickettsia	12ST	citmRICK	
			Salmonella	13ST	citmSALM	
			M. tuberculosis	14ST	citmMTUB	
			Autoantibodies	15ST	citmAUTO	
cIMMUNOELECTRO	String		H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
			Meningococcus	2IM	citmMENG	
			Pneumococcus	3IM	citmPNEU	
			Not resolved	4IM	citmNOTRES	

EPI-MALARIA-003 VS AME (115056): DIABETES MELLITUS () [AE.AECAT = "HOSPITALIZATION"]				
VISIT NO				
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4		
DIABETES MELLITUS [AE.AESCAT = "DIABETES MELLITUS"] [FA.FASCAT = "DIABETES MELLITUS"]				
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4		
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029)		
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐		
5.* ✓	Was the patient in coma on admission? [Was the patient in coma on admission?]	[FA.FACAT = "HOSPITALIZATION"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "IN COMA ON ADMISSION"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "GLASGOW COMA SCORE"] Yes -->record Glasgow coma scale N10		
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]				
Please record present signs and symptoms				
6.* ✓	Are any signs present? [Are any signs present?]	[FA.FAOBJ = "SIGNS AND SYMPTOMS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes -->select all that apply Signs and symptoms [A:009][FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAENVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:128] [A:129] [A:013] [A:130] [A:020] [A:132] [A:XX] [A:XX1] [A:137] [A:133] [A:066] [A:134] [A:136] [A:135] [A:138] [A:XX2] [A:XXX]		
		☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XX.X ☐ Polyuria ☐ Polydipsia/ thirst ☐ Loss of weight ☐ Polyphagia / Increased appetite ☐ Dehydration ☐ Ketoacidosis ☐ Polypnea ☐ Fruity smelling breath ☐ Alteration in mental status/coma ☐ Nausea ☐ Vomiting ☐ Wasting ☐ Abdominal pain ☐ Muscular cramping ☐ Urogenital infection ☐ Flushed face ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200		
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]				
7.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) [A:N] ☐ No		
8.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab		
9.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) [A:N] ☐ No		
BLOOD GLUCOSE [NOT SUBMITTED]				
10.* ✓	Were Glucose tests done? [Were Biochemistry tests done?]	[A:N] ☐ No [A:Y] ☐ Yes		
11. ✓				
BLOOD GLUCOSE TEST Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BLOOD GLUCOSE TEST"] [LB.LBSPEC = "SERUM"]				
11.1* ✓	Blood Glucose Test Done [Blood Glucose Test Done]	[LB.LBTST] ☐ [c BLDGLU] ☐		
11.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)		
11.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ1iA34jDOi6VG2C?domain=xxx.xxx		

11.4	Units [Units]	[LB.LBORRESU] A12
11.5*	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]		
12.*	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
13.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
14.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
15.		
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]		
15.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTTEST] ☐ [ciSEROTESTVIRAL] ☐
15.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
15.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
16.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
17.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
18.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
19.		
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
19.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTTEST] ☐ [ciTESTCATE] ☐
19.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
19.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]		
20.*	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply
21.	Autoantibodies [Autoantibodies]	[LB.LBTTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
22.	Rheumatoid factor [Rheumatoid factor]	[LB.LBTTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
23.	Medications	[LB.LBTTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
24.	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"]

		Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
25.	Other,Specify ☒ [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
26.	Other,Specify ☒ [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
URINE [LB.LBSPEC = "URINE"]		
27.*	Was a urine sample taken? ☒ [Was a urine sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
28.	For GSK: <i>[hidden]</i> [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
29.*	Were urine tests done? ☒ [Were urine tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
30.		
URINE DETAILS Entry [LB.LBCAT = "URINALYSIS"] [LB.LBSCAT = "URINE DETAILS"] [LB.LBSPEC = "URINE"]		
30.1*	Urine test Done	[LB.LBTTEST] ☐ [c]URINES
30.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
30.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
31.*	Was there a consultation with a specialist? ☒ [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
32.*	Is the disease fulfilling the protocol case definition (Job Aid) for diabetes mellitus type ? ☒ [Is the disease fulfilling the protocol case definition (Job Aid) for diabetes mellitus type ?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR DIABETES MELLITUS"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, --> what is the final diagnosis for this disease [A:Y] ☐ Yes
33.*	Can severity of the disease be evaluated at discharge? ☒ [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
34.*	Please record disease outcome at discharge: ☒ [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
35.*	What is the preferred term associated to this event after the 1st line laboratory results? ☒ [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Type 1 diabetes mellitus] ☐ Type 1 diabetes mellitus [A:99] [NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contains the preferred term given after second line lab results] Other, Please specify:
36.	What is the preferred term associated to this event after the 2nd line laboratory results? ☒ [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [A:Type 1 diabetes mellitus] ☐ Type 1 diabetes mellitus [A:99] [NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] Other, Please specify:

37.	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000
Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in Inform will override any settings made in Central Designer.		

Codelist Values Tables: DIABETES MELLITUS						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDGLU	String		Blood Glucose	1BLG	citmBLDGLU1	itmBLOODGLU
			Oral Glucose Tolerance Test	2BLG	citmBLDGLU2	
			Fasting Blood Sugar	3BLG	citmBLDGLU3	
			Hemoglobin A1c	4BLG	citmBLDGLU4	
ciSERO TESTVIRAL	String		Chickenpox (Varicella)	1STV	citmSERO TESTVIRAL1	itmSERO TESTVIRAL
			Chlamydia	2STV	citmSERO TESTVIRAL2	
			Chlamydia pneumonia	3STV	citmSERO TESTVIRAL3	
			Coronavirus	4STV	citmSERO TESTVIRAL4	
			Coxsackie	5STV	citmSERO TESTVIRAL5	
			CMV	6STV	citmSERO TESTVIRAL6	
			EBV	7STV	citmSERO TESTVIRAL7	
			Enterovirus	8STV	citmSERO TESTVIRAL8	
			Hepatitis A	9STV	citmSERO TESTVIRAL9	
			Hepatitis B	10STV	citmSERO TESTVIRAL10	
			Hepatitis C	11STV	citmSERO TESTVIRAL11	
			Hepatitis D	12STV	citmSERO TESTVIRAL12	
			HIV	13STV	citmSERO TESTVIRAL13	
			HSV	14STV	citmSERO TESTVIRAL14	
			Measles	15STV	citmSERO TESTVIRAL15	
			Mumps	16STV	citmSERO TESTVIRAL16	
			Parvovirus	17STV	citmSERO TESTVIRAL17	
			Rabies	18STV	citmSERO TESTVIRAL18	
			Rubella	19STV	citmSERO TESTVIRAL19	
			VZV	20STV	citmSERO TESTVIRAL20	
ciTESTCATE	String		Antistreptolysine O (ASLO)	1TC	citmTESTCATE1	itmTESTINFO
			Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
			Borrelia	3TC	citmTESTCATE3	
			H. influenzae type b	4TC	citmTESTCATE4	
			Leptospira	5TC	citmTESTCATE5	
			Mycoplasma	6TC	citmTESTCATE6	
			Mycoplasma pneumonia	7TC	citmTESTCATE7	
			Meningococcus	8TC	citmTESTCATE8	
			Pneumococcus	9TC	citmTESTCATE9	
			Rickettsia	10TC	citmTESTCATE10	
			Salmonella	11TC	citmTESTCATE11	
			M. tuberculosis	12TC	citmTESTCATE12	
			Typhoid fever	13TC	citmTESTCATE13	
ciURINE5	String		Urine blood	1UR	citmURINE51	itmURINE
			Urine leukocytes	2UR	citmURINE52	
			Urine total protein (Proteinuria)	3UR	citmURINE53	
			Urine glucose (Glycosuria)	4UR	citmURINE54	
			Urine Ketones	5UR	citmURINE55	

EPI-MALARIA-003 VS AME (115056): HEPATIC INSUFFICIENCY () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
HEPATIC INSUFFICIENCY [AE.AESCAT = "HEPATIC INSUFFICIENCY"] [FA.FASCAT = "HEPATIC INSUFFICIENCY"]		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029)
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] ongoing at discharge [A:IDC] ☐
5.* ✓	Was the patient in coma on admission? [Was the patient in coma on admission?]	[FA.FACAT = "HOSPITALIZATION"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "IN COMA ON ADMISSION"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Score"] [FA.FAOBJ = "GLASGOW COMA SCORE"] Yes --> record Glasgow coma scale N10
SIGN & SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
6.* ✓	Are any general signs present? [Are any general signs present?]	[FA.FAOBJ = "GENERAL SIGNS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes-->(Select all that apply) Signs and symptoms [A:009] [FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:0XX] [A:064] [A:139] [A:140] [A:141] [A:142] [A:143] [A:XXX] [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XX.X Asthenia Icterus/ Jaundice Pruritus Hepatomegaly Ascites Changed colour of stool Changed colour of urine [FA.FAORRES] [FA.FATEST = "Specification"] Other -- >Please Specify A200
7.* ✓	Are there any signs of encephalopathy? [Are there any signs of encephalopathy?]	[FA.FAOBJ = "SIGNS OF ENCEPHALOPATHY"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes-->(Select all that apply) Signs of encephalopathy [A:144] ☐ Apathy [A:145] ☐ Tremor [A:104] ☐ Lethargy [A:106] ☐ Decreased or absent eye contact [A:107] ☐ Decreased or absent response to stimuli (pain, heat, noise) [A:XX] ☐ Convulsion [A:XXX] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other --> Please Specify A20
8.* ✓	Are there any signs of coagulation disorder? [Are there any signs of coagulation disorder?]	[FA.FAOBJ = "SIGNS OF COAGULATION DISORDER"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes-->(Select all that apply) Signs of coagulation disorder [A:190] ☐ Ecchymoses [A:147] ☐ Gingival or nasal hemorrhage [A:103] ☐ Purpura [A:XXX] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other -->Please Specify A200
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
9.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
10.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
11.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No

12.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
13. ✓		
BLOOD TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD TEST"] [LB.LBSPEC = "BLOOD"]		
13.1* ✓	Blood Test Done [Blood Test Done]	[LB.LBTTEST] ☐ [clBLDTEST] ☐
13.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
13.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx
13.4 ✓	Units [Units]	[LB.LBORRESU] A12
13.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BIOCHEMISTRY [SDTM_1] [SDTM_2] [SDTM_3] [SDTM_4] [SDTM_5]		
14.* ✓	Were Biochemistry tests done? [Were Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
15. ✓		
BIOCHEMISTRY DET Entry		
15.1* ✓	Biochemistry Test Done [Biochemistry Test Done]	[LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY DET"] [LB.LBSPEC = "SERUM"] ☐ [clBIO_CHEM] ☐
15.2 ✓	Test Date [Test Date]	[LB.LBTTEST] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
15.3 ✓	Result [Result]	[SUPPLB.QVAL when QNAM = "TSTDTC"] https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx
15.4 ✓	Units [Units]	[LB.LBORRES] A12
15.5* ✓	Interpretation [Interpretation]	[LB.LBORRESU] [A:WNR][LB.LBNRIND] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
COAGULATION TEST		
16.* ✓	Were coagulation tests done? [Were coagulation tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
17. ✓		
COAGULATION TEST DETAILS Entry [LB.LBCAT = "COAGULATION"] [LB.LBSCAT = "COAGULATION TEST DETAILS"] [LB.LBSPEC = "BLOOD"]		
17.1* ✓	Coagulation test [Coagulation test]	[LB.LBTTEST] Coagulation Test Done ☐ [clCOAGTEST] ☐ [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
17.2 ✓	Bleeding time [Bleeding time]	[LB.LBTTEST = "Bleeding Time"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date Result [A:N] ☐ Normal ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:A] ☐ Abnormal
BLOOD SMEAR [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"] [LB.LBMETHOD = "SMEAR"]		
18.* ✓	Was blood smear done? [Was blood smear done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes

19.	Haemolysis [Haemolysis]	[LB.LBTEST = "Hemolytic Index"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
20.	Sickle cells anemia test [Sickle cells anemia test]	[LB.LBTEST = "Sickle Cell Anaemia"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
21.		
BLOOD SMEAR Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"]		
21.1*	Blood Content	[LB.LBTEST] [c]bloodContent
21.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)
21.3*	Result [Result]	[LB.LBORRES] [A:N] Normal [A:A] Abnormal
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]		
22.*	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
23.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
24.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
25.		
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]		
25.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTEST] [c]SEROTESTVIRAL
25.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)
25.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
26.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
27.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Specify: Test Date Result [A:POS] Positive A200 [NReq] / [NReq] / [NReq] (2018-2029) [A:NEG] Negative
28.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Specify: Test Date Result [A:POS] Positive A200 [NReq] / [NReq] / [NReq] (2018-2029) [A:NEG] Negative
29.		
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
29.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTEST] [c]TESTCATE
29.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)
29.3*	Result	[LB.LBORRES]

☒ [Result]		[A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER BLOOD TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]			
30.* ☒	Were other tests performed? [Were other tests performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
31. ☒	Autoantibodies [Autoantibodies]	[LB.LBTTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
32. ☒	Rheumatoid factor [Rheumatoid factor]	[LB.LBTTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
33. ☒	Medications [Medications]	[LB.LBTTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
34. ☒	Toxic nephropathies [Toxic nephropathies]	[LB.LBTTEST = "Toxic Nephropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
35. ☒	Other, specify: [Other, specify:]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTH1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
36. ☒	Other,Specify [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTH1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Specify: Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
37.* ☒	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) [A:N] ☐ No	
38.* ☒	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes --> Date of antibiotic started ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done	
39.* ☒	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other -> Please specify [A:5] ☐ Not documented	
40. ☒	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab	
41.* ☒	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No	
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
42.* ☒	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
43. ☒	CSF leukocytes [CSF leukocytes]	[LB.LBTTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result Units Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
44.* ☒	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
45. ☒	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NRReq ☐ / ☐ NRReq ☐ (2018-2029) Result Units Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	

46.	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx	[LB.LBORRESU] Units A12	[LB.LBNRIND] Interpretation [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range
CSF EXAMINATION/STAINING [NOT SUBMITTED]					
47.*	Were CSF Examination/Staining tests done? [Were CSF Examination/Staining tests done?]	[A:N] No [A:Y] Yes			
CSF CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]					
48.*	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes			
49.	CSF Culture [CSF Culture]	[MB.MBTEST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[MB.MBORRES] Result [A:POS] Positive, Please Specify [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[A:NEG] Negative	
CSF SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
50.*	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes			
51.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Specify: A200	Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative	
52.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Specify: A200	Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative	
53.					
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
53.1*	Serology Test Done [Serology Test Done]	[LB.LBTEST] [CISEROTEST]			
53.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)			
53.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative			
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
54.*	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes			
55.	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[LB.LBORRES] RESULT [A:NEG] Negative [A:POS] [LB.LBTEST when LBORRES = "POSITIVE"]	Negative [LB.LBORRES] Positive --> specify pathogen [A:ADENO] Adenovirus [A:CMV] CMV [A:EBV] EBV [A:ENTERO] Enterovirus [A:HIV01] HIV [A:HSV01] HSV1 [A:HHV-6] HHV-6 [A:HSV02] HSV2 [A:MUM] Mumps [A:RABIS] Rabies virus [A:VZV] VZV [A:INFLU] H. influenzae type b [A:CSF_LIST] Listeria [A:MEN01] Meningococcus [A:PNEU01] Pneumococcus [A:RICK] Rickettsia [A:SALSP] Salmonella sp [A:CSF_PFAL] P. falciparum [A:TUBR] M. tuberculosis [A:CSF_OTH] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] CSF Other, please specify A100	
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]					
56.*	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes			

57.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Specify: A200	Test Date [NReq] / [NReq] / [NReq] (2018-2029)	[LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
58.				
IMMUNO ELECTRO Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTRO"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]				
58.1*	CSF Immunelectrophoresis done [CSF Immunelectrophoresis done]	[LB.LBTTEST] [cIMMUNOELECTRO]		
58.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
58.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative		
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]				
59.*	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
60.	Toxin Investigation [Toxin Investigation]	[LB.LBTTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [A:POS] Positive [NReq] / [NReq] / [NReq] (2018-2029) [A:NEG] Negative		
61.	Other, Specify: [Other, Specify:]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Specify: A200 Test Date [A:NOR] Normal [NReq] / [NReq] / [NReq] (2018-2029) [A:ABN] Abnormal		
62.	Other, Specify: [Other, Specify:]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Specify: A200 Test Date [A:NOR] Normal [NReq] / [NReq] / [NReq] (2018-2029) [A:ABN] Abnormal		
URINE [LB.LBSPEC = "URINE"]				
63.*	Was a urine sample taken? [Was a urine sample taken?]	[NOT SUBMITTED] [A:Y] [LB.LBDTC] Yes --> sampling date [NReq] / [NReq] / [NReq] (2018-2029) [A:N] No		
64.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3 - Lost in second line lab		
65.*	Were urine tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
66.				
URINE DETAILS Entry [LB.LBCAT = "URINALYSIS"] [LB.LBSCAT = "URINE DETAILS"] [LB.LBSPEC = "URINE"]				
66.1*	Urine test Done	[LB.LBTTEST] [cURINES]		
66.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
66.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative		
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]				
67.*	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] No [A:Y] [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] No [A:Y] Yes		
68.*	Is the disease fulfilling the protocol case definition (Job Aid) for Hepatic insufficiency? [Is the disease fulfilling the protocol case definition (Job Aid) for Hepatic insufficiency?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR HEPATIC INSUFFICIENCY"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No,--> What is the final diagnosis for this disease A200		
69.*	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] No [A:Y] [AE.AESEV] Yes --> [A:MIL] Mild [A:MOD] Moderate [A:SEV] Severe [A:FAT] Fatal		
70.*	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] Fully recovered [A:RECOV] Recovering [A:SEQ] Sequelae [A:NRES] Not resolved		

71.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[A:DEA] ☐ Death [FA.FA0BJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FA0RRS] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Hepatic insufficiency] ☐ Hepatic insufficiency [A:99][NOT SUBMITTED] ☐ [FA.FA0RRS] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contains the preferred term given after second line lab results] Other, Please specify: A200
72. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FA0BJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FA0RRS] [FA.FATEST = "Diagnosis"] [A:Hepatic insufficiency] ☐ Hepatic insufficiency [A:99][NOT SUBMITTED] ☐ [FA.FA0RRS] [FA.FATEST = "Diagnosis"] Other, Please specify: A200
73. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
 Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: HEPATIC INSUFFICIENCY						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST
			Platelets	2BL	citmPLT	
			White blood cells	3BL	citmWBC	
			Neutrophils	4BL	citmNEUT	
			Lymphocytes	5BL	citmLYMP	
			Monocytes	6BL	citmMONO	
			Basophils	7BL	citmBASO	
			Eosinophils	8BL	citmEOS	
ciBIO_CHEM	String		Total bilirubin	1	citmBIO1	itmBIOCHEMTEST_HP
			Conjugated bilirubin	2	citmBIO2	
			Alanine amino transferase (ALT)	3	citmBIO3	
			Aspartate amino transferase (AST)	4	citmBIO4	
			Alkaline Phosphatase (ALP)	5	citmBIO5	
			Total protein	6	citmBIO6	
			Albumin	7	citmBIO7	
			Serum urea nitrogen	8	citmBIO8	
			Serum creatinine	9	citmBIO9	
			Serum sodium	10	citmBIO10	
			Serum potassium	11	citmBIO11	
			Serum chloride	12	citmBIO12	
			Serum calcium	14	citmBIO14	
			Serum magnesium	15	citmBIO15	
			Vitamin B12	16	citmBIO16	
			Folate	17	citmBIO17	
			Blood glucose	18	citmBIO18	
			Oral glucose tolerance test	19	citmBIO19	
			Fasting blood sugar	20	citmBIO20	

		Hemoglobin A1C	21	citmBIO21	
		Lipids	22	citmBIO22	
cCOAGTEST	String	Prothrombine time (PT)	1CT	citmPT	itmCOAGTST
		International normalized ratio (INR)	2CT	citmINTERNORM	
		Activated coagulation time (ACT)	3CT	citmACTCOAG	
		Activated partial thromboplastine time (APTT)	4CT	citmACTPART	
cBloodContent	String	Red cells	1	citmBloodContent1	itmBLOODCONTENT
		Platelets	2	citmPlatelet2	
		White cells	3	citmWhitecells3	
cISEROTESTVIRAL	String	Chickenpox (Varicella)	1STV	citmSEROTESTVIRAL1	itmSEROTESTVIRAL
		Chlamydia	2STV	citmSEROTESTVIRAL2	
		Chlamydia pneumonia	3STV	citmSEROTESTVIRAL3	
		Coronavirus	4STV	citmSEROTESTVIRAL4	
		Coxsackie	5STV	citmSEROTESTVIRAL5	
		CMV	6STV	citmSEROTESTVIRAL6	
		EBV	7STV	citmSEROTESTVIRAL7	
		Enterovirus	8STV	citmSEROTESTVIRAL8	
		Hepatitis A	9STV	citmSEROTESTVIRAL9	
		Hepatitis B	10STV	citmSEROTESTVIRAL10	
		Hepatitis C	11STV	citmSEROTESTVIRAL11	
		Hepatitis D	12STV	citmSEROTESTVIRAL12	
		HIV	13STV	citmSEROTESTVIRAL13	
		HSV	14STV	citmSEROTESTVIRAL14	
		Measles	15STV	citmSEROTESTVIRAL15	
		Mumps	16STV	citmSEROTESTVIRAL16	
		Parvovirus	17STV	citmSEROTESTVIRAL17	
		Rabies	18STV	citmSEROTESTVIRAL18	
		Rubella	19STV	citmSEROTESTVIRAL19	
		VZV	20STV	citmSEROTESTVIRAL20	
cTESTCATE	String	Antistreptolysine O (ASLO)	1TC	citmTESTCATE1	itmTESTINFO
		Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
		Borrelia	3TC	citmTESTCATE3	
		H. influenzae type b	4TC	citmTESTCATE4	
		Leptospira	5TC	citmTESTCATE5	
		Mycoplasma	6TC	citmTESTCATE6	
		Mycoplasma pneumonia	7TC	citmTESTCATE7	
		Meningococcus	8TC	citmTESTCATE8	
		Pneumococcus	9TC	citmTESTCATE9	
		Rickettsia	10TC	citmTESTCATE10	
		Salmonella	11TC	citmTESTCATE11	
		M. tuberculosis	12TC	citmTESTCATE12	
		Typhoid fever	13TC	citmTESTCATE13	
cISEROTEST	String	CMV	1ST	citmCMV	itmSEROTEST
		EBV	2ST	citmEBV	
		Enterovirus	3ST	citmENTVIR	
		HIV	4ST	citmHIVIR	
		HSV	5ST	citmHSV	
		Mumps	6ST	citmMUMPS	
		VZV	7ST	citmVZV	
		H. influenzae type b	8ST	citmHINFB	
		Listeria	9ST	citmLIST	
		Meningococcus	10ST	citmMENGS	
		Pneumococcus	11ST	citmPNEUM	
		Rickettsia	12ST	citmRICK	
		Salmonella	13ST	citmSALM	
		M. tuberculosis	14ST	citmMTUB	
		Autoantibodies	15ST	citmAUTO	
cIMMUNOELECTRO	String	H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
		Meningococcus	2IM	citmMENG	
		Pneumococcus	3IM	citmPNEU	
		Not resolved	4IM	citmNOTRES	
cURINE5	String	Urine blood	1UR	citmURINE51	itmURINE
		Urine leukocytes	2UR	citmURINE52	

			Urine total protein (Proteinuria)	3UR	citmURINE53	
			Urine glucose (Glycosuria)	4UR	citmURINE54	
			Urine Ketones	5UR	citmURINE55	

EPI-MALARIA-003 VS AME (115056): RENAL INSUFFICIENCY () [AE.AECAT = "HOSPITALIZATION"]				
VISIT NO				
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4		
RENAL INSUFFICIENCY [AE.AESCAT = "RENAL INSUFFICIENCY"] [FA.FASCAT = "RENAL INSUFFICIENCY"]				
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ RELREC.IDVARVAL when IDVAR = "AEGRPID" Yes -> Please specify Expedited AE Number N4		
3.*	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] ☐ NReq ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029)		
4.* ✓	End date of symptoms	[Note: See CRF Page 159 for corresponding AETERM annotation] [AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐		
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]				
5.* ✓	Are there any signs and symptoms? [Are there any of the following deformations on the foot?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS AND SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ Yes -> (select all that apply) Signs and symptoms [A:009][FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [FA.FATEST = "Temperature"] ☐ [FA.FAORRES] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] Temperature >=37.5°C (axillary). If ticked record highest Axillary temperature from onset until discharge XX.X ☐ Bilateral oedema in the lower extremities ☐ Oliguria ☐ Changed urine colour ☐ Haematuria ☐ Hypertension ☐ Lower back pain ☐ Pallor ☐ Purpura ☐ Petechiae ☐ Blood in stool ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other -> Please specify: A200		
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]				
6.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No		
7.	For GSK: [hidden] [Reconciled]	[LB.LBSTAT = "NOT DONE"] [LB.LBREASND = "SAMPLE NOT TAKEN"] [LB.LBTST = "Laboratory Data"] Reconciled (CDR only): [A:0][NOT SUBMITTED] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab		
8.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No		
BLOOD COUNT				
9.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes		
10. ✓				
BLOOD TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD TEST"] [LB.LBSPEC = "BLOOD"]				
10.1.* ✓	Blood Test Done [Blood Test Done]	[LB.LBTST] ☐ [c]BLDTST ☐		
10.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		
10.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ1iA34jDO16VG2C?domain=xxx.xxx		
10.4 ✓	Units [Units]	[LB.LBORRESU] A12		
10.5.* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
BIOCHEMISTRY [NOT SUBMITTED]				
11.* ✓	Were Biochemistry tests done? [Were Biochemistry tests done?]	[A:N] ☐ No [A:Y] ☐ Yes		

12.				
BIOCHEMISTRY DET Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY DET"] [LB.LBSPEC = "SERUM"]				
12.1*	Biochemistry Test Done [Biochemistry Test Done]	[LB.LBTTEST] [c]BIO_CHEM]		
12.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
12.3	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDO16VG2C?domain=xxx.xxx		
12.4	Units [Units]	[LB.LBORRESU] A12		
12.5*	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range		
BLOOD SMEAR [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"] [LB.LBMETHOD = "SMEAR"]				
13.*	Was blood smear done? [Was blood smear done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
14.	Haemolysis [Haemolysis]	[LB.LBTTEST = "Hemolytic Index"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
15.	Sickle cells anemia test [Sickle cells anemia test]	[LB.LBTTEST = "Sickle Cell Anaemia"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]				
16.*	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
17.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
18.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
19.				
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]				
19.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTTEST] [c]ISEROTESTVIRAL]		
19.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
19.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative		
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]				
BACTERIAL SEROLOGY				
20.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
21.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
22.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative		
23.				
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]				
23.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTTEST] [c]TESTCATE]		
23.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
23.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative		
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]				
24.*	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] No [A:Y] Yes --> Complete all that apply		

25. ✓	Autoantibodies [Autoantibodies]	[LB.LBTTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
26. ✓	Rheumatoid factor [Rheumatoid factor]	[LB.LBTTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
27. ✓	Medications	[LB.LBTTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
28. ✓	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
29. ✓	Other,Specify [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] A200 Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
30. ✓	Other,Specify [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] A200 Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative
URINE [LB.LBSPEC = "URINE"]		
31.* ✓	Was a urine sample taken? [Was a urine sample taken?]	[NOT SUBMITTED] [A:Y] [LB.LBDTC] Yes --> sampling date [NReq] [NReq] [NReq] (2018-2029) [A:N] No
32.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3 - Lost in second line lab
33.* ✓	Were urine tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
34. ✓		
URINE DETAILS Entry [LB.LBCAT = "URINALYSIS"] [LB.LBSCAT = "URINE DETAILS"] [LB.LBSPEC = "URINE"]		
34.1* ✓	Urine test Done	[LB.LBTTEST] [c]URINES
34.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] [NReq] [NReq] (2018-2029)
34.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative
BIOPSY [PR.PRCAT = "BIOPSY"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]		
35.* ✓	Was a biopsy performed? [Was a biopsy performed?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
36.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3 - Lost in second line lab
37. ✓	Others	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] A200 [PR.PRSTDTC] [PR.PRENDTC] [FA.FATEST = "Result"] [FA.FAORRES] Test Date [NReq] [NReq] [NReq] (2018-2029) Result [A:N] Normal [A:A] Abnormal
38. ✓		
BIOPSY DETAILS Entry [PR.PRCAT = "BIOPSY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]		
38.1 ✓	Biopsy Type 1 [Biopsy Type 1]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:2BP] Bone marrow culture [A:5BP] Skin culture [PR.PRSTDTC] [PR.PRENDTC] Test Date [NReq] [NReq] [NReq] (2018-2029) [FA.FATEST = "Result"] [FA.FAORRES] Result [A:POS] Positive [A:NEG] Negative
38.2 ✓	Biopsy Type 2 [Biopsy Type 2]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:1BMB] Bone marrow biopsy [A:3RB] Renal biopsy [A:4SB] Skin biopsy [PR.PRSTDTC] [PR.PRENDTC] Test Date [NReq] [NReq] [NReq] (2018-2029) [FA.FAORRES] [FA.FATEST = "Result"] Result [A:N] Normal [A:A] Abnormal
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
39.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
40. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other -> Please specify: A200

		[PR.PRSTDTCT] [PR.PRENDTCT] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? ☐ Yes ☐ No
41.		
✓		
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
41.1	* Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [cIRADIOEXAM] ☐
41.2	* Test Date [Test Date]	[PR.PRSTDTCT] [PR.PRENDTCT] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
41.3	* Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] ☐ Yes ☐ No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
42.	* Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] ☐ No ☐ Yes -> was the consultation with RAFT ☐ No ☐ Yes -> is a report available ☐ No ☐ Yes
43.	* Is the disease fulfilling the protocol case definition (Job Aid) for renal insufficiency? [Is the disease fulfilling the protocol case definition (Job Aid) for renal insufficiency?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR RENAL INSUFFICIENCY"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, --> What is the final diagnosis for this disease A200 ☐ Yes
44.	* Is it possible to determine probable etiology? [Is it possible to determine probable etiology?]	[FA.FAOBJ = "PROBABLE ETIOLOGY DETERMINED"] [FA.FAORRES] [FA.FATEST = "Occurrence"] ☐ No ☐ Yes -> ☐ infection ☐ trauma ☐ toxic ☐ congenital ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other -> Please specify: A200
45.	* Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] ☐ No ☐ Yes -> ☐ Mild ☐ Moderate ☐ Severe ☐ Fatal
46.	* Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] ☐ Fully recovered ☐ Recovering ☐ Sequelae ☐ Not resolved ☐ Death
47.	* What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] ☐ Renal insufficiency ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
48.	* What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] ☐ Renal insufficiency ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
49.	* Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

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		Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
		Borrelia	3TC	citmTESTCATE3	
		H. influenzae type b	4TC	citmTESTCATE4	
		Leptospira	5TC	citmTESTCATE5	
		Mycoplasma	6TC	citmTESTCATE6	
		Mycoplasma pneumonia	7TC	citmTESTCATE7	
		Meningococcus	8TC	citmTESTCATE8	
		Pneumococcus	9TC	citmTESTCATE9	
		Rickettsia	10TC	citmTESTCATE10	
		Salmonella	11TC	citmTESTCATE11	
		M. tuberculosis	12TC	citmTESTCATE12	
		Typhoid fever	13TC	citmTESTCATE13	
ciURINE5	String	Urine blood	1UR	citmURINE51	itmURINE
		Urine leukocytes	2UR	citmURINE52	
		Urine total protein (Proteinuria)	3UR	citmURINE53	
		Urine glucose (Glycosuria)	4UR	citmURINE54	
		Urine Ketones	5UR	citmURINE55	
ciRADIOEXAM	String	CT scan	1RE	citmRE1	itmRADIOEXAM
		Electrocardiogram	2RE	citmRE2	
		Electroencephalogram	3RE	citmRE3	
		Electromyogram	4RE	citmRE4	
		MRI	5RE	citmRE5	
		Non-barium or air-contrast enema	6RE	citmRE6	
		X-ray	7RE	citmRE7	
		X-ray abdomen	8RE	citmRE8	
		Ultrasound	9RE	citmRE9	
		Ultrasound &C" cardiac	10RE	citmRE10	

EPI-MALARIA-003 VS AME (115056): JUVENILE CHRONIC ARTHRITIS () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
JUVENILE CHRONIC ARTHRITIS [AE.AESCAT = "JUVENILE CHRONIC ARTHRITIS"] [FA.FASCAT = "JUVENILE CHRONIC ARTHRITIS"]		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.*	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] NRReq ☐ / Req ☐ / Req ☐ (2018-2029)
4.* ✓	End date of symptoms	[AE.AEENDTC] Req ☐ / Req ☐ / Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:IDC] ☐
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
Please record present signs and symptoms		
5.* ✓	Are there any signs and symptoms in the joints? [Are there any signs and symptoms in the joints?]	[FA.FAOBJ = "SIGNS AND SYMPTOMS IN THE JOINTS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes -> (select all that apply) [A:154] ☐ [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "AFFECTED JOINTS RIGHT SIDE"] Affected joints right side [A:LOC01] ☐ foot [A:LOC02] ☐ ankle [A:LOC03] ☐ knee [A:LOC04] ☐ hip [A:LOC05] ☐ finger/hand [A:LOC06] ☐ wrist [A:LOC07] ☐ elbow [A:LOC08] ☐ shoulder [A:LOC09] ☐ neck [A:155] ☐ [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "AFFECTED JOINTS LEFT SIDE"] Affected joints left side [A:LOC01] ☐ foot [A:LOC02] ☐ ankle [A:LOC03] ☐ knee [A:LOC04] ☐ hip [A:LOC05] ☐ finger/hand [A:LOC06] ☐ wrist [A:LOC07] ☐ elbow [A:LOC08] ☐ shoulder [A:LOC09] ☐ neck [A:172] ☐ Pain [A:157] ☐ Warmth [A:156] ☐ Redness [A:158] ☐ Swelling [A:159] ☐ Limited movement [A:161] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] [FA.FAOBJ = "HEIGHT BELOW AVERAGE"] Height below average [A:1] ☐ 1 DS [A:2] ☐ 2 DS [A:3] ☐ 3 DS or more [A:XXX] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200
6.* ✓	Are any general signs and symptoms present? [Are any general signs and symptoms present?]	[FA.FAOBJ = "GENERAL SIGNS AND SYMPTOMS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes -> (select all that apply) [A:009] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [FA.FATEST = "Temperature"] [A:162] [A:163] [A:XX] [A:164] [A:053] [A:140] [A:166] [A:168] [A:165] [A:233] [A:XXX] ☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary). If ticked record highest Axillary temperature from onset until discharge xxx.x [FA.FAORRES] [FA.FATEST = "Duration"] [A:LT2W] ☐ (< 2 weeks) [A:GT2W] ☐ (>= 2 weeks) ☐ Pain in the eyes ☐ Redness of the eyes ☐ Photophobia ☐ Skin rash ☐ Lymphadenopathy ☐ Hepatomegaly ☐ Splenomegaly ☐ Pericarditis ☐ Pneumonia ☐ Pleuritis ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
7.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date NRReq ☐ / NRReq ☐ / NRReq ☐ (2018-2029) [A:N] ☐ No
8.	For GSK: [hidden]	[NOT SUBMITTED]

	[Reconciled]	Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab			
9.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No			
DIAGNOSTIC TEST RESULTS [NOT SUBMITTED]					
10.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[A:N] ☐ No [A:Y] ☐ Yes			
11. ✓					
DIAGNOSTIC TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]					
11.1* ✓	Blood Test Done [Blood Test Done]	[LB.LBTST] ☐ [cIBLDTST] ☐			
11.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)			
11.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx			
11.4 ✓	Units [Units]	[LB.LBORRESU] A12			
11.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range			
ESR AND CRP [LB.LBCAT = "OTHER"] [LB.LBSCAT = "ESR AND CRP"] [LB.LBSPEC = "BLOOD"]					
12.* ✓	Were ESR or CRP tests done? [Were ESR or CRP tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes			
13. ✓	Erythrocytes Sedimentation Rates [Erythrocytes Sedimentation Rates]	[LB.LBTST = "Erythrocyte Sedimentation Rate"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range			
14. ✓	C- reactive Protein [C-reactive Protein]	[LB.LBTST = "C Reactive Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range			
BLOOD SMEAR [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"] [LB.LBMETHOD = "SMEAR"]					
15.* ✓	Was blood smear done? [Was blood smear done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes			
16. ✓	Haemolysis [Haemolysis]	[LB.LBTST = "Hemolytic Index"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative [LB.LBORRES]			
17. ✓	Sickle cells anemia test [Sickle cells anemia test]	[LB.LBTST = "Sickle Cell Anaemia"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative [LB.LBORRES]			
18. ✓					
BLOOD SMEAR Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"]					
18.1* ✓	Blood Content	[LB.LBTST] ☐ [cIbloodContent] ☐			
18.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)			
18.3* ✓	Result [Result]	[LB.LBORRES] [A:N] ☐ Normal [A:A] ☐ Abnormal			
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]					
19.* ✓	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes			
20. ✓	Other, Specify [Other, Specify]	[LB.LBTST = "Other"] [LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative			
21. ✓	Other, Specify [Other, Specify]	[LB.LBTST = "Other"] [LB.LBTST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative			

22.			
✓			
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]			
22.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTEST] [c]SEROTESTVIRAL ☐	
22.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)]	
22.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
23.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
24.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Other A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
25.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Other A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
26.			
✓			
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
26.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTEST] [c]TESTCATE ☐	
26.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)]	
26.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]			
27.*	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply	
28.	Autoantibodies [Autoantibodies]	[LB.LBTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
29.	Rheumatoid factor [Rheumatoid factor]	[LB.LBTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
30.	Medications	[LB.LBTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
31.	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
32.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Other A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
33.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Other A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "PCR"] [LB.LBSPEC = "BLOOD"]			
34.*	Was Blood PCR test done? [Was Blood PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
35.	BLOOD	[LB.LBTEST = "BLOOD TEST" when LBORRES = "NEGATIVE"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)]	

		[LB.LBORRES] [A:NEG] ☐ Negative [A:POS] ☐ [LB.LBTEST when LBORRES = "POSITIVE"] Positive -> specify pathogen Virus <table border="0"> <tr> <td>[A:TUBR]</td> <td>☐</td> <td>Tuberculosis</td> </tr> <tr> <td>[A:VAR]</td> <td>☐</td> <td>Chickenpox (Varicella)</td> </tr> <tr> <td>[A:CORO]</td> <td>☐</td> <td>Coronavirus</td> </tr> <tr> <td>[A:COX]</td> <td>☐</td> <td>Coxsackie</td> </tr> <tr> <td>[A:CMV]</td> <td>☐</td> <td>CMV</td> </tr> <tr> <td>[A:EBV]</td> <td>☐</td> <td>EBV</td> </tr> <tr> <td>[A:ENTERO]</td> <td>☐</td> <td>Enterovirus</td> </tr> <tr> <td>[A:HEPA]</td> <td>☐</td> <td>Hepatitis A</td> </tr> <tr> <td>[A:HEPB]</td> <td>☐</td> <td>Hepatitis B</td> </tr> <tr> <td>[A:HEPC]</td> <td>☐</td> <td>Hepatitis C</td> </tr> <tr> <td>[A:HEPD]</td> <td>☐</td> <td>Hepatitis D</td> </tr> <tr> <td>[A:HIV01]</td> <td>☐</td> <td>HIV</td> </tr> <tr> <td>[A:HSV]</td> <td>☐</td> <td>HSV</td> </tr> <tr> <td>[A:MEAS]</td> <td>☐</td> <td>Measles</td> </tr> <tr> <td>[A:MUM]</td> <td>☐</td> <td>Mumps</td> </tr> <tr> <td>[A:PARV01]</td> <td>☐</td> <td>Parvovirus</td> </tr> <tr> <td>[A:RABIES]</td> <td>☐</td> <td>Rabies</td> </tr> <tr> <td>[A:RUB]</td> <td>☐</td> <td>Rubella</td> </tr> <tr> <td>[A:VZV]</td> <td>☐</td> <td>VZV</td> </tr> <tr> <td>[A:OTH]</td> <td>☐</td> <td>[LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] Other A200 </td> </tr> </table> [LB.LBTEST when LBORRES = "POSITIVE"] Bacteria <table border="0"> <tr> <td>[A:BOR]</td> <td>☐</td> <td>Borrelia</td> </tr> <tr> <td>[A:CHLAM]</td> <td>☐</td> <td>Chlamydia</td> </tr> <tr> <td>[A:CHLAPN]</td> <td>☐</td> <td>Chlamydia pneumonia</td> </tr> <tr> <td>[A:INFLU]</td> <td>☐</td> <td>H. influenzae</td> </tr> <tr> <td>[A:LEPTO]</td> <td>☐</td> <td>Leptospira</td> </tr> <tr> <td>[A:MENO1]</td> <td>☐</td> <td>Meningococcus</td> </tr> <tr> <td>[A:TUB]</td> <td>☐</td> <td>M. Tuberculosis (only in CSF in CRF)</td> </tr> <tr> <td>[A:MYC]</td> <td>☐</td> <td>Mycoplasma</td> </tr> <tr> <td>[A:MYCPN]</td> <td>☐</td> <td>Mycoplasma pneumonia</td> </tr> <tr> <td>[A:PNEU01]</td> <td>☐</td> <td>Pneumococcus</td> </tr> <tr> <td>[A:RICK]</td> <td>☐</td> <td>Rickettsia</td> </tr> <tr> <td>[A:SP]</td> <td>☐</td> <td>Salmonella</td> </tr> <tr> <td>[A:TYPH01]</td> <td>☐</td> <td>Typhoid fever</td> </tr> <tr> <td>[A:OTH]</td> <td>☐</td> <td>[LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] Other A200 Please Specify A200 </td> </tr> </table>	[A:TUBR]	☐	Tuberculosis	[A:VAR]	☐	Chickenpox (Varicella)	[A:CORO]	☐	Coronavirus	[A:COX]	☐	Coxsackie	[A:CMV]	☐	CMV	[A:EBV]	☐	EBV	[A:ENTERO]	☐	Enterovirus	[A:HEPA]	☐	Hepatitis A	[A:HEPB]	☐	Hepatitis B	[A:HEPC]	☐	Hepatitis C	[A:HEPD]	☐	Hepatitis D	[A:HIV01]	☐	HIV	[A:HSV]	☐	HSV	[A:MEAS]	☐	Measles	[A:MUM]	☐	Mumps	[A:PARV01]	☐	Parvovirus	[A:RABIES]	☐	Rabies	[A:RUB]	☐	Rubella	[A:VZV]	☐	VZV	[A:OTH]	☐	[LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] Other A200	[A:BOR]	☐	Borrelia	[A:CHLAM]	☐	Chlamydia	[A:CHLAPN]	☐	Chlamydia pneumonia	[A:INFLU]	☐	H. influenzae	[A:LEPTO]	☐	Leptospira	[A:MENO1]	☐	Meningococcus	[A:TUB]	☐	M. Tuberculosis (only in CSF in CRF)	[A:MYC]	☐	Mycoplasma	[A:MYCPN]	☐	Mycoplasma pneumonia	[A:PNEU01]	☐	Pneumococcus	[A:RICK]	☐	Rickettsia	[A:SP]	☐	Salmonella	[A:TYPH01]	☐	Typhoid fever	[A:OTH]	☐	[LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] Other A200 Please Specify A200
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DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]																																																																																																								
36.* ☒	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes -> was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes -> is a report available [A:N] ☐ No [A:Y] ☐ Yes																																																																																																						
37.* ☒	Is the disease fulfilling the protocol case definition (Job Aid) for Juvenile Chronic Arthritis? [Is the disease fulfilling the protocol case definition (Job Aid) for Juvenile Chronic Arthritis?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR JUVENILE CHRONIC ARTHRITIS"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Yes -> please specify [A:PAU] ☐ Pauciartthritis [A:POL] ☐ Polyarthritits [A:SAR] ☐ Systemic Arthritis																																																																																																						
38.* ☒	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal																																																																																																						
39.* ☒	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death																																																																																																						
40.* ☒	Was diagnosis confirmed by the medical exam 3 months after its onset? [Was diagnosis confirmed by the medical exam 3 months after its onset?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "DIAGNOSIS CONFIRMED BY MEDICAL EXAM 3 MONTHS AFTER ONSET"] [A:N] ☐ No [A:Y] ☐ Yes																																																																																																						
41.* ☒	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Juvenile rheumatoid arthritis] ☐ Juvenile rheumatoid arthritis [A:99][NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contains the preferred term given after second line lab results] Other, Please specify: A200																																																																																																						

42.	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FA0B] = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS" [FA.FA0RRES] [FA.FATEST = "Diagnosis"] ☐ Juvenile rheumatoid arthritis ☐ [FA.FA0RRES] [FA.FATEST = "Diagnosis"] Other, Please specify: A200
43.	Comment	[C0.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
 Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: JUVENILE CHRONIC ARTHRITIS						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	ctmBLDTEST	itmBLOODTEST
			Platelets	2BL	ctmPLT	
			White blood cells	3BL	ctmWBC	
			Neutrophils	4BL	ctmNEUT	
			Lymphocytes	5BL	ctmLYMP	
			Monocytes	6BL	ctmMONO	
			Basophils	7BL	ctmBASO	
			Eosinophils	8BL	ctmEOS	
cibloodContent	String		Red cells	1	ctmblodContent1	itmBLOODCONTENT
			Platelets	2	ctmPlatelet2	
			White cells	3	ctmWhitecells3	
ciSEROESTVIRAL	String		Chickenpox (Varicella)	1STV	ctmSEROESTVIRAL1	itmSEROESTVIRAL
			Chlamydia	2STV	ctmSEROESTVIRAL2	
			Chlamydia pneumonia	3STV	ctmSEROESTVIRAL3	
			Coronavirus	4STV	ctmSEROESTVIRAL4	
			Coxsackie	5STV	ctmSEROESTVIRAL5	
			CMV	6STV	ctmSEROESTVIRAL6	
			EBV	7STV	ctmSEROESTVIRAL7	
			Enterovirus	8STV	ctmSEROESTVIRAL8	
			Hepatitis A	9STV	ctmSEROESTVIRAL9	
			Hepatitis B	10STV	ctmSEROESTVIRAL10	
			Hepatitis C	11STV	ctmSEROESTVIRAL11	
			Hepatitis D	12STV	ctmSEROESTVIRAL12	
			HIV	13STV	ctmSEROESTVIRAL13	
			HSV	14STV	ctmSEROESTVIRAL14	
			Measles	15STV	ctmSEROESTVIRAL15	
			Mumps	16STV	ctmSEROESTVIRAL16	
			Parvovirus	17STV	ctmSEROESTVIRAL17	
			Rabies	18STV	ctmSEROESTVIRAL18	
			Rubella	19STV	ctmSEROESTVIRAL19	
			VZV	20STV	ctmSEROESTVIRAL20	
ciTESTCATE	String		Antistreptolysine O (ASLO)	1TC	ctmTESTCATE1	itmTESTINFO
			Beta haemolytic Streptococcus	2TC	ctmTESTCATE2	
			Borrelia	3TC	ctmTESTCATE3	

		H. influenzae type b	4TC	citmTESTCATE4
		Leptospira	5TC	citmTESTCATE5
		Mycoplasma	6TC	citmTESTCATE6
		Mycoplasma pneumonia	7TC	citmTESTCATE7
		Meningococcus	8TC	citmTESTCATE8
		Pneumococcus	9TC	citmTESTCATE9
		Rickettsia	10TC	citmTESTCATE10
		Salmonella	11TC	citmTESTCATE11
		M. tuberculosis	12TC	citmTESTCATE12
		Typhoid fever	13TC	citmTESTCATE13

EPI-MALARIA-003 VS AME (115056): STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN) () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN) [AE.AESCAT = "STEVENS JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS"] [FA.FASCAT = "STEVENS JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS"]		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[A:N] ☐ No [A:Y] ☐ RELREC.IDVARVAL when IDVAR = "AEGRPID" Yes --> Please specify Expedited AE Number N4
3.* ✓	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] Ongoing at Discharge [A:1DC] ☐
5.* ✓	Was the onset sudden? [Was the onset sudden?]	[SUPPAE.QVAL when QNAM = "ONSETSUD"] [A:N] ☐ No [A:Y] ☐ Yes
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
Please record all signs and symptoms		
6.* ✓	Are there any mucosal lesions? [Are there any signs on the skin and mucosa?]	[FA.FAOBJ = "MUCOSAL LESIONS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ Yes -->(select all that apply) [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] SIGN AND SYMPTOMS [A:169] ☐ Conjunctivitis [A:170] ☐ Keratitis [A:171] ☐ Mouth, nose and genital ulcerations [A:3] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please specify A200
7.* ✓	Did skin symptoms occurred after mucus membrane symptoms? [Did skin symptoms occurred after mucus membrane symptoms?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SKIN SYMPTOMS OCCURRES AFTER MUCUS MEMBRANE SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ Yes
8.* ✓	Is there diffuse erythema? [Is there diffuse erythema?]	[FA.FAOBJ = "DIFFUSE ERYTHEMA"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FATEST = "Occurrence"] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "ERYTHEMA DISPERSION PROGRESSIVE"] Yes --> Is erythema dispersion progressive? [A:N] ☐ No [A:Y] ☐ Yes
9.* ✓	Are there epidermal detachments? [Are there epidermal detachments?]	[FA.FAOBJ = "EPIDERMAL DETACHMENTS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ Yes
10.* ✓	Is there Nikolsky sign? [Is there Nikolsky sign?]	[FA.FAOBJ = "NIKOLSKY SIGN"] [FA.FAORRES] [FA.FATEST = "Result"] [A:NEG] ☐ Negative [A:POS] ☐ Positive
11.* ✓	Can percentage of affected body surface be evaluated? [Can percentage of affected body surface be evaluated?]	[FA.FAOBJ = "PERCENTAGE OF AFFECTED BODY SURFACE EVALUATED"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Result"] Yes --> If Yes [A:LT10] ☐ <10% [A:RG10-30] ☐ 10 - 30% [A:GT30] ☐ >30%
12.* ✓	Lesion morphology [Lesion morphology]	[FA.FAOBJ = "LESION MORPHOLOGY"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Yes--> If Yes [A:0] ☐ Maculae [A:1] ☐ Bullae [A:2] ☐ Atypical target lesions
13.* ✓	Are other general signs present? [Are other general signs present?]	[FA.FAOBJ = "GENERAL SIGNS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ Yes -->(select all that apply) [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] SIGN AND SYMPTOMS [A:009] [FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX] ☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XXX.X ☐ Pain ☐ Malaise ☐ Signs of shock ☐ Respiratory distress ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other --> Please specify A128
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
14.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) [A:N] ☐ No
15.	For GSK: [hidden]	[NOT SUBMITTED]

24.* ✓	Were other tests performed? [Were other tests performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
25. ✓	Other, specify: [Other, specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
26. ✓	Medications [Medications]	[LB.LBTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BIOPSY [PR.PRCAT = "BIOPSY"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]			
27.* ✓	Was a biopsy performed? [Was a biopsy performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
28.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab	
29. ✓	Others	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] A200	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [FA.FATEST = "Result"] [FA.FAORRES] [A:N] ☐ Normal [A:A] ☐ Abnormal
30. ✓			
BIOPSY Entry [PR.PRCAT = "BIOPSY"] [PR.PRPRES = "Y"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]			
30.1* ✓	Biopsy Performed	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [clBiopsyPerf] ☐	
30.2 ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
30.3* ✓	Result [Result]	[FA.FAORRES] [FA.FATEST = "Result"] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]			
31.* ✓	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAOBJ = "CONSULTATION WITH RAFT"] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes	
32.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for SJS/TEN? [Is the disease fulfilling the protocol case definition (Job Aid) for SJS/TEN?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR STEVENS JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS"] [FA.FAORRES] [FA.FATEST = "Result"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -->What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Yes --> Please specify [A:1] ☐ STEVENS JOHNSON SYNDROME [A:2] ☐ SJS_TEN overlap [A:3] ☐ TOXIC EPIDERMAL NECROLYSIS	
33.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal	
34.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death	
35.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [A:Stevens Johnson syndrome] ☐ Stevens Johnson syndrome [A:Toxic epidermal necrolysis] ☐ Toxic epidermal necrolysis [A:99] [NOT SUBMITTED] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPPR.QVAL when QNAM = "RELDIS"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contains the preferred term given after second line lab results] Other, Please specify: A200	
36.	What is the preferred term associated to this event after the 2nd line	[FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [FA.FAORRES] [FA.FATEST	

✓	laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	= "Diagnosis"] [A:Stevens Johnson syndrome] [A:Toxic epidermal necrolysis] [A:99][NOT SUBMITTED] Stevens Johnson syndrome Toxic epidermal necrolysis [FA:FAORRES] [FA:FATEST = "Diagnosis"] Other, Please specify: A200
37. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST
			Platelets	2BL	citmPLT	
			White blood cells	3BL	citmWBC	
			Neutrophils	4BL	citmNEUT	
			Lymphocytes	5BL	citmLYMP	
			Monocytes	6BL	citmMONO	
			Basophils	7BL	citmBASO	
			Eosinophils	8BL	citmEOS	
ciBIO_CHEM	String		Total bilirubin	1	citmBIO1	itmBioChemTest
			Conjugated bilirubin	2	citmBIO2	
			Alanine amino transferase (ALT)	3	citmBIO3	
			Aspartate amino transferase (AST)	4	citmBIO4	
			Alkaline Phosphatase (ALP)	5	citmBIO5	
			Total protein	6	citmBIO6	
			Albumin	7	citmBIO7	
			Serum urea nitrogen	8	citmBIO8	
			Serum creatinine	9	citmBIO9	
			Serum sodium	10	citmBIO10	
			Serum potassium	11	citmBIO11	
			Serum chloride	12	citmBIO12	
			Serum calcium	14	citmBIO14	
			Serum magnesium	15	citmBIO15	
			Vitamin B12	16	citmBIO16	
			Folate	17	citmBIO17	
			Blood glucose	18	citmBIO18	
			Oral glucose tolerance test	19	citmBIO19	
			Fasting blood sugar	20	citmBIO20	
			Hemoglobin A1C	21	citmBIO21	
			Lipids	22	citmBIO22	
ciCOAGTEST1	String		Prothrombine time (PT)	1PT	citmCoagTest1	itmCOAGTEST1
			International normalized ratio (INR)	2IN	citmCoagTest2	
			Activated coagulation time (ACT)	3ACT	citmCoagTest3	
			Activated partial thromboplastine time (APTT)	4APT	citmCoagTest4	
ciBiopsyPerf	String		Bone marrow biopsy	1BMB	citmBiopsyPerf1	itmBiopsyPerf
			Bone marrow culture	2BP	citmBiopsyPerf2	
			Renal biopsy	3RB	citmBiopsyPerf3	

			Skin biopsy	4SB	cltmBiopsyPerf4	
			Skin culture	5BP	cltmBiopsyPerf5	

EPI-MALARIA-003 VS AME (115056): ANAPHYLAXIS () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO [AE.AESCAT = "ANAPHYLAXIS"] [FA.FASCAT = "ANAPHYLAXIS"]		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
ANAPHYLAXIS		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.* ✓	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)
4.* ✓	End date of symptoms	[Note: See CRF Page 181 for corresponding AETERM annotation] [AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐
5.* ✓	Was the onset sudden? [Was the onset sudden?]	[SUPPAE.QVAL when QNAM = "ONSETSUD"] [A:N] ☐ No [A:Y] ☐ Yes
6.* ✓	Was the study participant seen by physician during acute phase? [Was the study participant seen by physician during acute phase?]	[FA.FACAT = "HOSPITALIZATION"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEEN BY PHYSICIAN DURING ACUTE PHASE"] [A:N] ☐ No [A:Y] ☐ Yes
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
Please record all signs and symptoms		
7.* ✓	Are there any mucosal lesions? [Are there any signs on the skin and mucosa?]	[FA.FAOBJ = "MUCOSAL LESIONS"] [FA.FAORRES] [FA.FATEST = "Occurrence"] [A:N] ☐ No [A:Y] ☐ Yes-->(select all that apply) [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] Signs and symptoms [A:0] [A:1][Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:2] [A:175] [A:176] [A:177] [A:178] [A:7] ☐ Generalized urticarial or erythema ☐ Generalized pruritus with skin rash ☐ Angiodema ☐ Generalized pruritus without skin rash ☐ Generalized prickle sensation ☐ Localized injection site urticarial ☐ Red and itchy eyes ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please specify A200
8.* ✓	Are there any cardiovascular or respiratory signs? [Are there any cardiovascular or respiratory signs?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CARDIOVASCULAR OR RESPIRATORY SIGNS"] [A:N] ☐ No [A:Y] ☐ Yes-->(select all that apply) [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] Cardiovascular or Respiratory Signs [A:179][Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:174] [A:180] [A:181] [A:182] [A:183] [A:008] [A:184] [A:185] [A:188] [A:189] [A:234] [A:186] [A:13] ☐ Hypotension ☐ Signs of decompensated shock ☐ Reduced peripheral circulation ☐ Bilateral expiratory wheeze ☐ Stridor ☐ Upper airway swelling (lip, tongue, throat, uvula or larynx) ☐ Respiratory distress ☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat obstruction ☐ Sneezing ☐ Rhinorrhea ☐ Difficulty breathing without wheeze or stridor ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please specify A200
9.* ✓	Are there other general signs? [Are there other general signs?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "GENERAL SIGNS"] [A:N] ☐ No [A:Y] ☐ Yes-->(select all that apply) [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] General signs [A:009] ☐ [FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XX.X [A:065][FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [A:136] [A:133] [A:066] ☐ Diarrhoea ☐ Abdominal pain ☐ Nausea ☐ Vomiting
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
10.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) [A:N] ☐ No
11.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab

12.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No
BLOOD --> OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]		
13.* ✓	Were other tests performed? [Were other tests performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
14. ✓	Medications [Medications]	[LB.LBTTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
15. ✓	Toxic nephropathies [Toxic nephropathies]	[LB.LBTTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
16. ✓	Other, specify: [Other, specify:]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
17.* ✓	Please record duration of symptoms in hours [Please record duration of symptoms in hours]	[FA.FAORRES] [FA.FAORRESU = "HOURS"] [FA.FATEST = "Duration"] [FA.FAOBJ = "DURATION OF SYMPTOMS"] ☐ NReq ☐ 24-hour clock
18.* ✓	Was there a consultation with a specialist [Was there a consultation with a neurologist]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
19.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for Anaphylaxis? [Is the disease fulfilling the protocol case definition (Job Aid) for Anaphylaxis?]	[FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR ANAPHYLAXIS"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Result"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FATEST = "Level of Diagnostic Certainty"] [FA.FAORRES] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] ☐ 1 [A:2DGC] ☐ 2 [A:3DGC] ☐ 3
20.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
21.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
22.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [A:Anaphylaxis] ☐ Anaphylaxis [A:99] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] Other, Please specify: A200
23. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [A:Anaphylaxis] ☐ Anaphylaxis [A:99] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [AE.AETERM] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contains the preferred term given after second line lab results] Other, Please specify: A200
24. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): THROMBOCYTOPENIA () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
THROMBOCYTOPENIA [AE.AESCAT = "THROMBOCYTOPENIA"] [FA.FASCAT = "THROMBOCYTOPENIA"]		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.*	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] [NReq ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029)]
4.* ✓	End date of symptoms	[Note: See CRF Page 187 and 188 for corresponding AETERM annotation] [AE.AEENDTC] [Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029)] [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
Please record all signs and symptoms		
5.* ✓	Are there any signs of spontaneous bleeding from skin or mucous membranes?	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF SPONTANEOUS BLEEDING FROM SKIN OR MUCOUS MEMBRANES"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF SPONTANEOUS BLEEDING FROM SKIN OR MUCOUS MEMBRANES"] Yes --> Reported [A:N] ☐ No [A:Y] ☐ Yes [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SIGNS OF SPONTANEOUS BLEEDING FROM SKIN OR MUCOUS MEMBRANES"] -----> Seen [A:N] ☐ No [A:Y] ☐ Yes
6.* ✓	Are there any superficial wounds that bleed profusely?	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SUPERFICIAL WOUNDS THAT BLEED PROFUSELY"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SUPERFICIAL WOUNDS THAT BLEED PROFUSELY"] Yes --> Reported [A:N] ☐ No [A:Y] ☐ Yes [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SUPERFICIAL WOUNDS THAT BLEED PROFUSELY"] -----> Seen [A:N] ☐ No [A:Y] ☐ Yes
7.* ✓	Are there other bleeding signs? [Are there other bleeding signs?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "BLEEDING SIGNS"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes -> (select all that apply) Bleeding Signs [A:059] ☐ Petechiae [A:103] ☐ Purpura [A:190] ☐ Ecchymosis [A:191] ☐ Splenomegaly [A:099] ☐ Other Please Specify A200
8.* ✓	Are there other general signs? [Are there other general signs?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "GENERAL SIGNS"] [A:N] ☐ No [A:Y] ☐ Yes -> (select all that apply) General signs [A:009] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [FA.FATEST = "Temperature"] ☐ [FA.FAORRES] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] Temperature >=37.5°C (axillary) . If ticked record highest Axillary temperature from onset until discharge XX.X [FA.FAORRES] [FA.FATEST = "Specification"] Other A200 Please Specify
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]		
9.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date [NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
10.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
11.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date [Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No
DIAGNOSTIC TEST RESULTS		
Please complete the results of tests that were performed to diagnose this event		
BLOOD		
COMPLETE BLOOD COUNT (CBC)		
12.*	Were complete blood count tests done?	[NOT SUBMITTED]

✓	[Were complete blood count tests done?]	[A:N] ☐ No [A:Y] ☐ Yes
13. ✓		
DIAGNOSTIC TEST RESULTS Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]		
13.1* ✓	Blood Count Test	[LB.LBTEST] ☐ [c]BLDCNT ☐
13.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
13.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jD0I6VG2C?domain=xxx.xxx
13.4 ✓	Units [Units]	[LB.LBORRESU] A12
13.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
COAGULATION [LB.LBCAT = "COAGULATION"] [LB.LBSCAT = "COAGULATION"] [LB.LBSPEC = "BLOOD"]		
14.* ✓	Were coagulation tests done? [Were coagulation tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
15. ✓	Bleeding time [Bleeding time]	[LB.LBTEST = "Bleeding Time"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:N] ☐ Normal [A:A] ☐ Abnormal
16. ✓		
COAGULATION Entry [LB.LBCAT = "COAGULATION"] [LB.LBSCAT = "COAGULATION"] [LB.LBSPEC = "BLOOD"]		
16.1* ✓	Coagulation Test [Coagulation Test]	[LB.LBTEST] ☐ [c]COAGTEST1 ☐
16.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
16.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jD0I6VG2C?domain=xxx.xxx
16.4 ✓	Units [Units]	[LB.LBORRESU] A12
16.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BLOOD SMEAR [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "BLOOD SMEAR"] [LB.LBSPEC = "BLOOD"] [LB.LBMETHOD = "SMEAR"]		
17.* ✓	Was blood smear done? [Was blood smear done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
18. ✓	Haemolysis [Haemolysis]	[LB.LBTEST = "Hemolytic Index"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
19. ✓	Sickle cells anemia test [Sickle cells anemia test]	[LB.LBTEST = "Sickle Cell Anaemia"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]		
20.* ✓	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
21. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
22. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] A200 Test Date NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
23. ✓		
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]		

23.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTEST] [cISEROTESTVIRAL]
23.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] NReq / NReq / NReq (2018-2029)
23.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
24.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
25.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
26.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
27.		
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
27.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTEST] [cITESTCATE]
27.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] NReq / NReq / NReq (2018-2029)
27.3*	Result [Result]	[LB.LBORRES] [A:POS] Positive [A:NEG] Negative
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]		
28.*	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] No [A:Y] Yes --> Complete all that apply
29.	Autoantibodies [Autoantibodies]	[LB.LBTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date NReq / NReq / NReq (2018-2029) Result [A:POS] Positive [A:NEG] Negative
30.	Rheumatoid factor [Rheumatoid factor]	[LB.LBTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date NReq / NReq / NReq (2018-2029) Result [A:POS] Positive [A:NEG] Negative
31.	Medications [Medications]	[LB.LBTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
32.	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
33.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
34.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date NReq / NReq / NReq (2018-2029) [LB.LBORRES] Result [A:POS] Positive [A:NEG] Negative
BIOPSY [PR.PRCAT = "BIOPSY"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]		
35.*	Was a biopsy performed? [Was a biopsy performed?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes
36.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3 - Lost in second line lab
37.	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] A200 [PR.PRSTDTC] [PR.PRENDTC] Test Date NReq / NReq / NReq (2018-2029) [FA.FATEST = "Result"] [FA.FAORRES] Result [A:N] Normal [A:A] Abnormal

38.		
✓		
BIOPSY Entry [PR.PRCAT = "BIOPSY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]		
38.1	Biopsy Type 1 [Biopsy Type 1]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:2BP] Bone marrow culture [A:5BP] Skin culture [PR.PRSTDTCT] [PR.PRENDTCT] Test Date [NReq] / [NReq] / [NReq] (2018-2029) [FA.FATEST = "Result"] [FA.FAORRES] Result [A:POS] Positive [A:NEG] Negative
38.2	Biopsy Type 2 [Biopsy Type 2]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:1BMB] Bone marrow biopsy [A:3RB] Renal biopsy [A:4SB] Skin biopsy [PR.PRSTDTCT] [PR.PRENDTCT] Test Date [NReq] / [NReq] / [NReq] (2018-2029) [FA.FAORRES] [FA.FATEST = "Result"] Result [A:N] Normal [A:A] Abnormal
DISEASES EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
39.*	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes -> was the consultation with RAFT [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Report Available"] Yes -> is a report available [A:N] No [A:Y] Yes
40.*	Is the disease fulfilling the protocol case definition (Job Aid) for Thrombocytopenia? [Is the disease fulfilling the protocol case definition (Job Aid) for Thrombocytopenia?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR THROMBOCYTOPENIA"] [A:N] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -> What is the final diagnosis for this disease A200 [[A:Y] [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes -> please record the level of diagnostic certainty as defined in Job Aid [A:1] 1 [A:2] 2
41.*	Is it possible to identify likely etiology? [Is it possible to identify likely etiology?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "LIKELY ETIOLOGY IDENTIFIED"] [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Etiology"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] Yes -> Complete all that apply [A:AET1] ☐ Infection disease [A:AET2] ☐ Toxic exposure [A:AET3] ☐ Chemotherapy treatment [A:AET4] ☐ Autoimmune disease [A:AET5] ☐ Haematology disorders [A:AET6] ☐ Other treatment [A:AET7] ☐ Congenital disease [A:AET8] ☐ General malignancies [A:AET9] ☐ Other
42.*	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] No [A:Y] [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
43.*	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
44.*	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] [A:Thrombotopenia] ☐ Thrombocytopenia [A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
45.	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] [A:Thrombotopenia] ☐ Thrombocytopenia [A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
46.	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

CodeList RefName	CodeList Data Type	Subset	Label	Code	CodeList Item RefName	Data Variable RefName
ciBLCNNT	String		Red blood cells	1	citmBLCNNT1	itmBLCNNTTEST
			Platelets	2	citmBLCNNT2	
			Platelets 2nd count	3	citmBLCNNT3	
			Platelets 3rd count	4	citmBLCNNT4	
			White blood cells	5	citmBLCNNT5	
			Neutrophils	6	citmBLCNNT6	
			Lymphocytes	7	citmBLCNNT7	
			Monocytes	8	citmBLCNNT8	
			Eosinophils	9	citmBLCNNT9	
			Eosinophils	10	citmBLCNNT10	
ciCOAGTEST1	String		Prothrombine time (PT)	1PT	citmCoagTest1	itmCOAGTEST1
			International normalized ratio (INR)	2IN	citmCoagTest2	
			Activated coagulation time (ACT)	3ACT	citmCoagTest3	
			Activated partial thromboplastine time (APTT)	4APT	citmCoagTest4	
ciSERO TESTVIRAL	String		Chickenpox (Varicella)	1STV	citmSERO TESTVIRAL1	itmSERO TESTVIRAL
			Chlamydia	2STV	citmSERO TESTVIRAL2	
			Chlamydia pneumonia	3STV	citmSERO TESTVIRAL3	
			Coronavirus	4STV	citmSERO TESTVIRAL4	
			Coxsackie	5STV	citmSERO TESTVIRAL5	
			CMV	6STV	citmSERO TESTVIRAL6	
			EBV	7STV	citmSERO TESTVIRAL7	
			Enterovirus	8STV	citmSERO TESTVIRAL8	
			Hepatitis A	9STV	citmSERO TESTVIRAL9	
			Hepatitis B	10STV	citmSERO TESTVIRAL10	
			Hepatitis C	11STV	citmSERO TESTVIRAL11	
			Hepatitis D	12STV	citmSERO TESTVIRAL12	
			HIV	13STV	citmSERO TESTVIRAL13	
			HSV	14STV	citmSERO TESTVIRAL14	
			Measles	15STV	citmSERO TESTVIRAL15	
			Mumps	16STV	citmSERO TESTVIRAL16	
			Parvovirus	17STV	citmSERO TESTVIRAL17	
			Rabies	18STV	citmSERO TESTVIRAL18	
			Rubella	19STV	citmSERO TESTVIRAL19	
			VZV	20STV	citmSERO TESTVIRAL20	
ciTESTCATE	String		Antistreptolysine O(ASLO)	1TC	citmTESTCATE1	itmTESTINFO
			Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
			Borrelia	3TC	citmTESTCATE3	
			H. influenzae type b	4TC	citmTESTCATE4	
			Leptospira	5TC	citmTESTCATE5	
			Mycoplasma	6TC	citmTESTCATE6	
			Mycoplasma pneumonia	7TC	citmTESTCATE7	
			Meningococcus	8TC	citmTESTCATE8	
			Pneumococcus	9TC	citmTESTCATE9	
			Rickettsia	10TC	citmTESTCATE10	
			Salmonella	11TC	citmTESTCATE11	
			M. tuberculosis	12TC	citmTESTCATE12	

			Typhoid fever	13TC	ctmTESTCATE13	

EPI-MALARIA-003 VS AME (115056): HYPOTONIC HYPORESPONSIVE EPISODE () [AE.AECAT = "HOSPITALIZATION"]			
VISIT NO			
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4	
HYPOTONIC HYPORESPONSIVE EPISODE [AE.AESCAT = "HYPOTONIC HYPORESPONSIVE EPISODE"] [FA.FASCAT = "HYPOTONIC HYPORESPONSIVE EPISODE"]			
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4	
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029)	
4.* ✓	End date of symptoms	[Note: See CRF Page 195 and 196 for corresponding AETERM annotation] [AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐	
5.* ✓	Duration of symptoms : [Duration of symptoms :]	[FA.FAORRES] [FA.FATEST = "Duration"] [FA.FAOBJ = "DURATION OF SYMPTOMS"] [A:001] ☐ < 30 min [A:002] ☐ 30 to 60 min [A:003] ☐ > 60 min and <= 1day [A:004] ☐ >1day	
6.* ✓	Time to onset between vaccine dose and symptoms : [Time to onset between vaccine dose and symptoms :]	[FA.FAORRES] [FA.FATEST = "Duration"] [FA.FAOBJ = "TIME TO ONSET BETWEEN VACCINE DOSE AND SYMPTOMS"] [FA.FACAT = "HOSPITALIZATION"] [A:001] ☐ < 1h [A:002] ☐ < 2d [A:003] ☐ < 1w [A:004] ☐ 1 week or more	
7.* ✓	Type of onset: [Type of onset:]	[SUPPAE.QVAL when QNAM = "ONSETTYP"] [A:SUDD] ☐ Sudden [A:PROG] ☐ Progressive [A:SLOW] ☐ Slow	
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]			
8.* ✓	Are there any general signs present? [Are there any major signs and symptoms?]	[FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "GENERAL SIGNS"] Yes --> (select all that apply) [A:009] ☐ Temperature >=37.5°C (axillary) [A:058] ☐ Pallor [A:021] ☐ Cyanosis [A:208] ☐ Shallow breathing [A:209] ☐ Hypotonia [A:232] ☐ Reduction or absence to sensory or verbal stimuli [A:025] ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200	
BLOOD			
9.* ✓	Was a blood sample taken? [Was a blood sample taken?]	[LB.LBSPEC = "BLOOD" or "SERUM"] [NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No	
10.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab	
11.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No	
BIOCHEMISTRY			
12.* ✓	Were glucose tests done? [Were Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply	
13. ✓			
BIOCHEMISTRY Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY TEST"] [LB.LBSPEC = "SERUM"]			
13.1*	Biochemistry Test Done [Biochemistry Test Done]	[LB.LBTST] ☐ [clBIO_CHEM] ☐	
13.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
13.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jD0I6VG2C? domain=xxx.xxx	
13.4 ✓	Units [Units]	[LB.LBORRESU] A12	

13.5*	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
14.*	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
15.*	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"] Yes --> Date of antibiotic started ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done
16.*	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other --> Please specify A200 [A:5] ☐ Not documented
17.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
18.*	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
19.*	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
20.	CSF leukocytes [CSF leukocytes]	[LB.LBTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
21.*	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
22.	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
23.	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx [LB.LBORRESU] Units A12 [LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF EXAMINATION/STAINING		
24.*	Were CSF Examination/Staining tests done?	[NOT SUBMITTED]

✓	[Were CSF Examination/Staining tests done?]	[A:N] ☐ No [A:Y] ☐ Yes
25. ✓		
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
25.1* ✓	CSF test Done [CSF test Done]	[LB.LBTTEST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)
25.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
25.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF Culture [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]		
26.* ✓	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
27. ✓	CSF Culture [CSF Culture]	[MB.MBTTEST = "Organism Present"] [SUPPMB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [MB.MBORRES] Result [A:POS] ☐ [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHRI"] Positive, Please Specify A200 [A:NEG] ☐ Negative
CSF SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
28.* ✓	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
29. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHRI"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
30. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHRI"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
31. ✓		
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
31.1* ✓	Serology Test Done [Serology Test Done]	[LB.LBTTEST] ☐ [cISEROTEST] ☐
31.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
31.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
32.* ✓	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
33. ✓	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] RESULT [A:NEG] ☐ Negative [A:POS] ☐ [LB.LBTTEST when LBORRES = "POSITIVE"] ☐ [LB.LBORRES] Positive --> specify pathogen [A:ADENO] ☐ Adenovirus [A:CMV] ☐ CMV [A:EBV] ☐ EBV [A:ENTERO] ☐ Enterovirus [A:HIV01] ☐ HIV [A:HSV01] ☐ HSV1

		[A:HHV-6] ☐ HHV-6 [A:HSV02] ☐ HSV2 [A:MUM] ☐ Mumps [A:RABIS] ☐ Rabies virus [A:VZV] ☐ VZV [A:INFLU] ☐ H. influenzae type b [A:CSF_LIST] ☐ Listeria [A:MEN01] ☐ Meningococcus [A:PNEU01] ☐ Pneumococcus [A:RICK] ☐ Rickettsia [A:SALSP] ☐ Salmonella sp [A:CSF_PFAL] ☐ P. falciparum [A:TUBR] ☐ M. tuberculosis [A:CSF_OTH] ☐ [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] CSF Other, please specify A100
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
34.* ✓	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
35. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTOTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
36. ✓		
IMMUNO ELECTRO Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTROPHORESIS TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
36.1* ✓	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTTEST] ☐ [cIMMUNOELECTRO] ☐
36.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTOTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
36.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
37.* ✓	Was there a consultation with a specialist? [Was there a consultation with a neurologist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> was a consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
38.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for hypotonic hyposponsive episode? [Is the disease fulfilling the protocol case definition (Job Aid) for hypotonic hyposponsive episode?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR HYPOTONIC HYPORESPONSIVE EPISODE"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No --> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] ☐ 1 [A:2DGC] ☐ 2 [A:3DGC] ☐ 3
39.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
40.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
41.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] [A:hypotonic] ☐ Hypotonic-hyposponsive episode [A:99] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
42. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] [A:hypotonic] ☐ Hypotonic-hyposponsive episode

	laboratory results?]	[A:99]/[Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
43. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: HYPOTONIC HYPORESPONSIVE EPISODE						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBIO_CHEM	String		Total bilirubin	1	citmBIO1	itmBIOCHEMTEST1
			Conjugated bilirubin	2	citmBIO2	
			Alanine amino transferase (ALT)	3	citmBIO3	
			Aspartate amino transferase (AST)	4	citmBIO4	
			Alkaline Phosphatase (ALP)	5	citmBIO5	
			Total protein	6	citmBIO6	
			Albumin	7	citmBIO7	
			Serum urea nitrogen	8	citmBIO8	
			Serum creatinine	9	citmBIO9	
			Serum sodium	10	citmBIO10	
			Serum potassium	11	citmBIO11	
			Serum chloride	12	citmBIO12	
			Serum calcium	14	citmBIO14	
			Serum magnesium	15	citmBIO15	
			Vitamin B12	16	citmBIO16	
			Folate	17	citmBIO17	
			Blood glucose	18	citmBIO18	
			Oral glucose tolerance test	19	citmBIO19	
			Fasting blood sugar	20	citmBIO20	
			Hemoglobin A1C	21	citmBIO21	
			Lipids	22	citmBIO22	
ciSEROTEST	String		CMV	1ST	citmCMV	itmSEROTEST
			EBV	2ST	citmEBV	
			Enterovirus	3ST	citmENTVIR	
			HIV	4ST	citmHIVIR	
			HSV	5ST	citmHSV	
			Mumps	6ST	citmMUMPS	
			VZV	7ST	citmVZV	
			H. influenzae type b	8ST	citmHINFB	
			Listeria	9ST	citmLIST	
			Meningococcus	10ST	citmMENGS	
			Pneumococcus	11ST	citmPNEUM	
			Rickettsia	12ST	citmRICK	
			Salmonella	13ST	citmSALM	
			M. tuberculosis	14ST	citmMTUB	
			Autoantibodies	15ST	citmAUTO	
ciIMMUNOELECTRO	String		H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
			Meningococcus	2IM	citmMENG	

			Pneumococcus	3IM	citmPNEU	
			Not resolved	4IM	citmNOTRES	

EPI-MALARIA-003 VS AME (115056): HENOC SCHONLEIN PURPURA () [AE.AECAT = "HOSPITALIZATION"]			
VISIT NO			
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4	
HENOC SCHONLEIN PURPURA [AE.AESCAT = "HENOC SCHONLEIN PURPURA"] [FA.FASCAT = "HENOC SCHONLEIN PURPURA"]			
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] No [A:Y] [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4	
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] Req / Req / Req (2017-2029)	
4.* ✓	End date of symptoms	[Note: See CRF Page 208 and 209 for corresponding AETERM annotation] [AE.AEENDTC] Req / Req / Req (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:IDC]	
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]			
5.* ✓	Are there any major signs and symptoms? [Are there any major signs and symptoms?]	[FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [A:N] No [A:Y] [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> (select all that apply) Signs and symptoms [A:059] [A:103] [A:210] [A:211] [A:212] [A:213] [A:214] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:215] [A:216] [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5 °C (axillary) If ticked record highest Axillary temperature from onset until discharge [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "PETECHIAE"] Petechieae [A:LOCO1] Foot [A:LOCO10] Legs [A:LOCO12] Buttock [FA.FAORRES] [FA.FATEST = "Location"] [FA.FAOBJ = "PURPURA"] Purpura [A:LOCO1] Foot [A:LOCO10] Legs [A:LOCO12] Buttock Arthritis or Arthralgia Abdominal cramps GIT bleeding Haematuria Hypertension Scrotal pain Scrotal swelling	
BLOOD			
6.* ✓	Was a blood sample taken? [Was a blood sample taken?]	[LB.LBSPEC = "BLOOD" or "SERUM"] [NOT SUBMITTED] [A:Y] [LB.LBDTC] Yes --> sampling date NReq / NReq / NReq (2018-2029) [A:N] No	
7.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] 0 - Lost in transit [A:1] 1 - Lost in site [A:2] 2 - Scrapped [A:3] 3- Lost in second line lab	
8.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date Req / Req / Req (2018-2029) [A:N] No	
DIAGNOSTIC TEST RESULTS			
COMPLETE BLOOD COUNT (CBC)			
9.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes	
10. ✓			
DIAGNOSTIC TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]			
10.1* ✓	Blood Test Done [Blood Test Done]	[LB.LBTEST] [c]BLDTEST	
10.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] NReq / NReq / NReq (2018-2029)	
10.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ11A34JDOI6VG2C?domain=xxx.xxx	
10.4 ✓	Units [Units]	[LB.LBORRESU] A12	
10.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range	
BIOCHEMISTRY			
11.* ✓	Were Biochemistry tests done? [Were Biochemistry tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes	

12. ✓				
BIOCHEMISTRY TEST Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY TEST"] [LB.LBSPEC = "SERUM"]				
12.1* ✓	Biochemistry Test Done [Biochemistry Test Done]	[LB.LBTEST] [c]BIO_CHEM		
12.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
12.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx		
12.4 ✓	Units [Units]	[LB.LBORRESU] A12		
12.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range		
COAGULATION [LB.LBCAT = "COAGULATION"] [LB.LBSCAT = "COAGULATION"] [LB.LBSPEC = "BLOOD"]				
13.* ✓	Were coagulation tests done? [Were coagulation tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
14. ✓	Bleeding time [Bleeding time]	[LB.LBTEST = "Bleeding Time"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:N] Normal [A:A] Abnormal	[LB.LBORRES]	
15. ✓				
COAGULATION Entry [LB.LBCAT = "COAGULATION"] [LB.LBSCAT = "COAGULATION"] [LB.LBSPEC = "BLOOD"]				
15.1* ✓	Coagulation Test [Coagulation Test]	[LB.LBTEST] [c]COAGTEST1		
15.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq] / [NReq] / [NReq] (2018-2029)		
15.3 ✓	Result [Result]	[LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34jDOI6VG2C?domain=xxx.xxx		
15.4 ✓	Units [Units]	[LB.LBORRESU] A12		
15.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] [A:WNR] Within normal range [A:BNR] Below normal range [A:ANR] Above normal range		
BLOOD CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "BLOOD CULTURE"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "MICROBIAL CULTURE"]				
16.* ✓	Was Blood culture done? [Was Blood culture done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
17.* ✓	Blood culture [Blood culture]	[MB.MBTEST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive, Please Specify A200 [A:NEG] Negative	[MB.MBORRES]	[LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"]
18.* ✓	Other, Please specify:	[MB.MBORRES] [When this field is completed, then the submitted text is added to the calculated value of MB.MBORRES, separated by a comma] A200		
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]				
19.* ✓	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] No [A:Y] Yes		
20. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative	[LB.LBORRES]
21. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq] / [NReq] / [NReq] (2018-2029) Result [A:POS] Positive [A:NEG] Negative	[LB.LBORRES]

22.			
✓			
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]			
22.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTEST] [ciSEROTESTVIRAL] ☐	
22.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)]	
22.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
23.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
24.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
25.	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
26.			
✓			
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
26.1*	Bacterial Serology [Bacterial Serology]	[LB.LBTEST] [ciTESTCATE] ☐	
26.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)]	
26.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]			
27.*	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply	
28.	Autoantibodies [Autoantibodies]	[LB.LBTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
29.	Rheumatoid factor [Rheumatoid factor]	[LB.LBTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
30.	Medications	[LB.LBTEST = "Medications"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
31.	Toxic Neuropathies [Toxic Neuropathies]	[LB.LBTEST = "Toxic Neuropathies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
32.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
33.	Other,Specify [Other,Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
34.*	Was a lumbar puncture done ? [PUNCTURE DONE]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> specify lumbar puncture date [NReq ☐ / [NReq ☐ / [NReq ☐ (2018-2029)] [A:N] ☐ No	
35.*	Was antibiotic therapy started prior CSF sampling ? [Was antibiotic therapy started prior CSF sampling ?]	[SUPPLB.QVAL when QNAM = "ANTTHER"] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "ABSTDTC"]	

		Yes -> Date of antibiotic started ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No [A:ND] ☐ CSF Not done
36.* ✓	Please specify the aspect of the CSF [Please specify the aspect of the CSF]	[SUPPLB.QVAL when QNAM = "ASPECT"] [A:1] ☐ Clear [A:2] ☐ Turbid [A:3] ☐ Yellowish [A:4] ☐ [SUPPLB.QVAL when QNAM = "ASPECT"] Other -> Please specify A200 [A:5] ☐ Not documented
37.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
38.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No
CSF LEUKOCYTES [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "CSF LEUKOCYTES"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
39.* ✓	Was CSF Leukocytes test done? [Was CSF Leukocytes test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
40.* ✓	CSF leukocytes [CSF leukocytes]	[LB.LBTEST = "White Blood Cells"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF BIOCHEMISTRY [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "CSF BIOCHEMISTRY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
41.* ✓	Were CSF Biochemistry tests done? [Were CSF Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
42.* ✓	CSF total protein (proteinorachia) [CSF total protein (proteinorachia)]	[LB.LBTEST = "Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
43.* ✓	CSF glucose (glycorrachia) [CSF glucose (glycorrachia)]	[LB.LBTEST = "Glucose"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
CSF EXAMINATION/STAINING		
44.* ✓	Were CSF Examination/Staining tests done? [Were CSF Examination/Staining tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
45. ✓		
CSF TEST Entry [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
45.1* ✓	CSF test Done [CSF test Done]	[LB.LBTEST] [A:1CE] ☐ CSF Gram stain [A:2CE] ☐ CSF Ziehl-Neelsen stain [A:3CE] ☐ CSF Cryptococcus (Indian ink) [A:4CE] ☐ CSF P. falciparum (direct CSF examination or RDT)
45.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
45.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
CSF Culture [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "CEREBROSPINAL FLUID CULTURE"] [MB.MBSPEC = "CEREBROSPINAL FLUID"] [MB.MBMETHOD = "MICROBIAL CULTURE"]		
46.* ✓	Was CSF Culture done? [Was CSF Culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
47.* ✓	CSF Culture [CSF Culture]	[MB.MBTEST = "Organism Present"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [MB.MBORRES] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive, Please Specify A200 [A:NEG] ☐ Negative
CSF Serology [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF SEROLOGY"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]		
48.* ✓	Was CSF serology test done? [Was CSF serology test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
49.* ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES]

		A200	Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
50. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
51. ✓			
CSF SEROLOGY TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "CSF SEROLOGY TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
51.1* ✓	Serology Test Done [Serology Test Done]	[LB.LBTEST] ☐ [cISEROTEST] ☐	
51.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
51.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
CSF PCR [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF PCR"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
52.* ✓	Was CSF PCR test done? [Was CSF PCR test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
53. ✓	CSF Test [CSF Test]	[SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) RESULT [A:NEG] Date [A:POS] [LB.LBTEST when LBORRES = "POSITIVE"] ☐ Negative Positive - ☐ [A:ADENO] Adenovirus -> specify ☐ [A:CMV] CMV pathogen ☐ [A:EBV] EBV ☐ [A:ENTERO] Enterovirus ☐ [A:HIV01] HIV ☐ [A:HSV01] HSV1 ☐ [A:HHV-6] HHV-6 ☐ [A:HSV02] HSV2 ☐ [A:MUM] Mumps ☐ [A:RABIS] Rabies virus ☐ [A:VZV] VZV ☐ [A:INFLU] H. influenzae type b ☐ [A:CSF_LIST] Listeria ☐ [A:MEN01] Meningococcus ☐ [A:PNEU01] Pneumococcus ☐ [A:RICK] Rickettsia ☐ [A:SALSP] Salmonella sp ☐ [A:CSF_PFAL] P. falciparum ☐ [A:TUBR] M. tuberculosis ☐ [A:CSF_OTH] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR2"] CSF Other, please specify	A100
CSF IMMUNOELECTROPHORESIS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "CSF IMMUNOELECTROPHORESIS"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
54.* ✓	Was CSF immunoelectrophoresis performed? [Was CSF immunoelectrophoresis performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
55. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
56. ✓			
IMMUNO ELECTRO Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "IMMUNO ELECTROPHORESIS TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
56.1* ✓	CSF Immunoelectrophoresis done [CSF Immunoelectrophoresis done]	[LB.LBTEST] ☐ [cIMMUNOELECTRO] ☐	
56.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
56.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
OTHER CSF TEST [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER CSF TEST"] [LB.LBSPEC = "CEREBROSPINAL FLUID"]			
57.* ✓	Were other CSF tests conducted? [Were other CSF tests conducted?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
58. ✓	Toxin Investigation [Toxin Investigation]	[LB.LBTEST = "Toxin Investigation"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [LB.LBORRES] [A:POS] ☐ Positive	

		[A:NEG] ☐ Negative
59. ☒	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal [LB.LBORRES]
60. ☒	Other, Specify: [Other, Specify:]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:NOR] ☐ Normal [A:ABN] ☐ Abnormal [LB.LBORRES]
URINE [LB.LBSPEC = "URINE"]		
61.* ☒	Was a urine sample taken? [Was a urine sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ NO
62.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
63.* ☒	Were urine tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
64. ☒		
URINE DETAILS Entry [LB.LBCAT = "URINALYSIS"] [LB.LBSCAT = "URINE DETAILS"] [LB.LBSPEC = "URINE"]		
64.1* ☒	Urine test Done	[LB.LBTEST] ☐ [c]URINES ☐
64.2 ☒	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
64.3* ☒	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
STOOL TEST [LB.LBSPEC = "STOOL"]		
65.* ☒	Was a stool sample taken? [Was a stool sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> Sampling Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ NO
66.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
67.* ☒	Were stool tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
68. ☒	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative [LB.LBORRES]
69. ☒	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative [LB.LBORRES]
70. ☒	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative [LB.LBORRES]
71. ☒		
STOOL TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "STOOL TEST"] [LB.LBSPEC = "STOOL"]		
71.1* ☒	Stool Test [Stool Test]	[LB.LBTEST] ☐ [c]STLTS ☐
71.2 ☒	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
71.3* ☒	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
BIOPSY [PR.PRCAT = "BIOPSY"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]		
72.* ☒	Was a biopsy performed? [Was a biopsy performed?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes

73.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab	
74.	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] 	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:N] ☐ Normal [FA.FATEST = "Result"] [FA.FAORRES] [A:A] ☐ Abnormal
75.			
BIOPSY Entry [PR.PRCAT = "BIOPSY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: BIOPSY"]			
75.1	Biopsy Type 1 [Biopsy Type 1]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:2BP] ☐ Bone marrow culture [A:5BP] ☐ Skin culture [PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FATEST = "Result"] [FA.FAORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
75.2	Biopsy Type 2 [Biopsy Type 2]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Biopsy Performed [A:1BMB] ☐ Bone marrow biopsy [A:3RB] ☐ Renal biopsy [A:4SB] ☐ Skin biopsy [PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Result"] Result [A:N] ☐ Normal [A:A] ☐ Abnormal	
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			
76.*	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
77.	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other Please Specify	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
78.			
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]			
78.1*	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [c[RADIOEXAM]] ☐	
78.2	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)	
78.3*	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No	
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]			
79.*	Was there a consultation with a specialist? [Was there a consultation with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes	
80.*	Is the disease fulfilling the protocol case definition (Job Aid) for for Henoch SchÄ¶nlein Purpura? [Is the disease fulfilling the protocol case definition (Job Aid) for for Henoch SchÄ¶nlein Purpura?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR HENOCH SCHOLEIN PURPURA"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR HENOCH SCHOLEIN PURPURA"] No -> What is the final diagnosis for this disease [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes please record the level of diagnostic certainty as defined in Job Aid [A:1DGL] ☐ 1 [A:2DGL] ☐ 2	
81.*	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal	
82.*	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death	
83.*	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] [A:henochschonl] ☐ Henoch-Schonlein purpura	

	laboratory results?]	[A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
84. ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FA0BJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] ☐ [A:henochschonl] [A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ Henoch-Schonlein purpura ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
85. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
 Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: HENOC SCHONLEIN PURPURA					
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName
ciBLDTEST	String		Red Blood Cells	1BL	ctmBLDTEST
			Platelets	2BL	ctmPLT
			White blood cells	3BL	ctmWBC
			Neutrophils	4BL	ctmNEUT
			Lymphocytes	5BL	ctmLYMP
			Monocytes	6BL	ctmMONO
			Basophils	7BL	ctmBASO
			Eosinophils	8BL	ctmEOS
ciBIO_CHEM	String		Total bilirubin	1	ctmBIO1
			Conjugated bilirubin	2	ctmBIO2
			Alanine amino transferase (ALT)	3	ctmBIO3
			Aspartate amino transferase (AST)	4	ctmBIO4
			Alkaline Phosphatase (ALP)	5	ctmBIO5
			Total protein	6	ctmBIO6
			Albumin	7	ctmBIO7
			Serum urea nitrogen	8	ctmBIO8
			Serum creatinine	9	ctmBIO9
			Serum sodium	10	ctmBIO10
			Serum potassium	11	ctmBIO11
			Serum chloride	12	ctmBIO12
			Serum calcium	14	ctmBIO14
			Serum magnesium	15	ctmBIO15
			Vitamin B12	16	ctmBIO16
			Folate	17	ctmBIO17
			Blood glucose	18	ctmBIO18
			Oral glucose tolerance test	19	ctmBIO19
			Fasting blood sugar	20	ctmBIO20
			Hemoglobin A1C	21	ctmBIO21
			Lipids	22	ctmBIO22
ciCOAGTEST1	String		Prothrombine time (PT)	1PT	ctmCoagTest1
			International normalized ratio (INR)	2IN	ctmCoagTest2

		Activated coagulation time (ACT)	3ACT	citmCoagTest3	
		Activated partial thromboplastine time (APTT)	4APT	citmCoagTest4	
ciSEROESTVIRAL	String	Chickenpox (Varicella)	1STV	citmSEROESTVIRAL1	itmSEROESTVIRAL
		Chlamydia	2STV	citmSEROESTVIRAL2	
		Chlamydia pneumonia	3STV	citmSEROESTVIRAL3	
		Coronavirus	4STV	citmSEROESTVIRAL4	
		Coxsackie	5STV	citmSEROESTVIRAL5	
		CMV	6STV	citmSEROESTVIRAL6	
		EBV	7STV	citmSEROESTVIRAL7	
		Enterovirus	8STV	citmSEROESTVIRAL8	
		Hepatitis A	9STV	citmSEROESTVIRAL9	
		Hepatitis B	10STV	citmSEROESTVIRAL10	
		Hepatitis C	11STV	citmSEROESTVIRAL11	
		Hepatitis D	12STV	citmSEROESTVIRAL12	
		HIV	13STV	citmSEROESTVIRAL13	
		HSV	14STV	citmSEROESTVIRAL14	
		Measles	15STV	citmSEROESTVIRAL15	
		Mumps	16STV	citmSEROESTVIRAL16	
		Parvovirus	17STV	citmSEROESTVIRAL17	
		Rabies	18STV	citmSEROESTVIRAL18	
		Rubella	19STV	citmSEROESTVIRAL19	
		VZV	20STV	citmSEROESTVIRAL20	
ciTESTCATE	String	Antistreptolysine O (ASLO)	1TC	citmTESTCATE1	itmTESTINFO
		Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
		Borrelia	3TC	citmTESTCATE3	
		H. influenzae type b	4TC	citmTESTCATE4	
		Leptospira	5TC	citmTESTCATE5	
		Mycoplasma	6TC	citmTESTCATE6	
		Mycoplasma pneumonia	7TC	citmTESTCATE7	
		Meningococcus	8TC	citmTESTCATE8	
		Pneumococcus	9TC	citmTESTCATE9	
		Rickettsia	10TC	citmTESTCATE10	
		Salmonella	11TC	citmTESTCATE11	
		M. tuberculosis	12TC	citmTESTCATE12	
		Typhoid fever	13TC	citmTESTCATE13	
ciSEROEST	String	CMV	1ST	citmCMV	itmSEROEST
		EBV	2ST	citmEBV	
		Enterovirus	3ST	citmENTVIR	
		HIV	4ST	citmHIVIR	
		HSV	5ST	citmHSV	
		Mumps	6ST	citmMUMPS	
		VZV	7ST	citmVZV	
		H. influenzae type b	8ST	citmHINFB	
		Listeria	9ST	citmLIST	
		Meningococcus	10ST	citmMENGS	
		Pneumococcus	11ST	citmPNEUM	
		Rickettsia	12ST	citmRICK	
		Salmonella	13ST	citmSALM	
		M. tuberculosis	14ST	citmMTUB	
		Autoantibodies	15ST	citmAUTO	
ciIMMUNOELECTRO	String	H. influenzae type b	1IM	citmHINF	itmIMMUNELEC
		Meningococcus	2IM	citmMENG	
		Pneumococcus	3IM	citmPNEU	
		Not resolved	4IM	citmNOTRES	
ciURINE5	String	Urine blood	1UR	citmURINE51	itmURINE
		Urine leukocytes	2UR	citmURINE52	
		Urine total protein (Proteinuria)	3UR	citmURINE53	
		Urine glucose (Glycosuria)	4UR	citmURINE54	
		Urine Ketones	5UR	citmURINE55	
ciSTLTST	String	Stool Blood	1ST	citmSTLTST1	itmSTLTST
		Adenovirus	2ST	citmSTLTST2	
		Botulism Spore	3ST	citmSTLTST3	
		Campylobacter	4ST	citmSTLTST4	

		Enterovirus	5ST	citmSTLTST5	
		Poliovirus	6ST	citmSTLTST6	
		Salmonella	7ST	citmSTLTST7	
		Shigella	8ST	citmSTLTST8	
clRADIOEXAM	String	CT scan	1RE	citmRE1	itmRADIOEXAM
		Electrocardiogram	2RE	citmRE2	
		Electroencephalogram	3RE	citmRE3	
		Electromyogram	4RE	citmRE4	
		MRI	5RE	citmRE5	
		Non-barium or air-contrast enema	6RE	citmRE6	
		X-ray	7RE	citmRE7	
		X-ray abdomen	8RE	citmRE8	
		Ultrasound	9RE	citmRE9	
		Ultrasound & cardiac	10RE	citmRE10	

EPI-MALARIA-003 VS AME (115056): KAWASAKI DISEASE () [AE.AECAT = "HOSPITALIZATION"]				
VISIT NO				
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4		
KAWASAKI DISEASE [AE.AESCAT = "KAWASAKI DISEASE"] [FA.FASCAT = "KAWASAKI DISEASE"]				
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4		
3.* ✓	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRTPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐		
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]				
5.* ✓	Are there any major signs and symptoms? [Are there any major signs and symptoms?]	[FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes--> Complete all that apply [A:217] [A:009][FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:218] [A:219] [A:193] [A:220][Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:221] [A:XXX] ☐ Child is generally unwell ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge [FA.FAORRES] [FA.FATEST = "Duration"] °C [A:LT5] ☐ < 5 days If presence duration: [A:GT5] ☐ >= 5 days ☐ Conjunctivitis bilateral (non-exudative) ☐ Erythema (lips, oral mucosa) ☐ Oedema hands and feet ☐ Polymorphic cutaneous exanthem ☐ Neck lymphadenopathy ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please specify A200		
BLOOD				
6.* ✓	Was a blood sample taken?	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No		
7.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab		
8.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?]	[NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) [A:N] ☐ No		
DIAGNOSTIC TEST RESULT				
9.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes		
10. ✓				
DIAGNOSTIC TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]				
10.1* ✓	Blood Test Done [Blood Test Done]	[LB.LBTST] ☐ [CLBLDTST] ☐		
10.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		
10.3 ✓	Result [Result]	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1A34jDO16VG2C?domain=xxx.xxx		
10.4 ✓	Units [Units]	[LB.LBORRESU] Units A12		
10.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
BIOCHEMISTRY				
11.* ✓	Were Biochemistry tests done? [Were Biochemistry tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes		
12. ✓				

BIOCHEMISTRY TEST Entry [LB.LBCAT = "CHEMISTRY"] [LB.LBSCAT = "BIOCHEMISTRY TEST"] [LB.LBSPEC = "SERUM"]			
12.1*	Bio Chemistry Tests Done	[LB.LBTTEST] ☐ [cLBIO_CHEM]	
12.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)	
12.3	Result [Result]	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx	
12.4	Units [Units]	[LB.LBORRESU] Units A12	
12.5*	Interpretation [Interpretation]	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range	
ESR AND CRP [LB.LBCAT = "OTHER"] [LB.LBSCAT = "ESR AND CRP"] [LB.LBSPEC = "BLOOD"]			
13.*	Were ESR or CRP tests done? [Were ESR or CRP tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
14.	Erythrocytes Sedimentation Rates [Erythrocytes Sedimentation Rates]	[LB.LBTTEST = "Erythrocyte Sedimentation Rate"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx	
		[LB.LBORRES] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
15.	C- reactive Protein [C-reactive Protein]	[LB.LBTTEST = "C Reactive Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1iA34jDO16VG2C?domain=xxx.xxx	
		[LB.LBORRES] Units A12	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
BLOOD SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "BLOOD"]			
16.*	Were Viral serology tests done? [Were Viral serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
17.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	
		[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
18.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	
		[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative	
19.			
BLOOD SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BLOOD SEROLOGY"] [LB.LBSPEC = "SERUM"]			
19.1*	Viral Serology Tests [Viral Serology Tests]	[LB.LBTTEST] ☐ [cISEROTESTVIRAL]	
19.2	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)	
19.3*	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative	
BACTERIAL SEROLOGY [LB.LBCAT = "OTHER"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]			
20.*	Were Bacterial serology tests done? [Were Bacterial serology tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes	
21.	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200	
		[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq (2018-2029)	

		[LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
22. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
23. ✓		
BACTERIAL SEROLOGY Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "BACTERIAL SEROLOGY"] [LB.LBSPEC = "SERUM"]		
23.1* ✓	Bacterial Serology [Bacterial Serology]	[LB.LBTTEST] ☐ [c]TESTCATE ☐
23.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
23.3* ✓	Result [Result]	[LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
OTHER BLOOD TESTS [LB.LBCAT = "OTHER"] [LB.LBSCAT = "OTHER BLOOD TESTS"] [LB.LBSPEC = "BLOOD"]		
24.* ✓	Were other blood tests done? [Were other blood tests done]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes --> Complete all that apply
25. ✓	Autoantibodies [Autoantibodies]	[LB.LBTTEST = "Autoantibodies"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
26. ✓	Rheumatoid factor [Rheumatoid factor]	[LB.LBTTEST = "Rheumatoid Factor"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
27. ✓	Other,Specify [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
28. ✓	Other,Specify [Other,Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
URINE [LB.LBSPEC = "URINE"]		
29.* ✓	Was a urine sample taken? [Was a urine sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No
30.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3- Lost in second line lab
31.* ✓	Were urine tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
32. ✓		
URINE TEST Entry [LB.LBCAT = "URINALYSIS"] [LB.LBSCAT = "URINE DETAILS"] [LB.LBSPEC = "URINE"]		
32.1* ✓	Urine test Done	[LB.LBTTEST] ☐ [c]URINES ☐
32.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
32.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive

		[A:NEG] ☐ Negative
STOOL TEST [LB.LBSPEC = "STOOL"]		
33.* ✓	Was a stool sample taken? [Was a stool sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> Sampling Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ NO
34.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
35.* ✓	Was stool test done? [Was stool test done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
36. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
37. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
38. ✓	Other, Specify [Other, Specify]	[LB.LBTTEST = "Other"] [LB.LBTTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [LB.LBORRES] Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
39. ✓		
STOOL TEST 2 Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "STOOL TEST"] [LB.LBSPEC = "STOOL"]		
39.1* ✓	Stool Test [Stool Test]	[LB.LBTTEST] ☐ [clSTLTST] ☐
39.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
39.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
40.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
41. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other --> Please Specify A200 [PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistent with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
42. ✓		
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
42.1* ✓	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [clRADIOEXAM] ☐
42.2 ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)

42.* ✓	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
43.* ✓	Was there a consultation with a specialist (cardiologist/dermatologist)? [Was there a consultation with a specialist (cardiologist/dermatologist)?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
44.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for Kawasaki disease? [Is the disease fulfilling the protocol case definition (Job Aid)?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR KAWASAKI DISEASE"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No --> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes please record the level of diagnostic certainty as defined in Job Aid [A:1DK] ☐ 1 [A:2DK] ☐ 2 [A:3DK] ☐ 3
45.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
46.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
47.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] [A:Kawasaki's disease] [A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ Kawasaki's disease ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
48.* ✓	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] [A:Kawasaki's disease] [A:99][Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ Kawasaki's disease ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [SUPPMB.QVAL when QNAM = "RELDIS"] Other, Please specify: A200
49.* ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"] A1000

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: KAWASAKI DISEASE						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST
			Platelets	2BL	citmPLT	
			White blood cells	3BL	citmWBC	
			Neutrophils	4BL	citmNEUT	
			Lymphocytes	5BL	citmLYMP	

		Monocytes	6BL	citmMONO	
		Basophils	7BL	citmBASO	
		Eosinophils	8BL	citmEOS	
ciBIO_CHEM	String	Total bilirubin	1	citmBIO1	itmBIOCHEM6
		Conjugated bilirubin	2	citmBIO2	
		Alanine amino transferase (ALT)	3	citmBIO3	
		Aspartate amino transferase (AST)	4	citmBIO4	
		Alkaline Phosphatase (ALP)	5	citmBIO5	
		Total protein	6	citmBIO6	
		Albumin	7	citmBIO7	
		Serum urea nitrogen	8	citmBIO8	
		Serum creatinine	9	citmBIO9	
		Serum sodium	10	citmBIO10	
		Serum potassium	11	citmBIO11	
		Serum chloride	12	citmBIO12	
		Serum calcium	14	citmBIO14	
		Serum magnesium	15	citmBIO15	
		Vitamin B12	16	citmBIO16	
		Folate	17	citmBIO17	
		Blood glucose	18	citmBIO18	
		Oral glucose tolerance test	19	citmBIO19	
		Fasting blood sugar	20	citmBIO20	
		Hemoglobin A1C	21	citmBIO21	
		Lipids	22	citmBIO22	
ciSEROTESTVIRAL	String	Chickenpox (Varicella)	1STV	citmSEROTESTVIRAL1	itmSEROTESTVIRAL
		Chlamydia	2STV	citmSEROTESTVIRAL2	
		Chlamydia pneumonia	3STV	citmSEROTESTVIRAL3	
		Coronavirus	4STV	citmSEROTESTVIRAL4	
		Coxsackie	5STV	citmSEROTESTVIRAL5	
		CMV	6STV	citmSEROTESTVIRAL6	
		EBV	7STV	citmSEROTESTVIRAL7	
		Enterovirus	8STV	citmSEROTESTVIRAL8	
		Hepatitis A	9STV	citmSEROTESTVIRAL9	
		Hepatitis B	10STV	citmSEROTESTVIRAL10	
		Hepatitis C	11STV	citmSEROTESTVIRAL11	
		Hepatitis D	12STV	citmSEROTESTVIRAL12	
		HIV	13STV	citmSEROTESTVIRAL13	
		HSV	14STV	citmSEROTESTVIRAL14	
		Measles	15STV	citmSEROTESTVIRAL15	
		Mumps	16STV	citmSEROTESTVIRAL16	
		Parvovirus	17STV	citmSEROTESTVIRAL17	
		Rabies	18STV	citmSEROTESTVIRAL18	
		Rubella	19STV	citmSEROTESTVIRAL19	
		VZV	20STV	citmSEROTESTVIRAL20	
ciTESTCATE	String	Antistreptolysine O (ASLO)	1TC	citmTESTCATE1	itmTESTINFO
		Beta haemolytic Streptococcus	2TC	citmTESTCATE2	
		Borrelia	3TC	citmTESTCATE3	
		H. influenzae type b	4TC	citmTESTCATE4	
		Leptospira	5TC	citmTESTCATE5	
		Mycoplasma	6TC	citmTESTCATE6	
		Mycoplasma pneumonia	7TC	citmTESTCATE7	
		Meningococcus	8TC	citmTESTCATE8	
		Pneumococcus	9TC	citmTESTCATE9	
		Rickettsia	10TC	citmTESTCATE10	
		Salmonella	11TC	citmTESTCATE11	
		M. tuberculosis	12TC	citmTESTCATE12	
		Typhoid fever	13TC	citmTESTCATE13	
ciURINE5	String	Urine blood	1UR	citmURINE51	itmURINE
		Urine leukocytes	2UR	citmURINE52	
		Urine total protein (Proteinuria)	3UR	citmURINE53	
		Urine glucose (Glycosuria)	4UR	citmURINE54	
		Urine Ketones	5UR	citmURINE55	
ciSTLTST	String	Stool Blood	1ST	citmSTLTST1	itmSTLTST

		Adenovirus	2ST	citmSTLTST2	
		Botulism Spore	3ST	citmSTLTST3	
		Campylobacter	4ST	citmSTLTST4	
		Enterovirus	5ST	citmSTLTST5	
		Poliovirus	6ST	citmSTLTST6	
		Salmonella	7ST	citmSTLTST7	
		Shigella	8ST	citmSTLTST8	
ciRADIOEXAM	String	CT scan	1RE	citmRE1	itmRADIOEXAM
		Electrocardiogram	2RE	citmRE2	
		Electroencephalogram	3RE	citmRE3	
		Electromyogram	4RE	citmRE4	
		MRI	5RE	citmRE5	
		Non-barium or air-contrast enema	6RE	citmRE6	
		X-ray	7RE	citmRE7	
		X-ray abdomen	8RE	citmRE8	
		Ultrasound	9RE	citmRE9	
		Ultrasound & cardiac	10RE	citmRE10	

EPI-MALARIA-003 VS AME (115056): INTUSSUSCEPTION () [AE.AECAT = "HOSPITALIZATION"]	
VISIT NO	
1.	Hospitalisation number [read-only] [XX(Domain).VISITNUM] N4
INTUSSUSCEPTION [AE.AESCAT = "INTUSSUSCEPTION"] [FA.FASCAT = "INTUSSUSCEPTION"]	
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?] [NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms] [AE.AESTDTC] Req ☐ / Req ☐ / Req ☐ (2017-2029)
4.* ✓	End date of symptoms [Note: See CRF Pages 226 for corresponding AETERM annotation] [AE.AEENDTC] Req ☐ / Req ☐ / Req ☐ (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]	
5.* ✓	Are there any major signs and symptoms? [Are there any major signs and symptoms?] [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> (select all that apply) [A:009][FA.FAORRES] [FA.FATEST = "Temperature"] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XX.X ☐ Abdominal pain ☐ Vomiting ☐ Billious emesis ☐ Inconsolable crying ☐ Legs kept towards abdomen ☐ Lethargy ☐ Palpable abdominal mass ☐ Rectal prolapse ☐ Diarrhea ☐ Bloody Stools ☐ Bloody Stool with mucus (currant jelly stool) ☐ Rectal blood [FA.FAORRES] [FA.FATEST = "Specification"] Other Please Specify A200
BLOOD [LB.LBSPEC = "BLOOD" or "SERUM"]	
6.* ✓	Was a blood sample taken? [NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:N] ☐ No
7.	For GSK: [hidden] [Reconciled] [NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
8.* ✓	Was a sample shipped to 2nd line lab? [Was a sample shipped to 2nd line lab?] [NOT SUBMITTED] [A:Y] ☐ [SUPPLB.QVAL when QNAM = "SHIPDTC"] Yes --> shipment date Req ☐ / Req ☐ / Req ☐ (2018-2029) [A:N] ☐ No
DIAGNOSTIC TEST RESULT	
Please complete the results of tests that were performed to diagnose this event	
BLOOD	
COMPLETE BLOOD COUNT (CBC) </ b>	
9.* ✓	Were complete blood count tests done? [Were complete blood count tests done?] [NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
10. ✓	
DIAGNOSTIC TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]	
10.1.* ✓	Blood Test Done [Blood Test Done] [LB.LBTST] ☐ [cIBLDTST] ☐
10.2 ✓	Test Date [Test Date] [SUPPLB.QVAL when QNAM = "TSTDTC"] Req ☐ / Req ☐ / Req ☐ (2018-2029)
10.3 ✓	Result [Result] [LB.LBORRES] https://protect-eu.mimecast.com/s/TOJtCrZ1iA34jDO16VG2C?domain=xxx.xxx
10.4 ✓	Units [Units] [LB.LBORRESU] A12
10.5*	Interpretation [LB.LBNRIND]

✓	[Interpretation]	[A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range
STOOL TEST [LB.LBSPEC = "STOOL"]		
11.* ✓	Was a stool sample taken? [Was a stool sample taken?]	[NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> Sampling Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ NO
12.	For GSK: [hidden] [Reconciled]	[NOT SUBMITTED] Reconciled (CDR only): [A:0] ☐ 0 - Lost in transit [A:1] ☐ 1 - Lost in site [A:2] ☐ 2 - Scrapped [A:3] ☐ 3 - Lost in second line lab
13.* ✓	Were stool tests done? [Were urine tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
14. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
15. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
16. ✓	Other, Specify [Other, Specify]	[LB.LBTEST = "Other"] [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] A200 [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result [A:POS] ☐ Positive [A:NEG] ☐ Negative
17. ✓		
STOOL TEST Entry [LB.LBCAT = "IMMUNOLOGY"] [LB.LBSCAT = "STOOL TEST"] [LB.LBSPEC = "STOOL"]		
17.1* ✓	Stool Test [Stool Test]	[LB.LBTEST] ☐ [c]STLTST ☐
17.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
17.3* ✓	Result [Result]	[LB.LBORRES] [A:POS] ☐ Positive [A:NEG] ☐ Negative
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
18.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
19. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other Please Specify A200 [PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
20. ✓		
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
20.1* ✓	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [c]RADIOEXAM ☐
20.2 ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
20.3* ✓	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
21.* ✓	Was there consultation with a surgeon? [Was there consultation with a surgeon?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SURGEON"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> Is a report available [A:N] ☐ No [A:Y] ☐ Yes
22.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for intussusception? [Is the disease fulfilling the protocol case definition (Job Aid) for intussusception?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR INTUSSUSCEPTION"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No --> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes --> please record the level of diagnostic certainty as defined in Job Aid [A:1DGC] ☐ 1 [A:2DGC] ☐ 2

		[A:3DGC] 3
23.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
24.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ [SUPPAE.QVAL when QNAM = "RECVTYP"] Fully recovered => If ticked, please specify: [A:SPONT] ☐ Spontaneous [A:ENEMA] ☐ Enema [A:SURG] ☐ Surgery [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
25.* ✓	What is the preferred term associated to this event after the 1st line laboratory results? [What is the preferred term associated to this event after the 1st line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER FIRST LINE LAB RESULTS"] [AE.AETERM] [A:1] ☐ [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ Intussusception [A:99] ☐ [SUPPLB.QVAL when QNAM = "RELDIS"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] Other, Please specify:
26.	What is the preferred term associated to this event after the 2nd line laboratory results? [What is the preferred term associated to this event after the 2nd line laboratory results?]	[FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "PREFERRED TERM AFTER SECOND LINE LAB RESULTS"] [AE.AETERM] [A:1] ☐ [SUPPPR.QVAL when QNAM = "RELDIS"] ☐ Intussusception [A:99] ☐ [SUPPLB.QVAL when QNAM = "RELDIS"] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [Note: When preferred term is available for both first and second line lab results, AETERM and QVAL when QNAM = "RELDIS" contain the preferred term given after second line lab results] Other, Please specify:
27. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"]

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
Note: Source verification critical settings made in Inform will override any settings made in Central Designer.

Codelist Values Tables: INTUSSUSCEPTION						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
ciBLDTEST	String		Red Blood Cells	1BL	citmBLDTEST	itmBLOODTEST
			Platelets	2BL	citmPLT	
			White blood cells	3BL	citmWBC	
			Neutrophils	4BL	citmNEUT	
			Lymphocytes	5BL	citmLYMP	
			Monocytes	6BL	citmMONO	
			Basophils	7BL	citmBASO	
			Eosinophils	8BL	citmEOS	
ciSTLTST	String		Stool Blood	1ST	citmSTLTST1	itmSTLTEST
			Adenovirus	2ST	citmSTLTST2	
			Botulism Spore	3ST	citmSTLTST3	
			Campylobacter	4ST	citmSTLTST4	
			Enterovirus	5ST	citmSTLTST5	
			Poliovirus	6ST	citmSTLTST6	
			Salmonella	7ST	citmSTLTST7	

			Shigella	8ST	citmSTLTST8	
cIRADIOEXAM	String		CT scan	1RE	citmRE1	itmRADIOEXAM
			Electrocardiogram	2RE	citmRE2	
			Electroencephalogram	3RE	citmRE3	
			Electromyogram	4RE	citmRE4	
			MRI	5RE	citmRE5	
			Non-barium or air-contrast enema	6RE	citmRE6	
			X-ray	7RE	citmRE7	
			X-ray abdomen	8RE	citmRE8	
			Ultrasound	9RE	citmRE9	
			Ultrasound 3C° cardiac	10RE	citmRE10	

EPI-MALARIA-003 VS AME (115056): INJECTION SITE ABSCESS () [AE.AECAT = "HOSPITALIZATION"]				
VISIT NO [AE.AESCAT = "INJECTION SITE ABSCESS"] [FA.FASCAT = "INJECTION SITE ABSCESS"]				
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4		
INJECTION SITE ABSCESS				
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] [Note: See CRF Page 232 for corresponding AETERM annotation] Yes -> Please specify Expedited AE Number N4		
3.* ✓	Please record date of onset of first symptoms [Please record date of onset of first symptoms]	[AE.AESTDTC] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		
4.* ✓	End date of symptoms	[AE.AEENDTC] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐		
SIGNS AND SYMPTOMS [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]				
5.* ✓	Are there any major signs and symptoms? [Are there any major signs and symptoms?]	[FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "MAJOR SIGNS AND SYMPTOMS"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes--> Complete all that apply [A:009] [A:192][FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX = "BETWEEN ONSET AND DISCHARGE"] [A:194] [A:195][Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:196] [A:197] [A:199] [A:034] ☐ [FA.FAORRES] [FA.FATEST = "Temperature"] Temperature >=37.5°C (axillary) If ticked record highest Axillary temperature from onset until discharge XXX.X ☐ Localised injection site urticaria ☐ Erythema ☐ Pain to light touch ☐ Warmth to touch ☐ Localized collection of material in subcutaneous tissue at the site of injection ☐ Regional lymphadenopathy ☐ [FA.FAORRES] [FA.FATEST = "Specification"] Other Please specify A200		
BLOOD				
6.* ✓	Was a blood sample taken? [Was a blood sample taken?]	[LB.LBSPEC = "BLOOD" or "SERUM"] [NOT SUBMITTED] [A:Y] ☐ [LB.LBDTC] Yes --> sampling date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [A:N] ☐ No		
DIAGNOSTIC TEST RESULT				
7.* ✓	Were complete blood count tests done? [Were complete blood count tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes		
8. ✓				
DIAGNOSTIC TEST Entry [LB.LBCAT = "HEMATOLOGY"] [LB.LBSCAT = "DIAGNOSTIC TEST"] [LB.LBSPEC = "BLOOD"]				
8.1* ✓	Blood Test Done [Blood Test Done]	[LB.LBTTEST] ☐ [dBLDTEST] ☐		
8.2 ✓	Test Date [Test Date]	[SUPPLB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)		
8.3 ✓	Result [Result]	[LB.LBORRES] Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34JDOI6VG2C?domain=xxx.xxx		
8.4 ✓	Units [Units]	[LB.LBORRESU] Units A12		
8.5* ✓	Interpretation [Interpretation]	[LB.LBNRIND] Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
ESR AND CRP [LB.LBCAT = "OTHER"] [LB.LBSCAT = "ESR AND CRP"] [LB.LBSPEC = "BLOOD"]				
9.* ✓	Were ESR or CRP tests done? [Were ESR or CRP tests done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes		
10. ✓	Erythrocytes Sedimentation Rates [Erythrocytes Sedimentation Rates]	[LB.LBTTEST = "Erythrocyte Sedimentation Rate"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrRZ1IA34JDOI6VG2C?domain=xxx.xxx Units A12 Interpretation [A:WNR] ☐ Within normal range [A:BNR] ☐ Below normal range [A:ANR] ☐ Above normal range		
11. ✓	C- reactive Protein [C-reactive Protein]	[LB.LBTTEST = "C Reactive Protein"] [SUPPLB.QVAL when QNAM = "TSTDTC"] [LB.LBORRES] [LB.LBORRESU] [LB.LBNRIND]		

		Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) Result https://protect-eu.mimecast.com/s/TOJtCrZ1IA34jD0I6VG2C?domain=xxx.xxx Units A12 Interpretation ☐ [A:WNR] Within normal range ☐ [A:BNR] Below normal range ☐ [A:ANR] Above normal range
BLOOD CULTURE [MB.MBCAT = "MICROBIOLOGY"] [MB.MBSCAT = "BLOOD CULTURE"] [MB.MBSPEC = "BLOOD"] [MB.MBMETHOD = "MICROBIAL CULTURE"]		
12.* ✓	Was Blood culture done? [Was Blood culture done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
13.* ✓	Blood culture [Blood culture]	[MB.MBTEST = "Organism Present"] [SUPPMB.QVAL when QNAM = "TSTDTC"] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [MB.MBORRES] Result [A:POS] ☐ [LB.LBTEST = "Other"] [SUPPLB.QVAL when QNAM = "TSTOTHR1"] Positive, Please Specify A200 [A:NEG] ☐ Negative
14.* ✓	Other, Please specify:	[MB.MBORRES] [When this field is completed, then the submitted text is added to the calculated value of MB.MBORRES, separated by a comma] A200
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
15.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
16.* ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other --> Please Specify A200 [PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistant with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
17.* ✓		
RADIOLOGICAL EXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPRESP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
17.1.* ✓	Radiology Test Done [Radiology Test Done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] ☐ [c RADIOEXAM] ☐
17.2.* ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] Test Date ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029)
17.3.* ✓	Consistant with Diagnosis? [Consistant with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No
DISEASE EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
18.* ✓	Was there a consultation with a specialist? [Was there a consultation with a specialist (cardiologist/dermatologist)?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH RAFT"] Yes --> Was the consultation with RAFT [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Report Available"] Yes --> is a report available [A:N] ☐ No [A:Y] ☐ Yes
19.* ✓	Is the disease fulfilling the protocol case definition (Job Aid) for injection site abscess? [Is the disease fulfilling the protocol case definition (Job Aid)?]	[FA.FAORRES] [FA.FATEST = "Result"] [FA.FAOBJ = "DISEASE FULFILLED PROTOCOL CASE DEFINITION FOR INJECTION SITE ABSCESS"] [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "FINAL DIAGNOSIS FOR THIS DISEASE"] No, -> What is the final diagnosis for this disease A200 [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Level of Diagnostic Certainty"] Yes please record the level of diagnostic certainty as defined in Job Aid [A:1DGL] ☐ 1 [A:2DGL] ☐ 2
20.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV] Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
21.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
22.*	What is the preferred term associated to this event?	[AE.AETERM] [SUPPLB.QVAL when QNAM = "RELDIS"] [SUPPMB.QVAL when QNAM = "RELDIS"]

Key: [*] = Item is required [✔] = Source verification required [.] = Source verification critical

Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIBLDTST	String		Red Blood Cells	1BL	cltmBLDTST	ltmBLOODTEST
			Platelets	2BL	cltmPLT	
			White blood cells	3BL	cltmWBC	
			Neutrophils	4BL	cltmNEUT	
			Lymphocytes	5BL	cltmLYMP	
			Monocytes	6BL	cltmMONO	
			Basophils	7BL	cltmBASO	
			Eosinophils	8BL	cltmEOS	
cIRADIOEXAM	String		CT scan	1RE	cltmRE1	ltmRADIOEXAM
			Electrocardiogram	2RE	cltmRE2	
			Electroencephalogram	3RE	cltmRE3	
			Electromyogram	4RE	cltmRE4	
			MRI	5RE	cltmRE5	
			Non-barium or air-contrast enema	6RE	cltmRE6	
			X-ray	7RE	cltmRE7	
			X-ray abdomen	8RE	cltmRE8	
			Ultrasound	9RE	cltmRE9	
			Ultrasound &C" cardiac	10RE	cltmRE10	

EPI-MALARIA-003 VS AME (115056): FOOT POSITIONAL DEFORMATION () [AE.AECAT = "HOSPITALIZATION"]		
VISIT NO [AE.AESCAT = "FOOT POSITIONAL DEFORMATION"] [FA.FASCAT = "FOOT POSITIONAL DEFORMATION"]		
1.	Hospitalisation number [read-only]	[XX(Domain).VISITNUM] N4
FOOT POSITIONAL DEFORMATION		
2.* ✓	As per Study Protocol does this event need to be recorded in the Expedited AE screen? [As per Study Protocol does this event need to be recorded in the Expedited AE screen?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ [RELREC.IDVARVAL when IDVAR = "AEGRPID"] Yes -> Please specify Expedited AE Number N4
3.* ✓	Date of onset of first symptoms [Date of onset of first symptoms]	[AE.AESTDTC] Req ☐ / Req ☐ / Req ☐ (2017-2029)
4.* ✓	End date of symptoms	[Note: See CRF Pages 235 and 236 for corresponding AETERM annotation] [AE.AEENDTC] Req ☐ / Req ☐ / Req ☐ (2017-2029) [AE.AEENRPT = "ONGOING"] [AE.AEENTPT = "HOSPITAL DISCHARGE"] ongoing at discharge [A:1DC] ☐
SIGN AND SYMPTOMS FOOT POSITIONAL DEFORMATION [FA.FACAT = "HOSPITALIZATION: SIGNS AND SYMPTOMS"]		
5.* ✓	Are there any of the following deformations on the foot? [Are there any of the following deformations on the foot?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "DEFORMATION ON THE FOOT"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] Yes --> Select all that apply Signs and Symptoms [A:200] [A:201][Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:202] [A:203] [A:204] [A:205] [A:206] [A:207] [A:025] ☐ Medial deviation (adduction) of the forefoot ☐ Hindfoot in a normal position ☐ Hyperdorsiflexion of the foot ☐ Abduction of the forefoot ☐ Forefoot resting on the anterior surface of the lower leg ☐ Excessively plantar flexed foot ☐ Forefoot swung medially ☐ Sole facing inward [FA.FAORRES] [FA.FATEST = "Specification"] Other A200 Please Specify
6.* ✓	Are there other general signs? [Are there other general signs?]	[FA.FAORRES] [FA.FATEST = "Signs and Symptoms"] [FA.FAOBJ = "GENERAL SIGNS"] [Note: The calculated value of FA.FAORRES consists of all selected values, separated by a comma] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] Yes --> Select all that apply General signs [A:009][FA.FATEST = "Temperature"] [FA.FAOBJ = "HIGHEST TEMPERATURE RECORDED"] [FA.FAEVINTX ☐ [FA.FAORRES] [FA.FAORRESU = "C"] [FA.FALOC = "AXILLA"] Temperature >=37.5°C (axillary) XX.X If ticked record highest Axillary temperature from onset until discharge ☐ Others
RADIOLOGICAL EXAMS [PR.PRCAT = "RADIOLOGY"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
7.* ✓	Was any radiological exam done? [Was any radiological exam done?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
8. ✓	Other [Other]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] Other A200 Please Specify [PR.PRSTDTC] [PR.PRENDTC] Test Date NReq ☐ / NReq ☐ / NReq ☐ (2018-2029) [FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] Consistent with Diagnosis? [A:Y] ☐ Yes [A:N] ☐ No
9. ✓		
RADIOEXAM Entry [PR.PRCAT = "RADIOLOGY"] [PR.PRPREP = "Y"] [FA.FACAT = "HOSPITALIZATION: RADIOLOGY"]		
9.1*	Radio Exam done [Radio Exam done]	[PR.PROCCUR = "Y"] [PR.PRTRT] [FA.FAOBJ] [dRADIO_1] ☐
9.2 ✓	Test Date [Test Date]	[PR.PRSTDTC] [PR.PRENDTC] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029)
9.3* ✓	Consistent with Diagnosis? [Consistent with Diagnosis?]	[FA.FAORRES] [FA.FATEST = "Consistent with Diagnosis"] [A:Y] ☐ Yes [A:N] ☐ No
DISEASES EVALUATION [FA.FACAT = "HOSPITALIZATION: DISEASE EVALUATION"]		
10.* ✓	Does this diagnosis discussed with a specialist? [Does this diagnosis discussed with a specialist?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONSULTATION WITH SPECIALIST"] [A:N] ☐ No [A:Y] ☐ [FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "CONFIRMED BY SPECIALIST"] Yes --> If yes, does this diagnosis confirmed by a specialist [A:Y] ☐ Yes [A:N] ☐ [FA.FAORRES] [FA.FATEST = "Diagnosis"] [FA.FAOBJ = "DIFFERENTIAL DIAGNOSIS"] No --> If no, Please list the differential diagnosis: A200
11.* ✓	Can severity of the disease be evaluated at discharge? [Can severity of the disease be evaluated at discharge?]	[FA.FAORRES] [FA.FATEST = "Occurrence"] [FA.FAOBJ = "SEVERITY EVALUATED AT DISCHARGE"] [A:N] ☐ No [A:Y] ☐ [AE.AESEV]

		Yes --> [A:MIL] ☐ Mild [A:MOD] ☐ Moderate [A:SEV] ☐ Severe [A:FAT] ☐ Fatal
12.* ✓	Please record disease outcome at discharge: [Please record disease outcome at discharge:]	[AE.AEOUT] [A:FUREC] ☐ Fully recovered [A:RECOV] ☐ Recovering [A:SEQ] ☐ Sequelae [A:NRES] ☐ Not resolved [A:DEA] ☐ Death
13.* ✓	What is the preferred term associated to this event? [What is the preferred term associated to this event?]	[AE.AETERM] [SUPPPR.QVAL when QNAM = "RELDIS"] [A:Cleft foot] ☐ Cleft foot [A:Congenital clubfoot] ☐ Congenital clubfoot [A:Congenital foot malformation] ☐ Congenital foot malformation [A:Congenital valgus foot deformity] ☐ Congenital valgus foot deformity [A:Congenital varus deformity of foot NOS] ☐ Congenital varus deformity of foot NOS [A:Foot agenesis] ☐ Foot agenesis [A:Malformation foot] ☐ Malformation foot [A:99] ☐ [AE.AETERM] [SUPPPR.QVAL when QNAM = "RELDIS"] Other, Please specify:
14. ✓	Comment	[CO.COVAL when IDVAR = "AESEQ"]

Key: [*] = Item is required [✓] = Source verification required [.] = Source verification critical
 Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: FOOT POSITIONAL DEFORMATION						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
clRADIO_1	String		Clinical Examination	11	cltmRE1_1	itmRADIO1
			CT scan	1RE	cltmRE1	
			Electrocardiogram	2RE	cltmRE2	
			Electroencephalogram	3RE	cltmRE3	
			Electromyogram	4RE	cltmRE4	
			MRI	5RE	cltmRE5	
			Non-barium or air-contrast enema	6RE	cltmRE6	
			X-ray	7RE	cltmRE7	
			X-ray abdomen	8RE	cltmRE8	
			Ultrasound	9RE	cltmRE9	
			Ultrasound 36° cardiac	10RE	cltmRE10	

EPI-MALARIA-003 VS AME (115056): HOSPITAL CHECK-UP (AFTER DISCHARGE) ()	
VISIT NO	
1.	Hospitalisation number <i>[read-only]</i> XX(Domain).VISITNUM N4
HOSPITAL CHECK-UP (AFTER DISCHARGE) [HO.HOTERM = "HOSPITAL CHECK-UP"] [HO.HOCAT = "FOLLOW-UP CARE"]	
2.* ✓	Did the study participant come to the hospital one month after discharge? [Did the study participant come to the hospital one month after discharge?] [HO.HOOCUR] [HO.HOSCAT = "1 MONTH AFTER DISCHARGE"] [A:N] ☐ [SUPPHO.QVAL when QNAM = "REASNOCU"] No --> [A:1] ☐ Study Completed [A:2] ☐ [When this field is completed, then the value is added to the calculated value of SUPPHO.QVAL when QNAM = "REASNOCU" separated by a colon] Other Reason, please specify A200 [A:Y] ☐ [HO.HOSTDTC] [HO.HOENDTC] Yes, Please provide the Date ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) [SUPPHO.QVAL when QNAM = "SEQUELYN"] Is there any sequelae [A:Y] ☐ Yes [A:N] ☐ No [SUPPHO.QVAL when QNAM = "SEQUELAE"] Please report here any sequelae observed: A200 [A:UNK] ☐ Unknown [A:NAS] ☐ Not applicable for SAE other than AESI, Meningitis and Cerebral Malaria
3.* ✓	Did the study participant come to the hospital six months after discharge? [Did the study participant come to the hospital six months after discharge?] [HO.HOOCUR] [HO.HOSCAT = "6 MONTHS AFTER DISCHARGE"] [A:N] ☐ [SUPPHO.QVAL when QNAM = "REASNOCU"] No --> [A:1] ☐ Study Completed [A:2] ☐ [When this field is completed, then the value is added to the calculated value of SUPPHO.QVAL when QNAM = "REASNOCU" separated by a colon] Other Reason, Please specify A200 [A:Y] ☐ [HO.HOSTDTC] [HO.HOENDTC] Yes, Please provide the Date ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) [SUPPHO.QVAL when QNAM = "SEQUELYN"] Is there any sequelae [A:Y] ☐ Yes [A:N] ☐ No [SUPPHO.QVAL when QNAM = "SEQUELAE"] Please report here any sequelae observed: A200 [A:UNK] ☐ Unknown [A:NAS] ☐ Not applicable for SAE other than AESI, Meningitis and Cerebral Malaria
4.* ✓	Did the study participant come to the hospital one year after discharge? [HO.HOOCUR] [HO.HOSCAT = "1 YEAR AFTER DISCHARGE"] [A:N] ☐ [SUPPHO.QVAL when QNAM = "REASNOCU"] No --> [A:1] ☐ Study Completed [A:2] ☐ [HOSPDISC_DATA.OTH_SP] [When this field is completed, then the value is added to the calculated value of SUPPHO.QVAL when QNAM = "REASNOCU" separated by a colon] Other Reason, please specify A200 [A:Y] ☐ [HO.HOSTDTC] [HO.HOENDTC] Yes, Please provide the Date ☐ Req ☐ / ☐ Req ☐ / ☐ Req (2018-2029) [SUPPHO.QVAL when QNAM = "SEQUELYN"] Is there any sequelae [A:Y] ☐ Yes [A:N] ☐ No [SUPPHO.QVAL when QNAM = "SEQUELAE"] Please report here any sequelae observed: A200 [A:UNK] ☐ Unknown [A:NAS] ☐ Not applicable for SAE other than AESI, Meningitis and Cerebral Malaria

Key: [*] = Item is required [✓] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

EPI-MALARIA-003 VS AME (115056): OCCURRENCE OF ADVERSE EVENTS TO BE REPORTED IN THE EXPEDITED ADVERSE EVENT REPORT () [NOT SUBMITTED]		
OCCURRENCE OF ADVERSE EVENTS TO BE REPORTED IN THE EXPEDITED ADVERSE EVENT REPORT		
1. *	Did the subject experience any serious adverse events that are required to be reported per protocol? [Did the subject experience any serious adverse events that are required to be reported per protocol?]	[A:N] ☐ No [A:Y] ☐ Yes -> Please remember to complete an Expedited Adverse Event Report
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): EXPEDITED ADVERSE EVENTS () - Repeating Form													
#	ADVERSE EVENT	RELEVANT CONCOMITANT/TREATMENT MEDICATIONS/VACCINATIONS				RELEVANT MEDICAL CONDITION(S) / RISK FACTOR(S)				RELEVANT DIAGNOSTIC RESULT(S)			
1													
If you wish to record a new AE please determine if the new AE is clinically or temporally related to an AE previously entered on this form. If yes, record the details below using the 'Add Entry' button in this form. If not clinically or temporally related, create a new AE form for this subject by clicking on the 'New' button at the top of the page. Do not record pre and post randomization events on the same form.													
EXPEDITED AE REPORT NO.													
1.	No. [read-only] [No.]	[AE.AEGRPID] [AE.AESPID] N2											
2.	Start date of AE (minimum date from sctSAE) [hidden] [Start date if SAE (minimum date from sctSAE)]	[NOT SUBMITTED] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029)											
3.	Stop date of AE (maximum date from sctSAE) [hidden] [Stop date of SAE (maximum date from sctSAE)]	[NOT SUBMITTED] NReq ☐ / NReq ☐ / NReq ☐ (2018-2029)											
TYPE OF REPORT													
4.	Initial Report [hidden] [Initial Report]	[NOT SUBMITTED] [A:1] ☐ Initial											
5.	Follow-Up Report [hidden] [Follow-Up Report]	[NOT SUBMITTED] [A:2] ☐ Follow-Up											
RANDOMIZATION													
6.*	Did the subject receive at least one dose of RTS, S/AS01 Vaccine before this event? [Did the subject receive at least one dose of RTS, S/AS01 Vaccine before this event?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes											
7.	☒												
ADVERSE EVENT Entry													
Use the 'Add Entry' button to enter details of the AE. For additional AEs that are clinically or temporally related (e.g., AEs that occur during the same hospitalization) use the 'Add Entry' button to create a new row for entry of the additional AE. Enter ONE event per row.													
7.1	No. [read-only] [No.]	[AE.AESPID] N5											
7.2*	Event: Diagnosis only (if known), otherwise sign/symptom [Event]	[AE.AETERM] A100											
7.3*	Serious? [Serious?]	[AE.AESER] [A:3] ☐ Serious [A:1] ☐ Non-Serious											
7.4*	Adverse Event of Special Interest (AESI)?	[SUPPAE.QVAL when QNAM = "AESI"] [A:PIMD] ☐ AESI [A:NON PIMD] ☐ non AESI											
7.5	MedDRA synonym [hidden]	[NOT SUBMITTED] A100											
7.6	MedDRA lower level term code [hidden]	[AE.AELLTCD] A10											
7.7	Failed coding [hidden]	[NOT SUBMITTED] A10											
7.8*	Start date and time Hr:Min (00:00-23:59) [Start date and time]	[AE.AESTDTC] ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock											
7.9*	Outcome / End date and time Hr:Min (00:23-59) [Outcome / End date and time]	[AE.AEOUT] [A:1] [AE.AEENDTC] Recovered/Resolved, provide End Date and Time ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock [A:2] ☐ Recovering / resolving [A:3] ☐ Not recovered / not resolved [A:4] [AE.AEENDTC] Recovered/Resolved with sequelae, provide End Date and Time ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock [A:5] [AE.AEENDTC] [DM.DTHDTC] [DM.DTHFL] Fatal, record Date of Death and Time of Death ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock											
7.10*	Maximum Intensity Record maximum intensity throughout duration of event [Maximum Intensity]	[AE.AESEV] [A:1] ☐ Mild [A:2] ☐ Moderate [A:3] ☐ Severe [A:X] ☐ Not applicable											
7.11	Intensity at onset of event Record intensity at the onset of the event [hidden] [Intensity at onset of event]	[NOT SUBMITTED] [A:1] ☐ Mild [A:2] ☐ Moderate [A:3] ☐ Severe [A:X] ☐ Not applicable											
7.12	Maximum Grade	[NOT SUBMITTED]											

	Record maximum grade throughout duration of event [hidden] [Maximum Grade]	[A:1] ☐ Grade 1 [A:2] ☐ Grade 2 [A:3] ☐ Grade 3 [A:4] ☐ Grade 4 [A:5] ☐ Grade 5
7.13	Grade at onset of event Record grade at the onset of the event [hidden] [Grade at onset of event]	[NOT SUBMITTED] [A:1] ☐ Grade 1 [A:2] ☐ Grade 2 [A:3] ☐ Grade 3 [A:4] ☐ Grade 4 [A:5] ☐ Grade 5
7.14	Maximum Grade or Intensity Record maximum grade or intensity throughout duration of event [hidden] [Maximum Grade or Intensity]	[NOT SUBMITTED] [A:1] ☐ Mild or Grade 1 [A:2] ☐ Moderate or Grade 2 [A:3] ☐ Severe or Grade 3 [A:4] ☐ Grade 4 [A:X] ☐ Not applicable
7.15	Grade or Intensity at onset of event Record grade or intensity at the onset of the event [hidden] [Grade or Intensity at onset of event]	[NOT SUBMITTED] [A:1] ☐ Mild or Grade 1 [A:2] ☐ Moderate or Grade 2 [A:3] ☐ Severe or Grade 3 [A:4] ☐ Grade 4 [A:X] ☐ Not applicable
7.16*	Action taken with RTS,S/AS01 vaccine as a result of the event: [Action taken with RTS,S/AS01 vaccine as a result of the event:]	[AE.AEACN] [A:1] ☐ Study vaccine(s) withdrawn [A:4] ☐ Dose Not Changed [A:5] ☐ Dose delayed [A:X] ☐ Not Applicable
7.17	Modified term Do not query this item. it is not displayed for sites. [hidden] [Modified term]	[AE.AEMODIFY] A100
7.18*	Did the subject withdraw from study due to this event? [Did the subject withdraw from study due to this event?]	[AE.AEACNOTH = "WITHDRAWN FROM STUDY"] [A:Y] ☐ Yes [A:N] [NOT SUBMITTED] ☐ No
7.19*	Is there a reasonable possibility that the event may have been caused by the RTS,S/AS01 vaccine? Please provide rationale in narrative. Use best judgment at initial entry. May be amended when additional information becomes available. [Is there a reasonable possibility that the event may have been caused by the RTS,S/AS01 vaccine?]	[AE.AEREL] [A:N] ☐ No [A:Y] ☐ Yes
7.20	Related Investigational Product [hidden] [Related Investigational Product]	[NOT SUBMITTED] A100
7.21	Duration of AE if < 24 hours [hidden] [Duration of AE if < 24 hours]	[NOT SUBMITTED] [NOT SUBMITTED] Hr(s) 0 <= N2 <= 23 Min(s) 0 <= N2 <= 59
7.22	Time to Onset Since Last Dose [hidden] [Time to Onset]	[NOT SUBMITTED] [NOT SUBMITTED] Hr(s) Min(s) 0 <= N2 <= 23 0 <= N2 <= 59
7.23*	Was the AE caused by activities related to study participation and not by the RTS,S/AS01? [Was the AE caused by activities related to study participation and not by the RTS,S/AS01 vaccine?]	[NOT SUBMITTED] [A:Y] ☐ Yes [A:N] ☐ No
7.24	Was the event serious? [hidden] [Was the event serious?]	[NOT SUBMITTED] [A:Y] ☐ Yes [A:N] ☐ No
7.25	AE description: Diagnosis only (if known), otherwise sign/symptom [hidden] [AE description]	[NOT SUBMITTED] A100
7.26	AE description: Diagnosis only (if known), otherwise sign/symptom [hidden] [AE description]	[NOT SUBMITTED] A100
7.27	SAEEmailFlag [hidden] [SAEEmailFlag]	[NOT SUBMITTED] A6
7.28*	Medically attended visit: [Medically attended visit]	[SUPPAE.QVAL when QNAM = "AEMEDTYP"] [A:NONE] ☐ None [A:HOSPITALISATION] ☐ Hospitalisation [A:EMERGENCY ROOM] ☐ Emergency room [A:MEDICAL PERSONNEL] ☐ Medical personnel
7.29	Narrative include clinical [hidden]	[NOT SUBMITTED] A255
7.30*	Reserved to the investigator: The ticking of this box confirms that the causality of the RTS,S/AS01 vaccine and/or study participation entered for this AE has been reviewed. If any changes are made to the causality of the RTS,S/AS01 vaccine	[NOT SUBMITTED] [A:1] ☐ Reviewed

	and/or study participation after review, the investigator will be required to review and retick the box. <i>[read-only]</i> [Confirmation that the causality of the RTS,S/AS01 vaccine and/or study participation entered for this AE has been reviewed]	
7.31	Date when AETERM was first filled in <i>[hidden]</i>	[NOT SUBMITTED] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock
7.32	Date when ASSESS is filled in <i>[hidden]</i>	[NOT SUBMITTED] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock
7.33	Date when AEREL was modified <i>[hidden]</i>	[NOT SUBMITTED] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock
7.34	Date when AE is modified <i>[hidden]</i>	[NOT SUBMITTED] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) ☐ Req ☐ : ☐ Req ☐ : ☐ Req ☐ 24-hour clock
7.35	Previous value for AEREL & AESREL (ltmPREVREL) <i>[hidden]</i> [Previous value for AEREL & AESREL]	[NOT SUBMITTED] A128
7.36	Adverse Event Category <i>[hidden]</i>	[NOT SUBMITTED] ☐ [clAEFCAT_AECAT] ☐
7.37	Adverse Event Subcategory <i>[hidden]</i>	[NOT SUBMITTED] A128
7.38	Yes, tick the related study vaccines <i>[hidden]</i> [Related study vaccines]	[NOT SUBMITTED] [A:900] ☐ DTPa-HBV-IPV [A:901] ☐ DTPa-HBV-IPV/Hib
8.	Sequence Number <i>[hidden]</i> [Sequence Number]	[NOT SUBMITTED] N5
9.	AE description: Diagnosis only (if known), otherwise sign/symptom <i>[hidden]</i>	[NOT SUBMITTED] A100
10.	Start Date and Time of event segment Hr:Min (00:00-23:59) <i>[hidden]</i> [Start Date of event segment]	[NOT SUBMITTED] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2010-2018) ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock
11.	Intensity of event segment <i>[hidden]</i> [Intensity of event segment]	[NOT SUBMITTED] [A:1] ☐ Mild [A:2] ☐ Moderate [A:3] ☐ Severe
12.	Grade of event segment <i>[hidden]</i> [Grade of event segment]	[NOT SUBMITTED] [A:1] ☐ Grade 1 [A:2] ☐ Grade 2 [A:3] ☐ Grade 3 [A:4] ☐ Grade 4 [A:5] ☐ Grade 5
13.	Grade or Intensity of event segment <i>[hidden]</i> [Grade or Intensity of event segment]	[NOT SUBMITTED] [A:1] ☐ Mild or Grade 1 [A:2] ☐ Moderate or Grade 2 [A:3] ☐ Severe or Grade 3 [A:4] ☐ Grade 4 [A:5] ☐ Grade 5
SERIOUSNESS		
For Non-Serious AEFI, no seriousness criteria must be ticked		
14.	Specify the reason for considering this event as SAE. (Tick all that apply) [Seriousness]	[NOT SUBMITTED] [A:A] ☐ [AE.AESDTH] ☐ Result in death [A:B] ☐ [AE.AESLIFE] ☐ Is life-threatening (subject was at risk of death at time of event) [A:C] ☐ [AE.AESHOSES] ☐ Requires hospitalisation or prolongation of hospitalisation (Provide admission and discharge date(s) in narrative) [A:D] ☐ [AE.AESDTSAB] ☐ Results in disability/incapacity (substantial / permanent) [A:E] ☐ [AE.AESCONG] ☐ Congenital anomaly/birth defect (in offspring of subject) [A:F] ☐ [AE.AESMIE] ☐ Other, specify within general narrative comment
15.	Concatenation of Seriousness <i>[hidden]</i>	[NOT SUBMITTED] A128
16.		
✓		
RELEVANT CONCOMITANT/TREATMENT MEDICATIONS/VACCINATIONS Entry		
Use the 'Add Entry' button to enter details of any medication/vaccine that may help to explain the AE, may have caused the AE or was used to treat the AE. Ensure each concomitant vaccination or medication recorded in this section is also recorded in the corresponding form located in the LOGS section of the eCRF.		
16.1	CM Sequence Number <i>[hidden]</i> [CM Sequence Number]	[NOT SUBMITTED] A4
16.2*	Drug name: [Drug Name]	[NOT SUBMITTED] A100

16.3	Modified reported term [hidden] [Modified reported term]	[NOT SUBMITTED] A100
16.4*	Dose [Dose]	[NOT SUBMITTED] xxxxxxxxxx.
16.5*	Unit [Unit]	[NOT SUBMITTED] [cICMUNITSAE] ☐
16.6*	Frequency [Frequency]	[NOT SUBMITTED] [cISAECMFRQ] ☐
16.7*	Route [Route]	[NOT SUBMITTED] [cIMEDROUT_MEDSAE] ☐
16.8*	Start Date [Start Date]	[NOT SUBMITTED] Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2012-2029)
16.9	End date: or tick box if continuing at the end of the study [End date]	[NOT SUBMITTED] Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2012-2029) [NOT SUBMITTED] Continuing at the end of the study [A:Y] ☐
16.10	Medical indication Enter a medical diagnosis not description [Medical Indication]	[NOT SUBMITTED] A50
16.11	Modified reported term [hidden] [Modified reported term]	[NOT SUBMITTED] A100
16.12*	Type of drug: [Type of drug]	[NOT SUBMITTED] [cIDRUGTYP] ☐
16.13	CM COMPARE (Hidden) [hidden] [CM COMPARE (Hidden)]	[NOT SUBMITTED] A100
16.14	CMIN COMPARE (Hidden) [hidden] [CMIN COMPARE (Hidden)]	[NOT SUBMITTED] A100
17. ✓		
RELEVANT MEDICAL CONDITION(S) / RISK FACTOR(S) Entry		
Use the 'Add Entry' button to enter each past or current medical disorder, allergy or surgery that may be RELEVANT to the AE. Enter a diagnosis, not description. Relevant family or social history should be described in the 'General Narrative Comments' at the bottom of this form. Ensure each medical condition/risk factor recorded in this section is also recorded in the General Medical History form located at the beginning of the eCRF.		
17.1	MHx Sequence Number [hidden] [MHx Sequence Number]	[NOT SUBMITTED] A4
17.2*	Condition Enter a medical diagnosis not description. [Condition]	[NOT SUBMITTED] A100
17.3	Modified reported term [hidden] [Modified reported term]	[NOT SUBMITTED] A100
17.4*	Start date: [Start date]	[NOT SUBMITTED] Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2012-2029)
17.5*	Continuing at time of AE? [Continuing at time of AE?]	[NOT SUBMITTED] [A:Y] ☐ Yes [A:N] ☐ [NOT SUBMITTED] No, specify end date or date of last occurrence Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2012-2029) [A:U] ☐ Unknown, no information available
17.6	SAE MHX Compare (Hidden) [hidden] [SAE MHX Compare (Hidden)]	[NOT SUBMITTED] A100
18. ✓		
RELEVANT DIAGNOSTIC RESULT(S) Entry		
Use the 'Add Entry' button to enter details of relevant tests or procedures carried out to diagnose or confirm the AE or rule out other diagnoses		
18.1	Lab Sequence Number [hidden] [Lab Sequence Number]	[NOT SUBMITTED] A4
18.2*	Test name [Test name]	[NOT SUBMITTED] [cISALBTST] ☐
18.3*	Test date [Test date]	[NOT SUBMITTED] Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2018-2029)
18.4*	Test result [Test result]	[NOT SUBMITTED] A12
18.5*	Test units [Test units]	[NOT SUBMITTED] A12

18.6*	Normal low range [Normal low range]	[NOT SUBMITTED] xxxxxxxx.xx
18.7*	Normal high range [Normal high range]	[NOT SUBMITTED] xxxxxxxx.xx
19.	Enter here only the diagnostic results that could not be entered in the above grid, including procedure such as ECG, X rays, etc and tests on stool, CSF etc. Also provide dates. [Relevant diagnostic results not noted on the left columns]	[NOT SUBMITTED] A1000 [NOT SUBMITTED] A1000
20.	If investigational product(s) were stopped temporarily, did the reported event(s) recur after investigational products were restarted? <i>[hidden]</i> [If investigational product(s) were stopped temporarily, did the reported event(s) recur after investigation products were restarted?]	[NOT SUBMITTED] [A:N] ___ No [A:Y] ___ Yes [A:U] ___ Unknown at this time [A:X] ___ Not applicable
GENERAL NARRATIVE COMMENTS		
Provide a clear (this narrative will be provided to regulatory authorities) and brief chronological description (with dates) of the clinical course of the event including: - Associated signs and symptoms - Clinical evolution (hospitalisation, outcome, description of sequelae if any, autopsy results, etc.) - Non-drug treatment such as surgery - Other information useful for the medical assessment of the case (e.g. reason for diagnosis if not obvious or if diagnosis changed) - Relevant additional risk factors including family or social history (negative sentence can also be helpful) - Possible cause(s) of the event - Rationale for relationship when AE is possibly related to study product, concomitant product or study procedure, etc.		
Complete a new box only when the previous one is full.		
21.*	General narrative comments	[NOT SUBMITTED] A1000 [NOT SUBMITTED] A1000 [NOT SUBMITTED] A1000 [NOT SUBMITTED] A1000

NON CLINICAL		
22.	Send incomplete AE data to GSK Safety [hidden] [Send incomplete AE data to GSK Safety]	[NOT SUBMITTED] ☐ [cSENDI] ☐
23.	Receipt by GSK date [hidden] [Receipt by GSK date]	[NOT SUBMITTED] ☐ Req ☐ / ☐ Req ☐ / ☐ Req ☐ (2018-2029) ☐ Req ☐ : ☐ Req ☐ 24-hour clock
24.	Was the event serious? [hidden] [Was the event serious?]	[NOT SUBMITTED] [A:Y] ☐ Yes [A:N] ☐ No
25.	Sequence Number [hidden] [Sequence Number]	[NOT SUBMITTED] N5
26.	Version Number [hidden] [Version Number]	[NOT SUBMITTED] A4
27.	Case ID [hidden] [Case ID]	[NOT SUBMITTED] A20
28.	Randomisation Number [hidden] [Randomisation Number]	[NOT SUBMITTED] A255
29.	Safety case ID [hidden] [Safety case ID]	[NOT SUBMITTED] A13
30.	eMail flag [hidden]	[NOT SUBMITTED] A6
31.	Message sender identifier [hidden] [mssgsendid]	[NOT SUBMITTED] A128
32.	Study Type [hidden] [Study Type]	[NOT SUBMITTED] A128
33.	Modification datetime [hidden]	[NOT SUBMITTED] ☐ NReq ☐ / ☐ NReq ☐ / ☐ NReq ☐ (2018-2029) ☐ NReq ☐ : ☐ NReq ☐ : ☐ NReq ☐ 24-hour clock
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in Inform will override any settings made in Central Designer.		

Codelist Values Tables: EXPEDITED ADVERSE EVENTS						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cIAECAT_AECAT	String		Unsolicited Adverse Event	UNSOLICITED ADVERSE EVENT	ctmUNSOLICITED_ADVERSE_EVENT	AECAT_HID
cCMUNITSAE	String		ACTU	ACTU	cCMUNIT_ACTU	pdcCMUNIT
			AMP	AMP	cCMUNIT_AMP	
			application(s)	AP	cCMUNIT_AP	
			BT	BT	cCMUNIT_BT	
			capsule	CAP	cCMUNIT_CAP	
			Cubic centimeter	CC	cCMUNIT_CC	
			MBecquerel	16	ctmCMUNIT_MBQ	
			Variable dose	VA	ctmCMUNIT_VA	
			blister	BLS	ctmCMUNIT_BLS	
			caplet(s)	CAPL	ctmCMUNIT_CAPL	
			cg	CG	ctmCMUNIT_CG	
			drop(s)	31	ctmCMUNIT_DROP	
			elisa unit	EU	ctmCMUNIT_EU	
			g/L	GML	ctmCMUNIT_GML	
			g/M2	GM/M2	ctmCMUNIT_GMM2	

		g/kg	GM/KG	citmCMUNIT_GMKG	
		grain	GR	citmCMUNIT_GR	
		gram(s)	2	citmCMUNIT_G	
		inch	INCH	citmCMUNIT_INCH	
		injection	INJ	citmCMUNIT_INJ	
		iu	25	citmCMUNIT_IU	
		iu x 10**3	26	citmCMUNIT_IU3	
		iu x 10**6	27	citmCMUNIT_IU6	
		liter	11	citmCMUNIT_L	
		lozenge	LOZ	citmCMUNIT_LOZ	
		mCi	19	citmCMUNIT_MCI	
		mEq	29	citmCMUNIT_MEQ	
		mcg	4	citmCMUNIT_MCG	
		mcg/mg	MCG/MG	citmCMUNIT_MCGMG	
		Megaunits (million units)	MEGU	citmCMUNIT_MEGU	
		mg	3	citmCMUNIT_MG	
		mg/kg	7	citmCMUNIT_MGK	
		mg/m2	9	citmCMUNIT_MGM2	
		mg/min	MGM	citmCMUNIT_MGM	
		mg/ml	MGML	citmCMUNIT_MGML	
		micro unit	MCRU	citmCMUNIT_MCU	
		ml	12	citmCMUNIT_ML	
		ml/hr	MLH	citmCMUNIT_MLH	
		mm	MM	citmCMUNIT_MM	
		mmol	23	citmCMUNIT_MMOL	
		nebule(s)	NEB	citmCMUNIT_NEB	
		ng	5	citmCMUNIT_NG	
		ng/kg	NGK	citmCMUNIT_NGK	
		ounce	OZ	citmCMUNIT_OZ	
		patch	PAT	citmCMUNIT_PAT	
		percent	30	citmCMUNIT_PCT	
		puff(s)	PUFF	citmCMUNIT_PUFF	
		sachet	SAC	citmCMUNIT_SAC	
		spray	SPR	citmCMUNIT_SPR	
		suppository	SUP	citmCMUNIT_SUP	
		tablespoon	TBS	citmCMUNIT_TBS	
		tablet	TAB	citmCMUNIT_TAB	
		teaspoon	TSP	citmCMUNIT_TSP	
		uBecquerel	14	citmCMUNIT_UBQ	
		ugk	8	citmCMUNIT_UGK	
		umol	24	citmCMUNIT_UMOL	
		unit	UNT	citmCMUNIT_UNT	
		unknown	U	citmCMUNIT_U	
		vial(s)	VIA	citmCMUNIT_VIA	
cISAECMFRQ	String	2 times per week	2W	cISAECMFRQ_2W	pdcSAECMFRQ
		3 times per week	3W	cISAECMFRQ_3W	
		4 times per week	4W	cISAECMFRQ_4W	
		5 times per day	5D	cISAECMFRQ_5D	
		5 times per week	5W	cISAECMFRQ_5W	
		AC	AC	cISAECMFRQ_AC	
		BID	2D	cISAECMFRQ_2D	
		Continuous infusion	CO	cISAECMFRQ_CO	
		Every 2 weeks	FO	cISAECMFRQ_F	
		Every 3 weeks	Q3W	cISAECMFRQ_Q3W	
		Every 3 months	Q3M	cISAECMFRQ_Q3M	
		Every other day	AD	cISAECMFRQ_AD	
		Once a month	MO	cISAECMFRQ_MO	
		Once a week	WE	cISAECMFRQ_WE	
		Once daily	1D	cISAECMFRQ_1D	
		Once only	1S	cISAECMFRQ_1S	
		PC	PC	cISAECMFRQ_PC	
		PRN	PRN	cISAECMFRQ_PRN	
		Q2H	12D	cISAECMFRQ_Q2H	

			Q3D	Q3D	cISAECMFRQ_Q3D	
			Q4D	Q4D	cISAECMFRQ_Q4D	
			Q4H	6D	cISAECMFRQ_Q4H	
			QAM	1M	cISAECMFRQ_QAM	
			QH	24D	cISAECMFRQ_QH	
			QID	4D	cISAECMFRQ_QID	
			QPM	1N	cISAECMFRQ_QPM	
			TID	3D	cISAECMFRQ_TID	
cIMEDROUT_MEDSAE	String		Inhalation	055	citmINHALATION_SAE	pdcCMROUTCD
			Intraarticular	014	citmINTRAARTICULAR_SAE	
			Intradermal	023	citmINTRADERMAL_SAE	
			Intramuscular	030	citmINTRAMUSCULAR_SAE	
			Intranasal	045	citmINTRANASAL_SAE	
			Intravenous	042	citmINTRAVENOUS_SAE	
			Oral	048	citmPORAL_SAE	
			Parenteral	051	citmPARENTERAL_SAE	
			Rectal	054	citmRECTAL_SAE	
			Subcutaneous	058	citmSUBCUTANEOUS_SAE	
			Sublingual	060	citmSUBLINGUAL_SAE	
			Topical	061	citmTOPICAL_SAE	
			Transdermal	062	citmTRANSDERMAL_SAE	
			Vaginal	067	citmVAGINAL_SAE	
			Other	050	citmOTHER_SAE	
			Unknown	065	citmUNK_SAE	
cIDRUGTYP	String		Concomitant	2	cIDRUGTYP_01	pdcCMDRGTYTYP
			Treatment	T	cIDRUGTYP_02	
			Cause of AE	1	cIDRUGTYP_03	
cISAELBTST	String		Activated partial thromboplastin time	Activated partial thromboplastin time	SAELBTST01	pdcLBTST
			Alanine aminotransferase	Alanine Amino Transferase	SAELBTST79	
			Albumin	Albumin	SAELBTST02	
			Alkaline phosphatase	Alkaline phosphatase	SAELBTST03	
			Amylase	Amylase	SAELBTST04	
			Aspartate Amino Transferase	Aspartate Amino Transferase	SAELBTST80	
			Band Neutrophil count	Band Neutrophil count	SAELBTST81	
			Base Excess	Base Excess	SAELBTST82	
			Basophils	Basophils	SAELBTST05	
			Bicarbonate	Bicarbonate	SAELBTST06	
			Bilirubin	Bilirubin	SAELBTST07	
			Bilirubin direct	Bilirubin direct	SAELBTST08	
			Bilirubin total	Bilirubin total	SAELBTST09	
			Blood glucose	Blood glucose	SAELBTST83	
			Blood myoglobin	Blood myoglobin	SAELBTST10	
			Blood pH	Blood pH	SAELBTST11	
			Blood pressure	Blood pressure	SAELBTST12	
			Blood urea nitrogen	Blood urea nitrogen	SAELBTST13	
			Body temperature	Body temperature	SAELBTST14	
			Calcium	Calcium	SAELBTST15	
			Carbone dioxide	Carbone dioxide	SAELBTST84	
			CD4 lymphocytes	CD4 lymphocytes	SAELBTST16	
			CD8 lymphocytes	CD8 lymphocytes	SAELBTST17	
			Chloride	Chloride	SAELBTST18	
			Cholesterol total	Cholesterol total	SAELBTST19	
			C-reactive protein	C-reactive protein	SAELBTST20	
			Creatine	Creatine	SAELBTST21	
			Creatine phosphokinase	Creatine phosphokinase	SAELBTST22	
			Creatine phosphokinase MB	Creatine phosphokinase MB	SAELBTST23	
			Creatinine	Creatinine	SAELBTST24	
			Creatinine clearance	Creatinine clearance	SAELBTST25	
			Diastolic blood pressure	Diastolic blood pressure	SAELBTST26	
			Eosinophils	Eosinophils	SAELBTST27	
			Erythrocyte sedimentation rate	Erythrocyte sedimentation rate	SAELBTST28	
			Fasting blood glucose	Fasting blood glucose	SAELBTST29	
			FEV 1	FEV 1	SAELBTST30	

		Gamma-glutamyltransferase	Gamma-glutamyltransferase	SAELBTST31	
		Granulocyte count	Granulocyte count	SAELBTST85	
		HbA1c	HbA1c	SAELBTST34	
		HBV-DNA decreased	HBV-DNA decreased	SAELBTST35	
		HBV-DNA increased	HBV-DNA increased	SAELBTST36	
		Heart rate	Heart rate	SAELBTST37	
		Hematocrit	Hematocrit	SAELBTST38	
		Hemoglobin	Hemoglobin	SAELBTST39	
		High density lipoprotein	High density lipoprotein	SAELBTST40	
		HIV viral load	HIV viral load	SAELBTST41	
		INR	INR	SAELBTST42	
		International normalized ratio	International normalized ratio	SAELBTST88	
		Lactate dehydrogenase	Lactate dehydrogenase	SAELBTST43	
		Lipase	Lipase	SAELBTST44	
		Low density lipoprotein	Low density lipoprotein	SAELBTST45	
		Lymphocytes	Lymphocytes	SAELBTST46	
		Magnesium	Magnesium	SAELBTST47	
		Mean cell hemoglobin concentration	Mean cell hemoglobin concentration	SAELBTST48	
		Mean corpuscular hemoglobin	Mean corpuscular hemoglobin	SAELBTST49	
		Mean corpuscular volume	Mean corpuscular volume	SAELBTST50	
		Mean Platelet Volume	Mean Platelet Volume	SAELBTST89	
		Monocytes	Monocytes	SAELBTST51	
		Myoglobin urine	Myoglobin urine	SAELBTST90	
		Neutrophils	Neutrophils	SAELBTST52	
		Oxygen saturation	Oxygen saturation	SAELBTST53	
		pCO2	pCO2	SAELBTST54	
		pH	pH	SAELBTST55	
		pH urine	pH urine	SAELBTST91	
		Phosphate	Phosphate	SAELBTST56	
		Platelet count	Platelet count	SAELBTST57	
		pO2	pO2	SAELBTST58	
		Polymerase Chain Reaction	Polymerase Chain Reaction	SAELBTST92	
		Polymorphonuclear Count	Polymorphonuclear Count	SAELBTST93	
		Potassium	Potassium	SAELBTST59	
		Protein total	Protein total	SAELBTST60	
		Prothrombin time	Prothrombin time	SAELBTST61	
		Red blood cell count	Red blood cell count	SAELBTST62	
		Red Cell Distribution Width	Red Cell Distribution Width	SAELBTST94	
		Respiratory rate	Respiratory rate	SAELBTST63	
		Reticulocyte count	Reticulocyte count	SAELBTST64	
		Segmented Neutrophil Count	Segmented Neutrophil Count	SAELBTST95	
		Serum glucose	Serum glucose	SAELBTST65	
		Serum uric acid	Serum uric acid	SAELBTST66	
		Sodium	Sodium	SAELBTST67	
		Systolic blood pressure	Systolic blood pressure	SAELBTST68	
		Thrombin time	Thrombin time	SAELBTST69	
		Total lung capacity	Total lung capacity	SAELBTST70	
		Triglycerides	Triglycerides	SAELBTST71	
		Troponin	Troponin	SAELBTST72	
		Troponin I	Troponin I	SAELBTST73	
		Troponin T	Troponin T	SAELBTST74	
		Urine myoglobin	Urine myoglobin	SAELBTST75	
		Urine pH	Urine pH	SAELBTST76	
		Vital capacity	Vital capacity	SAELBTST77	
		White blood cell count	White blood cell count	SAELBTST78	
clSENDI	String	Incomplete SAE	3	clSENDI_3	chkSENDI

COVID-19 DIAGNOSIS [NOT SUBMITTED]

1.	Was the subject diagnosed with probable, suspected or confirmed COVID-19? [hidden] [Diagnosed with COVID-19]	[A:Y] ☐ Yes [A:N] ☐ No
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): COVID-19 CORONAVIRUS INFECTION ASSESSMENT (COVID-19 Assessment) - Repeating Form [NOT SUBMITTED]																							
#	No.	Expedited AE Report No.	Adverse Event No.	Case diagnosis	COVID-19 test performed	Subject travel 14 days prior to symptom onset	Subject health care facility 14 days prior to symptom onset	Subject contact case 14 days prior to symptom onset	COVID-19 medications	Fever	Cough	Shortness of breath	Sore throat	Loss of appetite	Nausea	Vomiting	Diarrhea	Abdominal pain	Fatigue	Loss of smell	Loss of taste	Asymptomatic	Subject in home quarantine or isolation
1																							
COVID-19 ASSESSMENT [NOT SUBMITTED]																							
1.	No. [read-only]					N3																	
2.	Expedited AE Report No. [Adverse Event Sequence Number]					N5																	
3.*	Adverse Event No. [Adverse Event Sequence Number]					N5																	
4.*	What was the case diagnosis? [Case diagnosis]					[A:CONFIRMED] ☐ Confirmed [A:PROBABLE] ☐ Probable [A:SUSPECTED] ☐ Suspected																	
5.*	Was a COVID-19 test performed? [COVID-19 test performed]					[A:Y] ☐ Yes What was the date of the COVID-19 test? ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req ☐ (2019-2026) What was the result of the COVID-19 test? [A:NEGATIVE] ☐ Negative [A:POSITIVE] ☐ Positive [A:INDETERMINATE] ☐ Indeterminate [A:N] ☐ No																	
6.*	Does the subject have a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset? [Subject travel 14 days prior to symptom onset]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
7.*	Did the subject visit any health care facility in the 14 days prior to symptom onset? [Subject health care facility 14 days prior to symptom onset]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
8.*	Did the subject have contact with a confirmed or probable case in the 14 days prior to symptom onset? [Subject contact case 14 days prior to symptom onset]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
9.*	Were any concomitant medications taken by the subject, including experimental medications, to treat COVID-19? If Yes, add medications to the Medication form. [COVID-19 medications]					[A:Y] ☐ Yes [A:N] ☐ No																	
COVID-19 SYMPTOMS																							
10.*	Did the subject have a fever? [Fever]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
11.*	Did the subject have a cough? [Cough]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
12.*	Did the subject have shortness of breath? [Shortness of breath]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
13.*	Did the subject have a sore throat? [Sore throat]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
14.*	Did the subject have a loss of appetite? [Loss of appetite]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
15.*	Did the subject have nausea? [Nausea]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
16.*	Did the subject have vomiting? [Vomiting]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
17.*	Did the subject have diarrhea? [Diarrhea]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
18.*	Did the subject have abdominal pain? [Abdominal pain]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
19.*	Did the subject have fatigue? [Fatigue]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
20.*	Did the subject have a loss of smell? [Loss of smell]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
21.*	Did the subject have a loss of taste? [Loss of taste]					[A:Y] ☐ Yes [A:N] ☐ No [A:U] ☐ Unknown																	
22.*	Was the subject asymptomatic? [Asymptomatic]					[A:Y] ☐ Yes [A:N] ☐ No																	
COVID-19 LEVEL OF CARE																							
23.*	Was the subject in home quarantine or isolation?					[A:Y] ☐ Yes																	

	[Subject in home quarantine or isolation]	[A:N] No
		[A:U] Unknown
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): PROTOCOL DEVIATION (Protocol Deviations) - Repeating Form [NOT SUBMITTED]						
#	Monitoring Report number	Protocol deviation category	Protocol deviation description	Visit Number	Other subjects	Requires medical oversight
1						
PROTOCOL DEVIATION						
Please do not enter any information that can lead to unblinding of the subject's treatment -						
1.	Protocol deviation identifier [hidden] [Protocol Deviation Id]	N3				
2.	Monitoring Report number [read-only] [Monitoring Report number]	A10				
3.*	What is the category of the protocol deviation? [read-only] [Protocol deviation category]	☐ [cIDVCAT] ☐				
4.	What is the protocol deviation description ? [read-only] [Protocol deviation description]	A200				
5.	At what visit did the protocol deviation occur [read-only] [VisitNumber]	[A:5] [A:10] [A:20] [A:30] [A:40] [A:50] [A:210] [A:220] [A:230] [A:240] [A:100] [A:60.001] [A:60.002] [A:60.003] [A:60.004] [A:60.005] [A:60.006] [A:60.007] [A:60.008] [A:60.009] [A:60.010] [A:60.011] [A:60.012] [A:60.013] [A:60.014] [A:60.015] [A:60.016] [A:60.017] [A:60.018] [A:60.019] [A:60.020] [A:60.021] [A:60.022] [A:60.023] [A:60.024] [A:60.025] [A:60.026] [A:60.027] [A:60.028] [A:60.029] [A:60.030] [A:60.031] [A:60.032] [A:60.033] [A:60.034] [A:60.035] [A:60.036] [A:60.037] [A:60.038] [A:60.039] [A:60.040] [A:65.001] [A:65.002] [A:65.003] [A:65.004] [A:65.005] [A:65.006] [A:65.007] [A:65.008] [A:65.009] [A:65.010] [A:65.011] [A:65.012] [A:65.013] [A:65.014] [A:65.015] [A:65.016] [A:65.017] [A:65.018] [A:65.019] [A:65.020] [A:NA] ☐ Screening ☐ Visit 1 ☐ Visit 2 ☐ Visit 3 ☐ Visit 4 ☐ Visit 5 ☐ Visit 6 ☐ Visit 7 ☐ Visit 8 ☐ Visit 9 ☐ Visit 10 ☐ OUTPATIENT VISIT 1 ☐ OUTPATIENT VISIT 2 ☐ OUTPATIENT VISIT 3 ☐ OUTPATIENT VISIT 4 ☐ OUTPATIENT VISIT 5 ☐ OUTPATIENT VISIT 6 ☐ OUTPATIENT VISIT 7 ☐ OUTPATIENT VISIT 8 ☐ OUTPATIENT VISIT 9 ☐ OUTPATIENT VISIT 10 ☐ OUTPATIENT VISIT 11 ☐ OUTPATIENT VISIT 12 ☐ OUTPATIENT VISIT 13 ☐ OUTPATIENT VISIT 14 ☐ OUTPATIENT VISIT 15 ☐ OUTPATIENT VISIT 16 ☐ OUTPATIENT VISIT 17 ☐ OUTPATIENT VISIT 18 ☐ OUTPATIENT VISIT 19 ☐ OUTPATIENT VISIT 20 ☐ OUTPATIENT VISIT 21 ☐ OUTPATIENT VISIT 22 ☐ OUTPATIENT VISIT 23 ☐ OUTPATIENT VISIT 24 ☐ OUTPATIENT VISIT 25 ☐ OUTPATIENT VISIT 26 ☐ OUTPATIENT VISIT 27 ☐ OUTPATIENT VISIT 28 ☐ OUTPATIENT VISIT 29 ☐ OUTPATIENT VISIT 30 ☐ OUTPATIENT VISIT 31 ☐ OUTPATIENT VISIT 32 ☐ OUTPATIENT VISIT 33 ☐ OUTPATIENT VISIT 34 ☐ OUTPATIENT VISIT 35 ☐ OUTPATIENT VISIT 36 ☐ OUTPATIENT VISIT 37 ☐ OUTPATIENT VISIT 38 ☐ OUTPATIENT VISIT 39 ☐ OUTPATIENT VISIT 40 ☐ HOSPITALISATION 1 ☐ HOSPITALISATION 2 ☐ HOSPITALISATION 3 ☐ HOSPITALISATION 4 ☐ HOSPITALISATION 5 ☐ HOSPITALISATION 6 ☐ HOSPITALISATION 7 ☐ HOSPITALISATION 8 ☐ HOSPITALISATION 9 ☐ HOSPITALISATION 10 ☐ HOSPITALISATION 11 ☐ HOSPITALISATION 12 ☐ HOSPITALISATION 13 ☐ HOSPITALISATION 14 ☐ HOSPITALISATION 15 ☐ HOSPITALISATION 16 ☐ HOSPITALISATION 17 ☐ HOSPITALISATION 18 ☐ HOSPITALISATION 19 ☐ HOSPITALISATION 20 ☐ Not applicable -> If visit is not applicable, what is the protocol deviation start date ? ☐ Req/Unk ☐ / ☐ Req/Unk ☐ / ☐ Req/Unk ☐ (2015-2025)				

6.	If this deviation is applicable for other subjects from this study please enter these subject numbers separated by a comma <i>[read-only]</i> [Other subjects]	A200
7.	Please tick if this PD requires medical oversight deviation <i>[read-only]</i> [Medical oversight]	[A:Y] ☐ Yes

Key: [*] = Item is required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: PROTOCOL DEVIATION					
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName
clDVCAT	String		Informed Consent-Signed informed consent not available on site	Informed Consent-Signed informed consent not available on site	cltmSIGNED_INFORMED_CONSENT_ASSENT_NOT_AVAILABLE_ON_SITE_1
			Informed Consent-Wrong informed consent version signed	Informed Consent-Wrong informed consent version signed	cltmWRONG_INFORMED_CONSENT
			Informed Consent-Informed consent not signed and/or dated by subject	Informed Consent-Informed consent not signed and/or dated by subject	cltmINFORMED_CONSENT_NOT_SIGNED_BY_SUBJECT
			Informed Consent-Informed consent not signed and/or dated by appropriate site staff	Informed Consent-Informed consent not signed and/or dated by appropriate site staff	cltmINFORMED_CONSENT_NOT_SIGNED_BY_SITE_STAFF
			Informed Consent-Informed consent not signed prior to any study procedure	Informed Consent-Informed consent not signed prior to any study procedure	cltmINFORMED_CONSENT_NOT_SIGNED_PRIOR_PROCEDURE
			Informed Consent-Other informed consent deviations	Informed Consent-Other informed consent deviations	cltmINFORMED_CONSENT_OTHER_DEVIATIONS
			Eligibility Criteria Not Met	Eligibility Criteria Not Met	cltmELIGIBILITY_CRITERIA_NOT_MET
			Visit completion - Missed visit/phone contact	Visit completion - Missed visit/phone contact	cltmVISIT_COMPLETION_MISSED_VISIT_PHONE_CONTACT
			Visit completion - Out of window visit/phone contact	Visit completion - Out of window visit/phone contact	cltmVISIT_COMPLETION_OUT_OF_WINDOW_VISIT_PHONE_CONTACT
			Study procedures - Biological sample specimen procedures - Refrigerator temperature deviations	Study procedures - Biological sample specimen procedures - Refrigerator temperature deviations	cltmSP_BSSPC_REFRIGERATOR_TEMP_DEVIATIONS
			Study procedures - Biological sample specimen procedures - -20 freezer temperature deviations	Study procedures - Biological sample specimen procedures - -20 freezer temperature deviations	cltmSP_BSSPC_20_FREEZER_TEMP_DEVIATIONS
			Study procedures - Biological sample specimen procedures - -70 freezer temperature deviations	Study procedures - Biological sample specimen procedures - -70 freezer temperature deviations	cltmSP_BSSPC_70_FREEZER_TEMP_DEVIATIONS
			Study procedures - Biological sample specimen procedures - testing performed on samples not aligned with ICF	Study procedures - Biological sample specimen procedures - testing performed on samples not aligned with ICF	cltmSP_BSSPC_TESTING_PERFORMED_ON_SAMPLES_NOT_ALIGNED_WITH_ICF
			Study procedures - Biological sample specimen procedures - Incorrect or expired sample tube used for sample type	Study procedures - Biological sample specimen procedures - Incorrect or expired sample tube used for sample type	cltmSP_BSSPC_INCORRECT_EXPIRED_SAMPLE_TUBE_USED_FOR_SAMPLE_TYPE
			Study procedures - Biological sample specimen procedures - Incorrect spinning/processing of sample	Study procedures - Biological sample specimen procedures - Incorrect spinning/processing of sample	cltmSP_BSSPC_INCORRECT_SPINNING_PROCESSING_OF_SAMPLE
			Study procedures - Biological sample specimen procedures - PII recorded on sample label	Study procedures - Biological sample specimen procedures - PII recorded on sample label	cltmSP_BSSPC_PII_RECORDED_ON_SAMPLE_LABEL
			Study procedures - Biological sample specimen procedures - Low volume (insufficient for testing)	Study procedures - Biological sample specimen procedures - Low volume (insufficient for testing)	cltmSP_BSSPC_LOW_VOLUME
			Study procedures - Biological sample specimen procedures - Sample discard/detruction not completed as per protocol/SPM/ICF	Study procedures - Biological sample specimen procedures - Sample discard/detruction not completed as per protocol/SPM/ICF	cltmSP_BSSPC_SAMPLE_DISCARD_DETRUC_NOT_COMPLETED_AP_PROT_SPMICF
			Study procedures - Biological sample specimen procedures - Sample destroyed and should not have been destroyed	Study procedures - Biological sample specimen procedures - Sample destroyed and should not have been destroyed	cltmSP_BSSPC_SAMPLE_DESTROYED_AN_SHOULD_NOT_HAVE_BEEN_DESTROYED
			Study procedures - Biological sample specimen procedures - Collection of multiple samples when not required	Study procedures - Biological sample specimen procedures - Collection of multiple samples when not required	cltmSP_BSSPC_COLLECTION_OF_MULTIPLE_SAMPLES_WHEN_NOT_REQUIRED
			Study procedures - Biological sample specimen procedures - Subject bled but not supposed to be bled	Study procedures - Biological sample specimen procedures - Subject bled but not supposed to be bled	cltmSP_BSSPC_SUBJECT_BLED_BUT_NOT_SUPPOSED_TO_BE_BLED
			Study procedures - Biological sample specimen procedures - No sample collected for subject (and should have been collected)	Study procedures - Biological sample specimen procedures - No sample collected for subject (and should have been collected)	cltmSP_BSSPC_NO_SAMPLE_COLLECTED_FOR_SUBJECT
			Study procedures - Biological sample specimen procedures - Central/internal/external lab deviations	Study procedures - Biological sample specimen procedures - Central/internal/external lab deviations	cltmSP_BSSPC_CENTRAL_INTERNAL_EXTERNAL_LAB_DEVIATIONS
			Study procedures - Biological sample specimen procedures - Mislabeling (sample tested)	Study procedures - Biological sample specimen procedures - Mislabeling (sample tested)	cltmSP_BSSPC_MISLABELING_SAMPLE_TESTED
			Study procedures - Biological sample specimen procedures - Mislabeling (sample not tested)	Study procedures - Biological sample specimen procedures - Mislabeling (sample not tested)	cltmSP_BSSPC_MISLABELING_SAMPLE_NOT_TESTED
			Study procedures - Biological sample specimen procedures - Wrong packaging that impacts quality of the sample	Study procedures - Biological sample specimen procedures - Wrong packaging that impacts quality of the sample	cltmSP_BSSPC_WRONG_PACKAGING_THAT_IMPACTS_QUALITY_OF_THE_SAMPLE
			Study procedures - Other deviation from study procedures - Enrolment in AS DTP group not done according to procedure or acceptable time frame	Study procedures - Other deviation from study procedures - Enrolment in AS DTP group not done according to procedure or acceptable time frame	cltmSP_ODSP_ENR_IN_AS_DTPGROUP_ND_ACC_TO_PROC_OR_ACCEPTABLE_TF
			Study procedures - Other deviation from study procedures - Enrolment in AS Catch up group not done according to procedure or acceptable time frame	Study procedures - Other deviation from study procedures - Enrolment in AS Catch up group not done according to procedure or acceptable time frame	cltmSP_ODSP_ENR_IN_AS_CATCHUPGROUP_ND_ACC_TO_PROC_OR_ACCEP_TF
			Study procedures - Other deviation from study procedures - Enrolment in EHS group not done according to procedure or acceptable time frame	Study procedures - Other deviation from study procedures - Enrolment in EHS group not done according to procedure or acceptable time frame	cltmSP_ODSP_ENR_IN_EHSGROUP_ND_ACC_TO_PROC_OR_ACCEP_TF
			Study procedures - Other deviation from study procedures - Hospital check-up visits not done	Study procedures - Other deviation from study procedures - Hospital check-up visits not done	cltmSP_OD_STUDY_PROC_HOSPITAL_CHECKUP_VISITS_NOT_DONE
			Failure to report safety events pr protocol - Expedited AE/SAE late reporting	Failure to report safety events pr protocol - Expedited AE/SAE	cltmEXPEDITED_AE
			Failure to report safety events pr protocol - Failure to confirm causality assessment	Failure to report safety events pr protocol - Failure to confirm causality assessment	cltmFAIL_REPORT_SAFETYEV_TF_FAILURE_TO_CONFIRM_CAUSASSESS
			Failure to report safety events pr protocol - Failure to confirm causality assessment - tick box not with 24 hrs	Failure to report safety events pr protocol - Failure to confirm causality assessment - tick box not with 24 hrs	cltmFAILREPORT_SAFEFTV_TF_FAILURE_TO_CONFIRM_CAUS_NOTTICK_24HR
			Failure to report safety events pr protocol - No safety follow up beyond the day of vaccination	Failure to report safety events pr protocol - No Safety follow up	cltmDVCAT4

	Fraudulent data	FRAUDULENT DATA	ctmFRAUDULENT_DATA
	Other	OTHER	ctmOTHER_2
	DO NOT USE - Study procedures - Other deviation from study procedures	Study procedures - Other deviation from study procedures	ctmOTHER_DEVIATION_FROM_STUDY_PROCEDURES
	DO NOT USE - Excluded medication, vaccine or device-Other excluded medication, vaccine or device deviation	Excluded medication, vaccine or device-Other excluded medication, vaccine or device deviation	ctmOTHER_EXCLUDED_MEDICATION_VACCINE_DEVICE
	DO NOT USE - Excluded medication, vaccine or device-Device, excluded by the protocol, was administered	Excluded medication, vaccine or device-Device, excluded by the protocol, was administered	ctmDEVICE_EXCLUDED_BY_PROTOCOL_ADMINISTERED
	DO NOT USE - Excluded medication, vaccine or device-Vaccine, excluded by the protocol, was administered	Excluded medication, vaccine or device-Vaccine, excluded by the protocol, was administered	ctmVACCINE_EXCLUDED_BY_PROTOCOL_ADMINISTERED
	DO NOT USE - Excluded medication, vaccine or device-Medication, excluded by the protocol, was administered	Excluded medication, vaccine or device-Medication, excluded by the protocol, was administered	ctmMEDICATION_EXCLUDED_BY_PROTOCOL_ADMINISTERED
	DO NOT USE - Assessment or time point completion-Assessment not properly performed	Assessment or time point completion-Assessment not properly performed	ctmASSESSMENT_NOT_PROPERLY_PERFORMED
	DO NOT USE - Assessment or time point completion - Out of window assessment for immunogenicity	Assessment or time point completion - Out of window assessment for immunogenicity	ctmASSESSMENT_OR_POINT_COMPLETION_OUT_OF_WINDOW_ASS_FOR_IMM
	DO NOT USE - Assessment or time point completion - Out of Window treatment administration	Assessment or time point completion - Out of Window treatment administration	ctmASSESSMENT_OR_POINT_COMPLETION_OUT_OF_WINDOW_TREAT_ADMIN
	DO NOT USE - Wrong study treatment/administration/dose - Study treatment not administered per protocol	Wrong study treatment/administration/dose - Study treatment not administered per protocol	ctmWRONG_STUDY_TREAT_ADMIN_DOSE
	DO NOT USE - Wrong study treatment/administration/dose - Expired study treatment administered	Wrong study treatment/administration/dose - Expired study treatment administered	ctmWRONG_STUDY_TREAT_ADMIN_DOSE_EXPIRE
	DO NOT USE - Wrong study treatment/administration/dose - Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use.	Wrong study treatment/administration/dose - Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use.	ctmDVCAT1
	DO NOT USE - Wrong study treatment/ administration/ dose - Study treatment not prepared as per protocol (e.g. reconstitution) or temperature excursions after opening package	Wrong study treatment/administration/dose - Study treatment not prepared as per protocol (e.g. reconstitution)	ctmTREATMENT_NOT_PREPARED_PER_PROTOCOL
	DO NOT USE - Wrong study treatment/ administration/ dose - Incorrect volume was given	Wrong study treatment/administration/dose - Incorrect Volume was given	ctmINCORRECT_VOLUME_GIVEN
	DO NOT USE - Wrong study treatment/administration/dose - Other deviations related to wrong study treatment/administration/dose	Wrong study treatment/administration/dose - Other deviations related to wrong study treatment/administration/dose	ctmOTHER_DEVIATIONS_RELATED_TO_WRONG_STUDY_TREATMENT
	DO NOT USE - Wrong study treatment/administration/dose - Not administering any study treatment	Wrong study treatment/administration/dose - Not administering any study treatment	ctmDVCAT2
	DO NOT USE - Study procedures - Randomization procedures Ie.g., subject assigned to wrong stratum, subject randomized out of order) - (if captured in another category do not capture here)	Study procedures - Randomization procedures Ie.g., subject assigned to wrong stratum, subject randomized out of order) - (if captured in another category do not capture here)	ctmDVCAT3
	DO NOT USE - Not withdrawn after developing withdrawal criteria - Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication	Not withdrawn after developing withdrawal criteria - Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication	ctmNOT_WITHDRAWN_AFTER_DEVELOPING_WITHDRAWAL_CRITERIA
	DO NOT USE - Study procedures - Study blinding/unblinding procedures	Study procedures - Study blinding/unblinding procedures	ctmSTUDY_BLINDING_UNBLINDING_PROCEDURES
	DO NOT USE - Study procedures - Non study treatment supply procedures	Study procedures - Non study treatment supply procedures	ctmNON_STUDY_TREATMENT_SUPPLY_PROCEDURES
	DO NOT USE - Study procedures - Diary procedures	Study procedures - Diary procedures	ctmDIARY_PROCEDURES
	DO NOT USE - Study procedures - Equipment procedures	Study procedures - Equipment procedures	ctmEQUIPMENT_PROCEDURES
	DO NOT USE - Study procedures - Biological sample specimen procedures	Study procedures - Biological sample specimen procedures	ctmBIOLOGICAL_SAMPLE_SPECIMEN_PROCEDURES
	DO NOT USE - Failure to report safety events pr protocol - Other deviations related to reporting safety events per protocol	Failure to report safety events pr protocol - Other deviations related to reporting safety events per protocol	ctmOTHER_DEVIATIONS_REPORTING_SAFETY_EVENTS_PER_PROTOCOL
	DO NOT USE - Failure to report safety events pr protocol - Pregnancy	Failure to report safety events pr protocol - Pregnancy	ctmPREGNANCY
	DO NOT USE - Failure to report safety events pr protocol - Other	Failure to report safety events pr protocol - Other	ctmDVCAT5

EPI-MALARIA-003 VS AME (115056): STUDY CONCLUSION ()
LAST INFORMATION [DS.DSCAT = "DISPOSITION EVENT"]

1.* Did the study participant finish its participation in the study prematurely ? ☒ [A:Y] Yes ☐ [A:N] No [Did the subject finish its participation in the study prematurely ?]	[NOT SUBMITTED] [A:Y] ☐ [DS.DSTERM] [DS.DSDECOD] Yes please specify the reason (select one that apply) [A:PTV] ☐ [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] Protocol violation, please specify: A200 [A:CWS3] ☐ Consent withdrawal [A:MIG] ☐ [SUPPDS.QVAL when QNAM = "MOVEDTC"] Migrated / moved from the study area (date of last contact) / / (2018-2029) [A:LFU] ☐ Lost to follow-up. [A:SST] ☐ Sponsor study termination. [A:DED] ☐ [DM.DTHDTC] [DM.DTHFL] Subject died -> Date of death / / (2018-2029) [DD.DDORRES] [DD.DDTEST = "Cause of Death"] [DD.DDCAT = "STUDY CONCLUSION"] Cause of Death A128 [DD.DDORRES] [DD.DDTEST = "Type of Diagnosis"] [DD.DDCAT = "STUDY CONCLUSION"] Cause of death --> [A:1] ☐ Verbal autopsy [A:2] ☐ Medical diagnosis [DD.DDORRES] [DD.DDTEST = "Death Due to AESI"] [DD.DDCAT = "STUDY CONCLUSION"] Tick box if death is due to an AESI [A:Y] ☐ Yes [DD.DDORRES] [DD.DDTEST = "Date of Interview for Verbal Autopsy"] Verbal autopsy -> Date of interview / / (2018-2029) [CO.COVAL when IDVAR = "DDSEQ"] -> Description A1000 [CO.COVAL when IDVAR = "DDSEQ"] A1000 [CO.COVAL when IDVAR = "DDSEQ"] A1000 [CO.COVAL when IDVAR = "DDSEQ"] A1000 [CO.COVAL when IDVAR = "DDSEQ"] A1000 [A:OTHER] ☐ [When this field is completed, then the value is added to the calculated value of DS.DSTERM, separated by a colon] Other, please specify: A128
2. In case the study participant migrated/moved from the study area for more than 3 months, please provide the date of migration (if done since last visit)	[SS.SSORRES] [SS.SSTEST = "Date of Migration When Moved for >3 Mths"] [SS.SSCAT = "STUDY CONCLUSION"] / / (2018-2029)
3. In case the study participant migrated/moved from study area for more than 3 months, please provide the date of return.	[SS.SSORRES] [SS.SSTEST = "Date of Return When Moved for >3 Months"] [SS.SSCAT = "STUDY CONCLUSION"] / / (2018-2029)
4.* Was the study participant suspected of having a disease specified as AESI or meningitis at any time during the study? [Was the subject suspected of having a disease specified as AESI or NC/NT-SAE at any time during the study?]	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
5.* Was the study participant confirmed with any disease specified as AESI or meningitis at any time during the study?	[NOT SUBMITTED] [A:N] ☐ No [A:Y] ☐ Yes
6. In case subject's parent(s) / legally acceptable representatives freely expressed objection for the use of his/her personal information, please tick the box	[DS.DSTERM and DS.DSDECOD = "SUBJECT(S) PARENTS / LEGALLY ACCEPTABLE REPRESENTATIVES FREELY EXPRESSED OBJECTION FOR THE USE OF HIS/HER PERSONAL INFORMATION"] [DS.DSCAT = "OTHER EVENT"] [DS.DSSCAT = "STUDY CONCLUSION"] [A:Y] ☐

LAST INFORMATION CONT

7.* Does study participant show at the time of conclusion any significant development delay or disability? [Does study participant show at the time of conclusion any significant development delay or disability?]	[CE.CEOCCUR] [CE.CETERM = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] [CE.CECAT = "DEVELOPMENTAL DELAY OR PHYSICAL DISABILITIES"] [CE.CEEVINTX = "AT END OF STUDY"] [CE.CEPRESP = "Y"] [A:N] ☐ No [A:Y] ☐ [SUPPCE.QVAL when QNAM = "DETENFU"] Yes --> Please specify ----> Was the development delay or disability detected at enrollment/FU visit 1 or FU visit 3? [A:N] ☐ No [A:Y] ☐ Yes
8.* Please record date of last contact or date when the last information was collected on the study participant's condition:	[DS.DSSTDTC] [DD.DDDTC] [DM.RFPENDTC] / / (2018-2029) [SUPPDS.QVAL when QNAM = "SUBJCND"] Was the study participant in good condition at this date? [A:N] ☐ No [A:Y] ☐ Yes
9. Tick box if the information was collected by phone call or other means of virtual contact [Tick box if the information was collected by phone call or other means	[SUPPDS.QVAL when QNAM = "COLMETH"] [A:Y] ☐ Yes

	of virtual contact]	
10.	For Data Managers only: Tick or untick this box to require the investigator to re-sign the form. <i>By ticking or unticking this box you are evoking a change to this form back to an unsigned state. This should be done for any change performed by site staff after the original signature. [hidden]</i>	[NOT SUBMITTED] [A:1] ☐ 1
11.	Disposition Event Category [hidden]	☐ [cIDSCAT_DSCAT] ☐
12.	Disposition Event Subcategory [hidden]	☐ [cIDSSCAT_DSSCAT] ☐
13.	Standardized Disposition Term [hidden]	☐ [cINCOMPLT_DSDECOD] ☐
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

Codelist Values Tables: STUDY CONCLUSION					
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName
cIDSCAT_DSCAT	String		Disposition Event	DISPOSITION EVENT	ctmDISPOSITION_EVENT
			Other Event	OTHER EVENT	ctmOTHER_EVENT
			Protocol Milestone	PROTOCOL MILESTONE	ctmPROTOCOL_MILESTONE
cIDSSCAT_DSSCAT	String		End of study	END OF STUDY	ctmEND_OF_STUDY
			Epoch continuation	EPOCH CONTINUATION	ctmEPOCH_CONTINUATION
			Informed consent	INFORMED CONSENT	ctmINFORMED_CONSENT1
			Randomisation agreement	RANDOMISATION AGREEMENT	ctmRANDOMISATION_AGREEMENT
			Screening failure	SCREENING FAILURE	ctmSCREENING_FAILURE
			Telephone contact	TELEPHONE CONTACT	ctmTELEPHONE_CONTACT
			Visit continuation	VISIT CONTINUATION	ctmVISIT_CONTINUATION
			Visit continuation by phone	VISIT CONTINUATION BY PHONE	ctmVISIT_CONTINUATION_BY_PHONE
cINCOMPLT_DSDECOD	String		Completed	COMPLETED	ctmCOMPLETED1
			Consent withdrawal, not due to an adverse event	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT	ctmCONSENT_WITHDRAWAL__NOT_DUE_TO_AN_ADVERSE_EVENT
			Consent withdrawal, not due to a serious adverse event	CONSENT WITHDRAWAL, NOT DUE TO A SERIOUS ADVERSE EVENT	ctmCONSENT_WITHDRAWAL__NOT_DUE_TO_A_SERIOUS_ADVERSE_EVENT
			Consent withdrawal / not willing to participate, not due to a (s)ae	CONSENT WITHDRAWAL / NOT WILLING TO PARTICIPATE, NOT DUE TO A (S)AE	ctmCONSENT_WITHDRAWAL__NOT_WILLING_TO_PARTICIPATE__NOT_DU
			Death	DEATH	ctmDEATH
			Eligibility criteria not fulfilled (inclusion and exclusion criteria)	ELIGIBILITY CRITERIA NOT FULFILLED (INCLUSION AND EXCLUSION CRITERIA)	ctmELIGIBILITY_CRITERIA_NOT_FULFILLED__INCLUSION_AND_EXCLU
			Informed consent obtained	INFORMED CONSENT OBTAINED	ctmINFORMED_CONSENT_OBTAINED
			Lost to follow-up	LOST TO FOLLOW-UP	ctmLOST_TO_FOLLOW_UP
			Migrated / moved from the study area	MIGRATED / MOVED FROM THE STUDY AREA	ctmMIGRATED_MOVED_FROM_THE_STUDY_AREA
			Missing confirmed	MISSING CONFIRMED	ctmMISSING_CONFIRMED_002
			Non-Serious Adverse Event onset in the course or after previous study epoch	NON-SERIOUS ADVERSE EVENT ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmNON_SERIOUS_ADVERSE_EVENT_ONSET_IN_THE_COURSE_OR_AFTER
			Non-Serious Adverse Event or non-serious pIMD onset in the course or after previous study epoch	NON-SERIOUS ADVERSE EVENT OR NON-SERIOUS PIMD ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmNON_SERIOUS_ADVERSE_EVENT_OR_NON_SERIOUS_PIMD_ONSET_IN
			Other	OTHER	ctmOTHER10
			Progressive disease	PROGRESSIVE DISEASE	ctmPROGRESSIVE_DISEASE
			Protocol violation	PROTOCOL VIOLATION	ctmPROTOCOL_VIOLATION
			Randomized	RANDOMIZED	ctmRANDOMIZED
			Same reason and decision as previous visit	SAME REASON AND DECISION AS PREVIOUS VISIT	ctmSAME_REASON_AND_DECISION_AS_PREVIOUS_VISIT
			Non-Serious Adverse Events or Serious Adverse Events	NON SERIOUS OR SERIOUS ADVERSE EVENT	ctmNON_SERIOUS_OR_SERIOUS_AE
			Serious Adverse Event or Non-Serious Related AE	SERIOUS ADVERSE EVENT AND/OR NON-SERIOUS RELATED ADVERSE EVENT	ctmSERIOUS_ADVERSE_EVENT_OR_NON_SERIOUS_RELATED_ADVERS
			Serious Adverse Event and/or pIMD	SERIOUS ADVERSE EVENT AND/OR PIMD	ctmSERIOUS_ADVERSE_EVENT_AND_OR_PIMD
			Serious Adverse Event and/ or pIMD and/or Non-Serious Related AE	SERIOUS ADVERSE EVENT AND/ OR PIMD AND/OR NON-SERIOUS RELATED ADVERSE EVENT	ctmSERIOUS_ADVERSE_EVENT_AND__OR_PIMD_AND_OR_NON_SERIOUS_R
			Serious adverse event not related to study participation or to a gsk concurrent medication	SERIOUS ADVERSE EVENT NOT RELATED TO STUDY PARTICIPATION OR TO A GSK CONCURRENT MEDICATION	ctmSERIOUS_ADVERSE_EVENT_NOT_RELATED_TO_STUDY_PARTICIPATIO
			Serious Adverse Event onset in the course or after previous study epoch	SERIOUS ADVERSE EVENT ONSET IN THE COURSE OR AFTER PREVIOUS STUDY EPOCH	ctmSERIOUS_ADVERSE_EVENT_ONSET_IN_THE_COURSE_OR_AFTER_PREV
			Serious adverse event related to study participation or to a gsk concurrent medication	SERIOUS ADVERSE EVENT RELATED TO STUDY PARTICIPATION OR TO A GSK CONCURRENT MEDICATION	ctmSERIOUS_ADVERSE_EVENT_RELATED_TO_STUDY_PARTICIPATION_OR
			Solicited Adverse Event	SOLICITED ADVERSE EVENT	ctmSOLICITED_ADVERSE_EVENT
			Sponsor study termination	SPONSOR STUDY TERMINATION	ctmSPONSOR_STUDY_TERMINATION
			Unsolicited Non-Serious Adverse Event	UNSOLICITED NON-SERIOUS ADVERSE EVENT	ctmUNSOLICITED_NON_SERIOUS_ADVERSE_EVENT
			Safety information obtained	SAFETY INFORMATION OBTAINED	ctmSAFETY_INFORMATION_OBTAINED
			Safety information not obtained	SAFETY INFORMATION NOT OBTAINED	ctmSAFETY_INFORMATION_NOT_OBTAINED
			Study ended	STUDY ENDED	ctmSTUDY_ENDED

EPI-MALARIA-003 VS AME (115056): MANUAL CLEANING STATUS () [NOT SUBMITTED]

DM CDR review	
1. study event reviewed [hidden]	[A:13] ☐ Eligibility [A:1] ☐ Visit 1 [A:2] ☐ Visit 2 [A:3] ☐ Visit 3 [A:4] ☐ Visit 4 [A:5] ☐ Visit 5 [A:9] ☐ Visit 6 [A:10] ☐ Visit 7 [A:11] ☐ Visit 8 [A:12] ☐ Visit 9 [A:7] ☐ Logs (medications and vaccinations) [A:6] ☐ Outpatient [A:1] ☐ 1 [A:2] ☐ 2 [A:3] ☐ 3 [A:4] ☐ 4 [A:5] ☐ 5 [A:6] ☐ 6 [A:7] ☐ 7 [A:8] ☐ 8 [A:9] ☐ 9 [A:10] ☐ 10 [A:11] ☐ 11 [A:12] ☐ 12 [A:13] ☐ 13 [A:14] ☐ 14 [A:15] ☐ 15 [A:16] ☐ 16 [A:17] ☐ 17 [A:18] ☐ 18 [A:19] ☐ 19 [A:20] ☐ 20 [A:21] ☐ 21 [A:22] ☐ 22 [A:23] ☐ 23 [A:24] ☐ 24 [A:25] ☐ 25 [A:26] ☐ 26 [A:27] ☐ 27 [A:28] ☐ 28 [A:29] ☐ 29 [A:30] ☐ 30 [A:31] ☐ 31 [A:32] ☐ 32 [A:33] ☐ 33 [A:34] ☐ 34 [A:35] ☐ 35 [A:36] ☐ 36 [A:37] ☐ 37 [A:38] ☐ 38 [A:39] ☐ 39 [A:40] ☐ 40 [A:41] ☐ 41 [A:42] ☐ 42 [A:43] ☐ 43 [A:44] ☐ 44 [A:45] ☐ 45 [A:46] ☐ 46 [A:47] ☐ 47 [A:48] ☐ 48 [A:49] ☐ 49 [A:50] ☐ 50 [A:51] ☐ 51 [A:52] ☐ 52 [A:53] ☐ 53 [A:54] ☐ 54 [A:55] ☐ 55 [A:56] ☐ 56 [A:57] ☐ 57 [A:58] ☐ 58 [A:59] ☐ 59 [A:60] ☐ 60 [A:61] ☐ 61 [A:62] ☐ 62 [A:63] ☐ 63 [A:64] ☐ 64 [A:65] ☐ 65 [A:66] ☐ 66 [A:67] ☐ 67 [A:68] ☐ 68 [A:69] ☐ 69 [A:70] ☐ 70 [A:71] ☐ 71 [A:72] ☐ 72 [A:73] ☐ 73 [A:74] ☐ 74 [A:75] ☐ 75 [A:76] ☐ 76 [A:77] ☐ 77 [A:78] ☐ 78 [A:79] ☐ 79 [A:80] ☐ 80 [A:81] ☐ 81 [A:82] ☐ 82 [A:83] ☐ 83 [A:84] ☐ 84 [A:85] ☐ 85 [A:86] ☐ 86 [A:87] ☐ 87 [A:88] ☐ 88 [A:89] ☐ 89 [A:90] ☐ 90 [A:91] ☐ 91 [A:92] ☐ 92 [A:93] ☐ 93 [A:94] ☐ 94 [A:95] ☐ 95 [A:96] ☐ 96 [A:97] ☐ 97 [A:98] ☐ 98 [A:99] ☐ 99 [A:100] ☐ 100 [A:101] ☐ 101 [A:102] ☐ 102 [A:103] ☐ 103 [A:104] ☐ 104 [A:105] ☐ 105 [A:106] ☐ 106 [A:107] ☐ 107 [A:108] ☐ 108 [A:109] ☐ 109 [A:110] ☐ 110 [A:111] ☐ 111 [A:112] ☐ 112 [A:113] ☐ 113 [A:114] ☐ 114 [A:115] ☐ 115 [A:116] ☐ 116 [A:117] ☐ 117 [A:118] ☐ 118 [A:119] ☐ 119 [A:120] ☐ 120 [A:121] ☐ 121 [A:122] ☐ 122 [A:123] ☐ 123 [A:124] ☐ 124 [A:125] ☐ 125 [A:126] ☐ 126 [A:127] ☐ 127 [A:128] ☐ 128 [A:129] ☐ 129 [A:130] ☐ 130 [A:131] ☐ 131 [A:132] ☐ 132 [A:133] ☐ 133 [A:134] ☐ 134 [A:135] ☐ 135 [A:136] ☐ 136 [A:137] ☐ 137 [A:138] ☐ 138 [A:139] ☐ 139 [A:140] ☐ 140 [A:141] ☐ 141 [A:142] ☐ 142 [A:143] ☐ 143 [A:144] ☐ 144 [A:145] ☐ 145 [A:146] ☐ 146 [A:147] ☐ 147 [A:148] ☐ 148 [A:149] ☐ 149 [A:150] ☐ 150 [A:151] ☐ 151 [A:152] ☐ 152 [A:153] ☐ 153 [A:154] ☐ 154 [A:155] ☐ 155 [A:156] ☐ 156 [A:157] ☐ 157 [A:158] ☐ 158 [A:159] ☐ 159 [A:160] ☐ 160 [A:161] ☐ 161 [A:162] ☐ 162 [A:163] ☐ 163 [A:164] ☐ 164 [A:165] ☐ 165 [A:166] ☐ 166 [A:167] ☐ 167 [A:168] ☐ 168 [A:169] ☐ 169 [A:170] ☐ 170 [A:171] ☐ 171 [A:172] ☐ 172 [A:173] ☐ 173 [A:174] ☐ 174 [A:175] ☐ 175 [A:176] ☐ 176 [A:177] ☐ 177 [A:178] ☐ 178 [A:179] ☐ 179 [A:180] ☐ 180 [A:181] ☐ 181 [A:182] ☐ 182 [A:183] ☐ 183 [A:184] ☐ 184 [A:185] ☐ 185 [A:186] ☐ 186 [A:187] ☐ 187 [A:188] ☐ 188 [A:189] ☐ 189 [A:190] ☐ 190 [A:191] ☐ 191 [A:192] ☐ 192 [A:193] ☐ 193 [A:194] ☐ 194 [A:195] ☐ 195 [A:196] ☐ 196 [A:197] ☐ 197 [A:198] ☐ 198 [A:199] ☐ 199 [A:200] ☐ 200 [A:201] ☐ 201 [A:202] ☐ 202 [A:203] ☐ 203 [A:204] ☐ 204 [A:205] ☐ 205 [A:206] ☐ 206 [A:207] ☐ 207 [A:208] ☐ 208 [A:209] ☐ 209 [A:210] ☐ 210 [A:211] ☐ 211 [A:212] ☐ 212 [A:213] ☐ 213 [A:214] ☐ 214 [A:215] ☐ 215 [A:216] ☐ 216 [A:217] ☐ 217 [A:218] ☐ 218 [A:219] ☐ 219 [A:220] ☐ 220 [A:221] ☐ 221 [A:222] ☐ 222 [A:223] ☐ 223 [A:224] ☐ 224 [A:225] ☐ 225 [A:226] ☐ 226 [A:227] ☐ 227 [A:228] ☐ 228 [A:229] ☐ 229 [A:230] ☐ 230 [A:231] ☐ 231 [A:232] ☐ 232 [A:233] ☐ 233 [A:234] ☐ 234 [A:235] ☐ 235 [A:236] ☐ 236 [A:237] ☐ 237 [A:238] ☐ 238 [A:239] ☐ 239 [A:240] ☐ 240 [A:241] ☐ 241 [A:242] ☐ 242 [A:243] ☐ 243 [A:244] ☐ 244 [A:245] ☐ 245 [A:246] ☐ 246 [A:247] ☐ 247 [A:248] ☐ 248 [A:249] ☐ 249 [A:250] ☐ 250 [A:251] ☐ 251 [A:252] ☐ 252 [A:253] ☐ 253 [A:254] ☐ 254 [A:255] ☐ 255 [A:256] ☐ 256 [A:257] ☐ 257 [A:258] ☐ 258 [A:259] ☐ 259 [A:260] ☐ 260 [A:261] ☐ 261 [A:262] ☐ 262 [A:263] ☐ 263 [A:264] ☐ 264 [A:265] ☐ 265 [A:266] ☐ 266 [A:267] ☐ 267 [A:268] ☐ 268 [A:269] ☐ 269 [A:270] ☐ 270 [A:271] ☐ 271 [A:272] ☐ 272 [A:273] ☐ 273 [A:274] ☐ 274 [A:275] ☐ 275 [A:276] ☐ 276 [A:277] ☐ 277 [A:278] ☐ 278 [A:279] ☐ 279 [A:280] ☐ 280 [A:281] ☐ 281 [A:282] ☐ 282 [A:283] ☐ 283 [A:284] ☐ 284 [A:285] ☐ 285 [A:286] ☐ 286 [A:287] ☐ 287 [A:288] ☐ 288 [A:289] ☐ 289 [A:290] ☐ 290 [A:291] ☐ 291 [A:292] ☐ 292 [A:293] ☐ 293 [A:294] ☐ 294 [A:295] ☐ 295 [A:296] ☐ 296 [A:297] ☐ 297 [A:298] ☐ 298 [A:299] ☐ 299 [A:300] ☐ 300 [A:301] ☐ 301 [A:302] ☐ 302 [A:303] ☐ 303 [A:304] ☐ 304 [A:305] ☐ 305 [A:306] ☐ 306 [A:307] ☐ 307 [A:308] ☐ 308 [A:309] ☐ 309 [A:310] ☐ 310 [A:311] ☐ 311 [A:312] ☐ 312 [A:313] ☐ 313 [A:314] ☐ 314 [A:315] ☐ 315 [A:316] ☐ 316 [A:317] ☐ 317 [A:318] ☐ 318 [A:319] ☐ 319 [A:320] ☐ 320 [A:321] ☐ 321 [A:322] ☐ 322 [A:323] ☐ 323 [A:324] ☐ 324 [A:325] ☐ 325 [A:326] ☐ 326 [A:327] ☐ 327 [A:328] ☐ 328 [A:329] ☐ 329 [A:330] ☐ 330 [A:331] ☐ 331 [A:332] ☐ 332 [A:333] ☐ 333 [A:334] ☐ 334 [A:335] ☐ 335 [A:336] ☐ 336 [A:337] ☐ 337 [A:338] ☐ 338 [A:339] ☐ 339 [A:340] ☐ 340 [A:341] ☐ 341 [A:342] ☐ 342 [A:343] ☐ 343 [A:344] ☐ 344 [A:345] ☐ 345 [A:346] ☐ 346 [A:347] ☐ 347 [A:348] ☐ 348 [A:349] ☐ 349 [A:350] ☐ 350 [A:351] ☐ 351 [A:352] ☐ 352 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[A:566] ☐ 566 [A:567] ☐ 567 [A:568] ☐ 568 [A:569] ☐ 569 [A:570] ☐ 570 [A:571] ☐ 571 [A:572] ☐ 572 [A:573] ☐ 573 [A:574] ☐ 574 [A:575] ☐ 575 [A:576] ☐ 576 [A:577] ☐ 577 [A:578] ☐ 578 [A:579] ☐ 579 [A:580] ☐ 580 [A:581] ☐ 581 [A:582] ☐ 582 [A:583] ☐ 583 [A:584] ☐ 584 [A:585] ☐ 585 [A:586] ☐ 586 [A:587] ☐ 587 [A:588] ☐ 588 [A:589] ☐ 589 [A:590] ☐ 590 [A:591] ☐ 591 [A:592] ☐ 592 [A:593] ☐ 593 [A:594] ☐ 594 [A:595] ☐ 595 [A:596] ☐ 596 [A:597] ☐ 597 [A:598] ☐ 598 [A:599] ☐ 599 [A:600] ☐ 600 [A:601] ☐ 601 [A:602] ☐ 602 [A:603] ☐ 603 [A:604] ☐ 604 [A:605] ☐ 605 [A:606] ☐ 606 [A:607] ☐ 607 [A:608] ☐ 608 [A:609] ☐ 609 [A:610] ☐ 610 [A:611] ☐ 611 [A:612] ☐ 612 [A:613] ☐ 613 [A:614] ☐ 614 [A:615] ☐ 615 [A:616] ☐ 616 [A:617] ☐ 617 [A:618] ☐ 618 [A:619] ☐ 619 [A:620] ☐ 620 [A:621] ☐ 621 [A:622] ☐ 622 [A:623] ☐ 623 [A:624] ☐ 624 [A:625] ☐ 625 [A:626] ☐ 626 [A:627] ☐ 627 [A:628] ☐ 628 [A:629] ☐ 629 [A:630] ☐ 630 [A:631] ☐ 631 [A:632] ☐ 632 [A:633] ☐ 633 [A:634] ☐ 634 [A:635] ☐ 635 [A:636] ☐ 636 [A:637] ☐ 637 [A:638] ☐ 638 [A:639] ☐ 639 [A:640] ☐ 640 [A:641] ☐ 641 [A:642] ☐ 642 [A:643] ☐ 643 [A:644] ☐ 644 [A:645] ☐ 645 [A:646] ☐ 646 [A:647] ☐ 647 [A:648] ☐ 648 [A:649] ☐ 649 [A:650] ☐ 650 [A:651] ☐ 651 [A:652] ☐ 652 [A:653] ☐ 653 [A:654] ☐ 654 [A:655] ☐ 655 [A:656] ☐ 656 [A:657] ☐ 657 [A:658] ☐ 658 [A:659] ☐ 659 [A:660] ☐ 660 [A:661] ☐ 661 [A:662] ☐ 662 [A:663] ☐ 663 [A:664] ☐ 664 [A:665] ☐ 665 [A:666] ☐ 666 [A:667] ☐ 667 [A:668] ☐ 668 [A:669] ☐ 669 [A:670] ☐ 670 [A:671] ☐ 671 [A:672] ☐ 672 [A:673] ☐ 673 [A:674] ☐ 674 [A:675] ☐ 675 [A:676] ☐ 676 [A:677] ☐ 677 [A:678] ☐ 678 [A:679] ☐ 679 [A:680] ☐ 680 [A:681] ☐ 681 [A:682] ☐ 682 [A:683] ☐ 683 [A:684] ☐ 684 [A:685] ☐ 685 [A:686] ☐ 686 [A:687] ☐ 687 [A:688] ☐ 688 [A:689] ☐ 689 [A:690] ☐ 690 [A:691] ☐ 691 [A:692] ☐ 692 [A:693] ☐ 693 [A:694] ☐ 694 [A:695] ☐ 695 [A:696] ☐ 696 [A:697] ☐ 697 [A:698] ☐ 698 [A:699] ☐ 699 [A:700] ☐ 700 [A:701] ☐ 701 [A:702] ☐ 702 [A:703] ☐ 703 [A:704] ☐ 704 [A:705] ☐ 705 [A:706] ☐ 706 [A:707] ☐ 707 [A:708] ☐ 708 [A:709] ☐ 709 [A:710] ☐ 710 [A:711] ☐ 711 [A:712] ☐ 712 [A:713] ☐ 713 [A:714] ☐ 714 [A:715] ☐ 715 [A:716] ☐ 716 [A:717] ☐ 717 [A:718] ☐ 718 [A:719] ☐ 719 [A:720] ☐ 720 [A:721] ☐ 721 [A:72

EPI-MALARIA-003 VS AME (115056): SAMPLE RETENTION PERIOD () - Repeating Form [NOT SUBMITTED]					
#					
1					
SRP					
1.	SRP form version [read-only] [SRP form version]	N10			
Type 3A tests					
2.*	Use of samples to improve, develop or assess tests related to the disease(s) under study that will allow more reliable measurement of the response. This excludes testing related to genesâ€™™ hereditary characteristics and HIV [Use of samples to improve, develop or assess tests related to the disease(s) under study that will allow more reliable measurement of the response. This excludes testing related to genesâ€™™ hereditary characteristics and HIV]	[A:Y] ☐ Yes [A:N] ☐ No			
Type 3B tests					
3.*	With the prior permission of the institution independent Ethics Committee / Institutional Review Board: Use of samples to improve, develop or assess tests related to the disease(s) under study that will allow more reliable measurement of the response. This excludes testing related to genesâ€™™ hereditary characteristics and HIV [With the prior permission of the institution independent Ethics Committee / Institutional Review Board: Use of samples to improve, develop or assess tests related to the disease(s) under study that will allow more reliable measurement of the response. This excludes testing related to genesâ€™™ hereditary characteristics and HIV]	[A:Y] ☐ Yes [A:N] ☐ No			
Type 4 tests					
4.*	With the prior permission of the subject: Further research by GSK Biologicals that is NOT RELATED to the disease(s) under study. This research is done on an anonymous basis (any identification linking the subject to the sample is destroyed), excludes testing related to genesâ€™™ hereditary characteristics and HIV, and does not affect the subject participation in the study. [With the prior permission of the subject: Further research by GSK Biologicals that is NOT RELATED to the disease(s) under study. This research is done on an anonymous basis (any identification linking the subject to the sample is destroyed), excludes testing related to genesâ€™™ hereditary characteristics and HIV, and does not affect the subject participation in the study.]	[A:Y] ☐ Yes [A:N] ☐ No			
SAMPLE STORAGE PERIOD					
5.*	Please check GSK Biologicals sample storage period specified in the ICF in use at your centre. [Please check GSK Biologicals sample storage period specified in the ICF in use at your centre.]	[A:20] ☐ For a maximum of 20 years [A:9] ☐ Other, please specify: A200			
IF NEW VERSION OF SRP					
Complete and submit a new Sample Retention Period Form for each change in the ICF that affects the retention period of samples.					
6.	Date at which the new ICF version was first signed by a Subject in your centre : [If new version of SRP: Date at which the new ICF version was first signed by a Subject :]	Req ☐ / Req ☐ / Req ☐ (2018-2029)			
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.					

EPI-MALARIA-003 VS AME (115056): CLUSTER INFORMATION () [NOT SUBMITTED]		
CLUSTER INFORMATION		
1. ✓	Please select appropriate cluster [Please select appropriate cluster]	[A:1] ☐ Exposed Cluster 1 [A:2] ☐ Unexposed Cluster 1
Key: [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): HOSPITAL STUDY LOGBOOK () - Repeating Form [SI.STUDYID]		
#		
1		
HOSPITAL LOGBOOK DETAILS [SI.SIGRPID = "LOG [form number attached to this occurrence]"]		
1.* ✓	Month and year of clinical visit [Month and year of clinical visit]	[SI.SIVAL] [SI.SIPARM = "Month and Year of Clinical Visit"] [SI.SIPARMCD="CLVISDTC"] ☐ Req / ☐ Req (2018-2029)
2.* ✓	Total number of children between 0 - 60 month of age admitted in the hospital for any cause within this month [Total number of children between 0 - 60 month of age admitted in the hospital for any cause within this month]	[SI.SIVAL] [SI.SIPARM = "Children 0-60 Months Admitted This Month"] [SI.SIPARMCD="CHLDADM"] Ad
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		

EPI-MALARIA-003 VS AME (115056): STUDY DSS DENOMINATOR LOGBOOK () [SI.STUDYID]							
1. ✓							
MONTH 0 - 60 Entry [SI.SIGRPID = "MONTH 0" to SI.SIGRPID = "MONTH 60"]							
1.1*	Please select the month				[SI.SIPARM = "Please select the month"] [SI.SIVAL] [cMONTH1]		
1.2*	Month and year of census [Month and year of census]				[SI.SIPARM = "Month and year of census"] [SI.SIVAL] Req [] / Req [] (2015-2029)		
1.3*	Overall number of children in DSS (0 - <1 year)				[SI.SIPARM = "Number of Children 0 - <1 Year in DSS"] [SI.SIVAL] Overall Number [N5] [SI.SIPARM = "Number of Boys 0 - <1 Year in DSS"] [SI.SIVAL] Number of Boys [N5] [SI.SIPARM = "Number of Girls 0 - <1 Year in DSS"] [SI.SIVAL] Number of Girls [N5]		
1.4*	Overall number of children registered in DSS (1 - <2 years)				[SI.SIPARM = "Number of Children 1 - <2 Year in DSS"] [SI.SIVAL] Overall Number [N5] [SI.SIPARM = "Number of Boys 1 - <2 Year in DSS"] [SI.SIVAL] Number of Boys [N5] [SI.SIPARM = "Number of Girls 1 - <2 Year in DSS"] [SI.SIVAL] Number of Girls [N5]		
1.5*	Overall number of children registered in DSS (2 - <3 years)				[SI.SIPARM = "Number of Children 2 - <3 Year in DSS"] [SI.SIVAL] Overall Number [N5] [SI.SIPARM = "Number of Boys 2 - <3 Year in DSS"] [SI.SIVAL] Number of Boys [N5] [SI.SIPARM = "Number of Girls 2 - <3 Year in DSS"] [SI.SIVAL] Number of Girls [N5]		
1.6*	Overall number of children registered in DSS (3 - <4 years)				[SI.SIPARM = "Number of Children 3 - <4 Year in DSS"] [SI.SIVAL] Overall Number [N5] [SI.SIPARM = "Number of Boys 3 - <4 Year in DSS"] [SI.SIVAL] Number of Boys [N5] [SI.SIPARM = "Number of Girls 3 - <4 Year in DSS"] [SI.SIVAL] Number of Girls [N5]		
1.7*	Overall number of children registered in DSS (4 - <5 years)				[SI.SIPARM = "Number of Children 4 - <5 Year in DSS"] [SI.SIVAL] Overall Number [N5] [SI.SIPARM = "Number of Boys 4 - <5 Year in DSS"] [SI.SIVAL] Number of Boys [N5] [SI.SIPARM = "Number of Girls 4 - <5 Year in DSS"] [SI.SIVAL] Number of Girls [N5]		
Key: [*] = Item is required [✓] = Source verification required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.							

Codelist Values Tables: STUDY DSS DENOMINATOR LOGBOOK						
Codelist RefName	Codelist Data Type	Subset	Label	Code	Codelist Item RefName	Data Variable RefName
cMONTH1	String		Month 0	0	ctmM0	itmMONTH
			Month 6	6	ctmM6	
			Month 12	12	ctmM012	
			Month 18	18	ctmM18	
			Month 24	24	ctmM24	
			Month 30	30	ctmM30	
			Month 36	36	ctmM36	
			Month 42	42	ctmM42	
			Month 48	48	ctmM48	
			Month 54	54	ctmM54	
			Month 60	60	ctmM60	

EPI-MALARIA-003 VS AME (115056): INVESTIGATOR SIGNATURE () [NOT SUBMITTED]		
INVESTIGATOR SIGNATURE		
1. *	Is this casebook ready to sign? If not, click on the RETURN button below	[A:Y] ☐ Ready to sign
2.	For Data Managers only: Tick or untick this box to require the investigator to re-sign the form. <i>By ticking or unticking this box you are evoking a change to this form back to an unsigned state. This should be done for any change performed by site staff after the original signature. [hidden]</i>	[A:1] ☐ 1
Key: [*] = Item is required Note: Source verification critical settings made in InForm will override any settings made in Central Designer.		