NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

COMPOUND: STAMARIL®

Effectiveness evaluation of the local additional risk minimisation measures for STAMARIL® in the United Kingdom: a survey for healthcare professionals and vaccinees

STUDY NUMBER: STA00059

The Study is conducted by Sanofi/IQVIA hereinafter referred also as the "MAH/MAH representative".

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PASS Information

Title	Effectiveness evaluation of the local additional risk minimisation measures for STAMARIL® in the United Kingdom: a survey for healthcare professionals and vaccinees
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Medicinal product	STAMARIL®
Product reference	PL 46602/0007
Procedure number	DE/H/0476/001
Marketing authorisation holder(s)	Sanofi Pasteur
Joint PASS	No
Research question and objectives	**Primary objectives:** 1. To measure: a. Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist by qualified healthcare professionals (HCPs) of designated authorised yellow fever vaccination centres (YFVCs) in the UK b. Utilisation of any standardised yellow fever pre-vaccination checklist(s) by qualified HCPs of designated authorised YFVCs in the UK c. Distribution of the STAMARIL® Patient Information Leaflet (PIL) by qualified HCPs of designated authorised YFVCs to yellow fever vaccinees in the UK 2. To evaluate knowledge and understanding of the key safety messages associated with yellow fever vaccination in any standardised yellow fever pre-vaccination checklist(s) among qualified HCPs of designated authorised YFVCs in the UK. 3. To verify the receipt of the STAMARIL® PIL by yellow fever vaccinees at the time they get vaccination consultation in the UK. **Secondary objective: None** 1.
Country of study	United Kingdom
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2 LIST OF ABBREVIATIONS

AE	adverse event
aRMMs	additional risk minimisation measures
CI	confidence interval
EDC	electronic data capture
EMA	European medicines agency
ENCePP	European network of centres for pharmacoepidemiology and pharmacovigilance
EphMRA	European pharmaceutical Marketing Research Association
GVP	good pharmacovigilance practices
HCP	healthcare professional
HPS	Health Protection Scotland
ICVP	international certificate of vaccination or prophylaxis
IEC	institutional ethics committee
IHR	international health regulations
IRB	institutional review board
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency
NaTHNaC	National Travel Health Network and Centre
PASS	Post-authorisation safety study
PGD	patient group direction
PHS	Public Health Scotland
PIL	patient information leaflet
QMS	quality management system
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SmPC	summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

UK	United Kingdom
YFVCs	yellow fever vaccination centres

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Title: Effectiveness evaluation of the local additional risk minimisation measures for STAMARIL® in the United Kingdom: a survey for healthcare professionals and vaccinees

Rationale and background:

STAMARIL® is a live attenuated yellow fever 17D-204 strain vaccine which is prepared by culturing the virus in embryonated eggs. It is indicated for active immunisation against yellow fever caused by yellow fever virus in people over 9-months of age who are travelling to or living in areas or countries with a risk of yellow fever transmission, as well as laboratory workers handling potentially infectious materials.

Sanofi Pasteur is the only marketing authorisation holder (MAH) for yellow fever vaccine (STAMARIL®) in the United Kingdom (UK). Following two fatal adverse reactions to yellow fever vaccine in the UK in 2018-2019, due to unapproved use in both cases, the UK Medicines and Healthcare products Regulatory Agency (MHRA) requested the MAH to add a standardised UK checklist, developed by MHRA (hereby referred to as 'UK (STAMARIL®) yellow fever pre-vaccination checklist' in this protocol), as part of the local additional risk minimisation measures (aRMMs) in the STAMARIL® Risk Management Plan, to support the UK healthcare professionals (HCPs) in the benefit-risk assessment process. The objective of this checklist is to ensure compliance of HCPs of designated authorised yellow fever vaccination centres (YFVCs) with indications, contraindications, warnings, and precautions as per the Summary of Product Characteristics (SmPC) and to support the appropriate evaluation of individual risk-benefit balance. The most recent SmPC (dated 15 Feb 2021) details the consideration of risk-benefit balance for individual travellers. In addition to the UK (STAMARIL®) yellow fever pre-vaccination checklist, another yellow fever pre-vaccination checklist has been issued by the National Travel Health Network and Centre (NaTHNaC)/ Public Health Scotland (PHS) which is intended for vaccinees (travellers) to read and complete in advance of, or during, the travel health consultation; it is also commonly called the 'traveller's checklist'. Because the contents of both these checklists (i.e. UK (STAMARIL®) yellow fever pre-vaccination checklist and NaTHNaC/PHS yellow fever pre-vaccination checklist) are similar, 'standardised yellow fever pre-vaccination checklist(s)' refers to either or both of these checklists throughout this protocol.

Furthermore, a patient information leaflet (PIL) should be provided by HCPs to each yellow fever vaccinee which was amended in line with the revisions of the most recent SmPC (dated 15 Feb 2021).

The MAH is also asked to evaluate the effectiveness of implementation of the UK checklist and PIL. Therefore, this post-authorisation safety study (PASS) survey is designed to assess the effectiveness of the UK (STAMARIL®) yellow fever pre-vaccination checklist among the qualified HCPs of designated authorised YFVCs. In addition, this survey will also assess the effectiveness of the the STAMARIL® PIL among yellow fever vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK.

Research question and objectives:

The aim of the current study is to examine the effectiveness of the UK (STAMARIL®) yellow fever pre-vaccination checklist among qualified HCPs of designated authorised YFVCs and of the STAMARIL® PIL among yellow fever vaccinees in the UK, by conducting a survey in this population.

The primary objectives of this study are:

1. To measure:
    a. Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist by qualified HCPs of designated authorised YFVCs in the UK.
    b. Utilisation of any standardised yellow fever pre-vaccination checklist(s) by qualified HCPs of designated authorised YFVCs in the UK.
    c. Distribution of the STAMARIL® PIL by qualified HCPs of designated authorised YFVCs to yellow fever vaccinees in the UK.
2. To evaluate knowledge and understanding of the key safety messages associated with yellow fever vaccination in any standardised yellow fever pre-vaccination checklist(s) among qualified HCPs of designated authorised YFVCs in the UK.
3. To verify the receipt of the STAMARIL® PIL by yellow fever vaccinees at the time they get vaccination consultation in the UK.

There is no secondary objective. **Study design:**

This will be a national, multicentre, prospective, cross-sectional, and multi-channel survey based on primary data collection conducted separately among qualified HCPs (physicians, nurses and pharmacists) and STAMARIL® vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK (England, Wales, Northern Ireland and Scotland). The survey will be conducted primarily through a web (and/or paper for vaccinees) questionnaire. The survey will be conducted within 12 to 18 months following the implementation of the local aRMM in the UK as per the European guideline on good pharmacovigilance practices (GVP) – Module XVI (Rev 3).

Population:

The target population of the survey will be qualified HCPs (physicians, nurses and pharmacists) providing consultation for yellow fever vaccine administration and/or administering yellow fever vaccine (STAMARIL®), and yellow fever vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK. Based on the NaTHNaC Annual Return 2020 report, there were a total of 2,295 YFVCs that remained designated in 2020 in England, Wales, and Northern Ireland. Based on the information provided on PHS website, as of January 2022, there are 123 YFVCs in Scotland.

Inclusion criteria

The following criteria must be met in order to be enrolled in the study:

1. For HCPs: Qualified HCPs from designated authorised YFVCs who have provided consultation for yellow fever vaccine administration and/or administered yellow fever vaccines in the UK in the past 12 months and are willing to consent to participate in the survey. A qualified HCP refers to the one who has undertaken the yellow fever training programme, sponsored by the NaTHNaC or PHS during the past 24 months.

2. For vaccinees: Individuals who receive yellow fever vaccine in the UK and are willing to consent (or their parents/guardians if individuals are younger than 18 years old) to participate in the survey.

Exclusion criteria

Individuals meeting any of the following criteria are not eligible for participation:

1. For HCPs:
    a. Who declare having a conflict of interest with the survey (i.e., HCPs employed by regulatory bodies, or pharmaceutical industries etc).
    b. Who are unable or not willing to provide voluntary consent to participate in this survey conducted in the UK.
    c. Who are not qualified to provide consultation for yellow fever vaccine administration and/or administer yellow fever vaccines in the UK (i.e., HCPs who have not undertaken yellow fever training sponsored by the NaTHNaC or PHS in the past 24 months).
2. For vaccinees (or their parents/guardians if vaccinees are younger than 18 years old):
    a. Who declare having a conflict of interest with the survey (i.e., employed by regulatory bodies, or pharmaceutical industries etc., or are immediate family of qualified HCP's of designated authorised YFVCs or are employed by YFVCs).
    b. Who are unable or not willing to provide voluntary consent to participate in this survey conducted in the UK.

Variables:

HCP questionnaire

The following variables will be collected through the HCP survey:

- Variables related to HCPs' practice:
    - Demographic information (age range, gender and region)
    - HCP profession (physician, nurse or pharmacist)
    - Type of work setting (General Practice [National Health Service], General Practice [Private], pharmacy, travel clinic, occupational health department, hospital, or other)
    - Years of experience in the profession

- Prescriber administering STAMARIL® against a Patient Group Direction (PGD)[1]
- Experience with STAMARIL® (whether providing consultation and/or administering STAMARIL®, years of experience in providing consultation and/or administering STAMARIL® and number of patients administered with STAMARIL® and/or provided consultation for the administration of STAMARIL® in the past 12 months)
- Yellow fever training sponsored by NaTHNaC or PHS (HCP trained ≤12 months ago or >12 months ago)

- Variables related to the HCPs awareness, utilisation, and distribution of the aRMM materials:
  - Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist by the HCPs
  - Use of the UK (STAMARIL®) yellow fever pre-vaccination checklist by the HCPs
  - Use of the NaTHNaC/PHS yellow fever pre-vaccination checklist[2] by the HCPs
  - Distribution of STAMARIL® PIL by the HCPs to yellow fever vaccinees
- Variables related to the knowledge and understanding of the key safety messages in any standardised yellow fever pre-vaccination checklist(s)
  - Indications (e.g. yellow fever activity at travel destination) and contraindications (e.g. hypersensitivity to vaccine components, immunosuppression [congenital or acquired], thymus dysfunction, thymoma, thymectomy, or age less than 6-months), or precautions (e.g. infants from 6 up to 9 months of age, advanced age, pregnancies and breastfeeding)
  - Possible side effects (including signs and symptoms of yellow fever vaccine-associated viscerotropic disease and yellow fever vaccine-associated neurotropic disease, hypersensitivity)

Vaccinee questionnaire

[1] Patient Group Directions (PGDs) provide a legal framework that allows some registered HCPs to supply and/or administer specified medicines to a pre-defined group of patients, without them having to see a prescriber (such as a doctor or nurse prescriber)

[2] Note: In addition to the checklist developed by MHRA, NaTHNaC/PHS has also issued a checklist which aligns with the Green Book (the Green Book has the latest information on vaccines and vaccination procedures for all the vaccine preventable infectious diseases that may occur in the UK) and is intended for travellers to read and complete for yellow fever consultation with HCPs; both checklists are similar in content.

The following variables will be collected through the vaccinee survey:

- Variables related to vaccinees' demographic information (age range, gender, region and education level)
- Variables related to vaccinee's receipt of the STAMARIL® PIL.

Data sources:

The survey is a primary data collection conducted through two questionnaires (HCP and vaccinee) administered mainly by web; paper will be a supplement to web for vaccinee questionnaire. It is estimated to take 10 to 15 minutes to complete HCP questionnaire, and up to 5 minutes to complete vaccinee questionnaire.

Study size:

Considering an expected proportion of interest of 50% (the most conservative), approximately 300 completed questionnaires per target population (300 HCPs and 300 vaccinees)[3] will be ideal goal, providing a precision of 5.7% for confidence interval (CI) of 95%.

Due to COVID-19 pandemic, the feasibility assessment will be done close to the start of fieldwork to predict the likelihood of achieving the desired sample size. For this survey, a minimum sample size of 200 HCPs (a 7% precision) and 150 vaccinees (an 8% precision) will be targeted assuming an expected proportion of interest of 50%. However, if the minimal sample size is not achieved within the allocated fieldwork timelines, the data collection will then be stopped and the study report will be written and submitted based on the analysis of all available data.

Data analysis:

The statistical analysis will be conducted using the SAS® software V9.4 (SAS Institute, North Carolina, USA) or R version 3.6 or higher on Windows™. All the analyses will be descriptive. Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, and median, Q1, Q3, minimum and maximum. Categorical variables will be described as the total number and relative percentage per category.

In case of multiple-choice questions, the frequency of each option provided by the HCPs/vaccinees will be reported as the total number and relative percentage per category. Different combinations of the answers provided (if any) will not be considered.

Wilson CI of 95% will be evaluated on the overall result.

The participation rate will be analysed overall and per region for HCPs and vaccinees separately.

The proportions of correct and desirable answers to the selected questions asked in the questionnaire will be separately expressed for HCPs and vaccinees (or their parents/guardians if

[3] *In the years following the COVID-19 pandemic these numbers may drop due to the reduced frequency of travelling*

vaccinees are younger than 18 years old) who provide answers to those questions (missing data will not be counted as a denominator in proportions). Success indicators by objectives will be presented separately for HCPs and vaccinees.

In the first step, calculations will be performed overall and per region on raw data. In the second step, only overall results will be weighted according to the proportion of HCPs and vaccinees in each region in order to accurately reflect the population that the survey seeks to measure. Estimation of the HCP universe will be determined using the number of YFVCs in each region and median of qualified HCPs in YFVCs based on the official websites (https://nathnacyfzone.org.uk and https://www.hps.scot.nhs.uk/a-to-z-of-topics/yellow-fever-vaccination-centres/find-a-yellow-fever-vaccination-centre). For vaccinees, an approximation of vaccinees universe will be obtained from the vaccine sales data of each region, provided by the MAH.

The statistical results will be presented in the same report, as overall and per region for both the questionnaires.

Milestones:

The data collection is planned to start in March-April 2023 and end in August-September 2023. The final study report will be submitted in January-February 2024.

5 AMENDMENTS AND UPDATES

DOCUMENT HISTORY

Number	Date	Section of study protocol	Amendment or update	Reason
1	31 May 2023	Refer to protocol amendment summary of changes	Amendment	Refer to protocol amendment summary of changes

AMENDED PROTOCOL 1 (31 MAY 2023)

This amended protocol (amendment 1) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union as well as the Medicines for Human Use (Clinical Trials) Regulations 2004 in the UK. This is because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

As stated in the study protocol v2.0, a minimal sample size of 150 vaccinees (an 8% precision) would be targeted assuming an expected proportion of interest of 50%. The vaccinee questionnaire collection started on 16 March 2023. As of 24 May 2023, only 9 vaccinees completed questionnaires within 2 months of vaccinee data collection, although 123 vaccinees clicked the survery link based on IQVIA tracking. According to some HCPs who agreed to distribute the survey flyers to vaccinees, there are three possible explanations for the extremely low response rate among vaccinees:

- Difficulty to follow up with vaccinees because HCPs do not see vaccinees after yellow fever vaccination
- Vaccinees lost interest in participation when they realize they would not receive an honorarium
- Vaccination on-demand varies and low season for yellow fever vaccination

For the vaccinee survey, the primary objective is “To verify the receipt of the STAMARIL® PIL by yellow fever vaccinees at the time they get vaccination consultation in the UK”, and the secondary objective is “To evaluate the yellow fever vaccinees’ knowledge and understanding of the key safety messages in the STAMARIL® PIL in the UK”. To increase the response rate among vaccinees, the MAH will remove secondary objective, amend the study protocol on conducting and reporting this survery according to the rationale summarized in the table below, and in line with the following plan:

- Shorten the vaccinee questionnaire by removing four questions designed for secondary objective

- Provide an honorarium to each vaccinee who participate in the survey

Section # and Name	Description of Changes	Brief Rationale
PASS Information	Added EU PAS register number: EUPAS50782; Added "None" after "Secondary objective:" and deleted "1. To evaluate the yellow fever vaccinees' knowledge and understanding of the key safety messages in the STAMARIL® PIL in the UK."	The study was registered at ENCePP website on 22 February 2023 before questionnaire collection. Remove secondary objective in order to shorten vaccinee questionnaire to decrease the time to completion.
Section 3: Responsible parties	Name and email updated in Sanofi team	The names and emails are updated for Global Safety Officer and Statistician.
Section 4: Abstract (Research question and objectives)	Deleted "The secondary objective of this study is: 1. To evaluate the yellow fever vaccinees' knowledge and understanding of the key safety messages in the STAMARIL® PIL in the UK." Updated as "There is no secondary objective."	Shorten vaccinee questionnaire to decrease the time to completion.
Section 4: Abstract (Vaccinee questionnaire)	Deleted "• Variables related to the knowledge and understanding of the key safety messages in the STAMARIL® PIL (including risk factors and awareness of serious adverse reactions)"	Shorten vaccinee questionnaire by removing variables related to secondary objective to decrease the time to completion.
Section 4: Abstract (Data sources)	The sentence "Each questionnaire is estimated to take 10 to 15 minutes to complete" is changed to "It is estimated to take 10 to 15 minutes to complete HCP questionnaire, and up to 5 minutes to complete vaccinee questionnaire".	Update the time for a vaccinee to complete the shortened questionnaire.
Section 4: Abstract (Milestones)	Study milestones updated.	The end of data collection and the final study report submission are updated based on up to 24-week of data collection period.

Section 5: Amendments and updates	Deleted the words “None” and “Not applicable”. Section was written as per amendment instructions in the template i.e., document history, and rationale for amending the protocol.	Because of very low response rate for vaccinee survey after two months of data collection, the MAH plans to shorten vaccinee questionnaire to decrease the time to completion and provide an honorariumto each vaccinee to motivate them to participate in the survey.
Section 6: Milestones	The words “After MHRA approval and before start of data collection” are changed to “February 2023 (actual)”. Study milestones updated.	The study was registered at ENCePP website on 22 February 2023 before questionnaire collection. The start of data collection date was updated from planned date to actual date. The end of data collection and the final report of study results are updated based on up to 24-week of data collection period.
Section 8: Research question and objectives (Table 1)	Added “None” after “Secondary objective:”; Deleted “1. To evaluate the yellow fever vaccinees’ knowledge and understanding of the key safety messages in the STAMARIL® PIL in the UK.” and the related endpoints.	Remove secondary objective in order to shorten vaccinee questionnaire to decrease the time to completion.
Section 9.2.4.2: Vaccinee selection	Changed the sentence “Likewise, there will be no incentive for the vaccinees, which might otherwise cause them to worry about the answer they provide about the use of the checklist by their HCPs” to “There will be incentive for the vaccinees. As there will be no information linking the vaccinees’ identities with the recruiting HCP, vaccinees will be unlikely to worry about the answer they provide about the use of the checklist by their HCPs.”	The MAH plans to provide an honorarium to each vaccinee to motivate them to participate in the survey.

Section 9.3.2: Vaccinee questionnaire	Deleted "• Variables related to the knowledge and understanding of the key safety messages in the STAMARIL® PIL (including risk factors and awareness of serious adverse reactions)."	Shorten vaccinee questionnaire by removing variables related to secondary objective to decrease the time to completion.
Section 9.4.1 Questionnaire description (Vaccinee questionnaire will include questions on)	Deleted "• knowledge and understanding of the key safety messages in the STAMARIL® PIL"	Shorten vaccinee questionnaire by removing the questions designed for secondary objective to decrease the time to completion.
Section 9.4.3 Time to completion	Changed the word "Each" to "HCP". Added the sentence "Vaccinee questionnaire is estimated to take up to 5 minutes to complete."	Update the time for a vaccinee to complete the shortened questionnaire.
Section 9.4.4 Approaches for increasing response rate	Added "and an honorariumafter they complete the survey" at the end of this section.	The MAH plans to provide an honorarium to each vaccinee to motivate them to participate in the survey.
Section 9.5.2 Sample size feasibility	The number of vaccinees possible to recruit assuming 160,000 or 46,000 yearly population of vaccinees and 20% response rate was updated in text to be 174 and 37, respectively.	Corrected the wrong numbers presented in the protocol. The correct numbers, as presented in Table 3, are 174 and 37, respectively.
Section 9.7.1 Primary analysis (Secondary endpoint)	Added "None" after "Secondary endpoint:". Deleted " • Knowledge and understanding of the key safety messages will be assessed through the percentage of vaccinees who provide desirable responses to the related questions on the key safety messages in the STAMARIL® PIL."	Shorten vaccinee questionnaire by removing secondary endpoint collected for secondary objective to decrease the time to completion.
Section 10.3.9 Compensation	Added the paragraph below at the end of the section. "Vaccinees will be offered an honorarium for the time they will spend while participating in this survey (which they may refuse). The time to complete the survey is estimated to be up to 5 minutes. The amount of the	The MAH plans to provide an honorarium to each vaccinee to motivate them to participate in the survey.

	honorarium will be determined according to fair market value"	
Annex 1 List of stand-alone documents	Updated vaccinee questionnaire being updated date	Vaccinee questionnaire was shortened on 31 May 2023 by removing Q1-Q4 designed for secondary objective.
Annex 6.1 Assessment of success (HCP questionnaire)	Objective "Awareness and Utilization" was split into two separate objectives, "Awareness (2 questions)" and "Utilization (7 questions)" Added "An HCP is considered successful for utilization when he/she utilizes either the UK (STAMARIL®) yellow fever pre-vaccination checklist or traveller checklist Success for utilization if ≥80% of HCPs are successful." Q11 was changed from "Complementary question" to "Question completed desirably [Answers: 1 or 2 are desirable]"	Split objective "Awareness and Utilization" for clarity: Awareness (Q6-Q7) and Utilization (Q8-Q14). Added assessment of success for "Utilization" objective. Q11 was incorrectly listed as complementary question. Corrected the error.
Annex 6.2 Assessment of success (Vaccinee questionnaire)	Deleted "Knowledge and Understanding (4 questions)" in Objectives and relevant contents related to this objective.	The MAH plans to shorten vaccinee questionnaire by removing 4 questions designed for secondary objective to decrease the time to completion.

6 MILESTONES

Milestone	Planned date*
Submission of study protocol	April 2022 (actual)
Start of data collection	March 2023 (actual)
End of data collection	August-September 2023
Registration in the EU PAS register®	February 2023 (actual)
Final report of study results	January-February 2024

**The timelines may vary depending on the MHRA approval and the recruitment (please refer to section 9.5.2).*

7 RATIONALE AND BACKGROUND

Epidemiology of yellow fever and yellow fever vaccination

Yellow fever is an acute viral haemorrhagic illness caused by infection with the mosquito-borne yellow fever flavivirus. The main urban vector is the *Aedes aegypti* mosquito, which is found throughout the tropics.[1] The presentation of yellow fever disease ranges in severity from a subclinical, non-specific viral illness to a sudden onset systemic disease including fever, jaundice, haemorrhage, and renal failure. Differences in yellow fever virus strains, as well as host immune factors that are not fully understood, are likely responsible for the range of clinical symptoms. Mortality can be as high as 50%.[2] Nowadays the disease occurs in the tropical regions of Africa and Central and South America.[2] Recent epidemics of yellow fever in Brazil and sub-Saharan Africa have become major public health concerns for resident populations as well as travellers.[3] Accurate data on the burden of yellow fever are difficult to obtain because of the variable quality of disease surveillance and under reporting of the disease.[2] Approximately 138,000 cases of yellow fever, including 78,000 deaths, occur annually, with the vast majority of reported cases and deaths (>90%) occurring in sub-Saharan Africa. Mosquitoes capable of transmitting yellow fever virus exist in regions where the disease does not presently occur and in regions, such as Asia, where yellow fever has never occurred. However, there is no risk of transmission in the United Kingdom (UK) from imported cases since the mosquito vectors are not present in the UK.[1, 2]

Yellow fever vaccines have been available for about 80 years. The currently available yellow fever vaccines are live, attenuated preparations of the 17D strain of yellow fever virus.[4] As of 2021, more than 600 million doses of 17D yellow fever vaccines have been used worldwide.[5] In the UK, Sanofi Pasteur is the only marketing authorisation holder (MAH) for yellow fever vaccine (STAMARIL®). STAMARIL® is a live attenuated yellow fever 17D-204 strain vaccine which is prepared by culturing the virus in embryonated eggs.

Vaccination is recommended for people over 9 months of age who are travelling to or living in areas or countries with a risk of yellow fever transmission, as well as laboratory workers handling potentially infectious materials.[6] Under the International Health Regulations (IHR) 2005 and to limit the spread of yellow fever, some countries require evidence of immunisation against yellow fever as a condition of entry, in the form of an International Certificate of Vaccination or Prophylaxis (ICVP). As a single dose of yellow fever vaccine is expected to confer life-long immunity, since July 2016 the ICVP is valid for the duration of the life of the person vaccinated.[7]

Vaccination guidelines

Current guidelines for the practice of travel medicine advise that the risk of travel-associated yellow fever disease, the country ICVP requirements, and the potential for serious adverse events (SAE) following yellow fever vaccination are considered as part of the individual risk assessment undertaken during a consultation at a travel clinic. Aside from the ICVP requirements, the IHR 2005 mandate that yellow fever vaccine can only be administered at yellow fever vaccination centres (YFVCs), designated by the health administration for the territory in which they are situated. These conditions are designed to ensure that individuals seeking yellow fever vaccine prior to travelling abroad have access to a formally registered YFVC, are provided with appropriate travel advice, and to help assure the quality and the safety of the procedures and

materials employed. Such centres have to be suitably qualified and follow a specific code of practice. In the UK, expert advice on travellers' yellow fever exposure risk, designation of centres and country ICVP requirements are available through the National Travel Health Network and Centre (NaTHNaC)[8] and Public Health Scotland (PHS).[9] Each YFVC has to nominate a Responsible Supervising Clinician, who must be a doctor, nurse or pharmacist and implements the Conditions of Designation and code of practice. The YFVCs are responsible under the Conditions of Designation, for the reporting and follow-up of all vaccine adverse events (AEs) to the Medicines and Healthcare products Regulatory Agency (MHRA), MAH (Sanofi Pasteur), NaTHNaC and Health Protection Scotland (HPS). The YFVCs are also required to submit an annual return of yellow fever vaccine use.

UK (STAMARIL®) yellow fever pre-vaccination checklist (for HCPs) (Annex 3)

Following two fatal adverse reactions to yellow fever vaccine in the UK in 2018-2019, due to unapproved use in both cases, the UK MHRA requested the MAH to add a standardised UK checklist, developed by MHRA (hereby referred to as 'UK (STAMARIL®) yellow fever pre-vaccination checklist' in this protocol), as part of local additional risk minimisation measures (aRMMs) in the STAMARIL® Risk Management Plan, to support the UK healthcare professionals (HCPs) in the benefit-risk assessment process. The objective of this checklist is to ensure compliance of HCPs from designated authorised YFVCs with indications, contraindications, warnings, and precautions of the yellow fever vaccine as per the Summary of Product Characteristics (SmPC) and to support the appropriate evaluation of individual travellers' risk-benefit balance. The most recent SmPC (dated 15 Feb 2021) details the required considerations of risk-benefit balance for individual travellers. The UK (STAMARIL®) yellow fever pre-vaccination checklist (Annex 3 has been published on 16 Nov 2021, on the MHRA Drug Safety Update website.[10]

NaTHNaC/PHS yellow fever pre-vaccination checklist (Traveller's checklist) (Annex 4)

In the UK, NaTHNaC first published a yellow fever pre-vaccination checklist in July 2019, which was updated in January 2020 in accordance with the recommendations in the Commission on Human Medicine's Expert Working Group report.[11] In September 2021, NaTHNaC and PHS produced a new version of the yellow fever pre-vaccination checklist (Annex 4).[12] This checklist is a screening tool and is intended for vaccinees (travellers) to read and complete in advance of, or during, the travel health consultation; it is also commonly called the 'traveller's checklist'. Based on the Annual Return 2020[13] report published by NaTHNaC, >90% of YFVCs in England, Wales, and Northern Ireland used a traveller (vaccinee) checklist during the travel health consultation to assist with yellow fever vaccine risk assessment. The contents of this checklist are similar to that of the UK (STAMARIL®) yellow fever pre-vaccination checklist. Therefore, throughout this protocol, 'standardised yellow fever pre-vaccination checklist' refers to either or both these checklists (i.e. 'UK (STAMARIL®) yellow fever pre-vaccination checklist' and 'NaTHNaC/PHS yellow fever pre-vaccination checklist').

Furthermore, since a patient information leaflet (PIL) should be provided to each vaccinee by their HCPs during the vaccination consultation, therefore the STAMARIL® PIL was also amended in line with the revisions of the most recent SmPC (dated 15 Feb 2021). In view of the important role of a PIL in risk minimisation, the MAH was also asked to evaluate the effectiveness of the STAMARIL® PIL.

In this light, the present post-authorisation safety study (PASS) survey is designed to assess the effectiveness of the UK (STAMARIL®) yellow fever pre-vaccination checklist, among the qualified HCPs of designated authorised YFVCs. In addition, this survey will also assess the effectiveness of the STAMARIL® PIL among yellow fever vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK.

8 RESEARCH QUESTION AND OBJECTIVES

The aim of the current study is to examine the effectiveness of the UK (STAMARIL®) yellow fever pre-vaccination checklist among the qualified HCPs of designated authorised YFVCs and of the STAMARIL® PIL among the yellow fever vaccinees in the UK by conducting a survey in this population.

The objectives and endpoints of this study are presented in **Table 1**.

Table 1 Objectives and endpoints

Objectives	Endpoints
Primary objectives	
1. To measure: a. Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist by qualified HCPs of designated authorised YFVCs in the UK.	a. The proportion of qualified HCPs who are aware of the UK (STAMARIL®) yellow fever pre-vaccination checklist. Success indicator for awareness: if ≥80% of qualified HCPs are successful (a qualified HCP is considered successful when he/she is aware of the UK (STAMARIL®) yellow fever pre-vaccination checklist).
b. Utilisation of any standardised yellow fever pre-vaccination checklist(s) by qualified HCPs of designated authorised YFVCs in the UK.	b. The proportion of qualified HCPs who frequently or always use one or both the standardised yellow fever pre-vaccination checklists. Success indicator for utilisation: if ≥80% of qualified HCPs are successful (a qualified HCP is considered successful when he/she frequently or always uses at least one of the standardised yellow fever pre-vaccination checklists).
c. Distribution of the STAMARIL® PIL by qualified HCPs of designated authorised YFVCs to yellow fever vaccinees in the UK.	c. The proportion of HCPs who frequently or always distribute the STAMARIL® PIL to yellow fever vaccinees in the UK. Success indicator for distribution of the STAMARIL® PIL by HCPs: if ≥80% of qualified HCPs are successful (a qualified HCP is considered successful when he/she is frequently or always distributes the STAMARIL® PIL).

2. To evaluate knowledge and understanding of the key safety messages associated with yellow fever vaccination in any standardised yellow fever pre-vaccination checklist(s) among qualified HCPs of designated authorised YFVCs in the UK.	a. The proportion of qualified HCPs who provide desirable responses for each question related to knowledge and understanding of key safety messages. Success indicator for knowledge and understanding: If ≥80% of qualified HCPs are successful (a qualified HCP is considered successful when he/she provides at least 80% of desirable responses to questions related to knowledge and understanding).
3. To verify the receipt of the STAMARIL® PIL by yellow fever vaccinees at the time they get vaccination consultation in the UK.	a. The proportion of yellow fever vaccinees who receive the STAMARIL® PIL Success indicator for receipt of STAMARIL® PIL: If ≥80% of vaccinees are successful (a vaccinee is considered successful when he/she receives the STAMARIL® PIL).
Secondary objective: None	
1.	

9 RESEARCH METHODS

The research methods described here have been endorsed by European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee in several protocols available at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website.[14]

9.1 STUDY DESIGN

This will be a national, multicentre, prospective, cross-sectional, and multi-channel survey based on primary data collection, conducted separately among qualified HCPs (physicians, nurses and pharmacists) and STAMARIL® vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK (England, Wales, Northern Ireland and Scotland).

The survey will be conducted primarily through a web questionnaire. Also, a paper version of the questionnaire will be offered to vaccinees only.

9.2 SETTING

The survey will be conducted among qualified HCPs from designated authorised YFVCs and yellow fever vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) in the UK.

Based on the NaTHNaC Annual Return 2019 report,[13] there were a total of 2,821 YFVCs that were designated in 2019 in England, Wales, and Northern Ireland, and 168 YFVCs in January 2021 in Scotland based on Scotland's NHS website. Based on the NaTHNaC Annual Return 2020[13] report, there were a total of 2,295 YFVCs that remained designated in 2020 in England, Wales, and Northern Ireland. In addition, 123 YFVCs remained designated in Scotland as of January 2022.[15]

9.2.1 Duration of the study

The fieldwork will start after the aRMMs have been implemented to enable the assessment of effectiveness. Generally, a 6 to 12month period is considered after the implementation of the aRMMs to allow for their completion. The survey will be conducted within 12 to 18 months following the distribution of the local aRMMs in the UK as per the European guideline on good pharmacovigilance practices (GVP) – Module XVI (Rev 3).

9.2.2 Eligibility criteria

The target population of the survey will be qualified HCPs (physicians, nurses and pharmacists) and yellow fever vaccinees (or their parents/guardians if vaccinees are younger than 18 years old).

9.2.2.1 *Inclusion criteria*

The following criteria must be met in order to be enrolled in the study:

1. For HCPs: Qualified HCPs from designated authorised YFVCs who have provided consultation for yellow fever vaccine administration and/or administered yellow fever vaccines in the UK in the past 12 months and are willing to consent to participate in the

survey. A qualified HCP refers to the one who has undertaken the yellow fever training programme, sponsored by the NaTHNaC or PHS during the past 24 months.

2. For vaccinees: Individuals who receive yellow fever vaccine in the UK and are willing to consent (or their parents/guardians, if individuals are younger than 18 years old) to participate in the survey.

9.2.2.2 *Exclusion criteria*

Individuals meeting any of the following criteria are not eligible for participation:

1. For HCPs:
    a. Who declare having conflict of interest with the survey (i.e., HCPs employed by regulatory bodies, or pharmaceutical industries, etc).
    b. Who are unable or not willing to provide voluntary consent to participate in this survey conducted in the UK.
    c. Who are not qualified to provide consultation for yellow fever vaccine administration and/or administer yellow fever vaccines in the UK (i.e., HCPs who have not undertaken yellow fever training sponsored by the NaTHNaC or PHS in the past 24 months).

2. For vaccinees (or their parents/guardians if vaccinees are younger than 18 years old):
    a. Who declare having a conflict of interest with the survey (i.e., employed by regulatory bodies, or pharmaceutical industries etc., or are immediate family of qualified HCP's of designated authorised YFVCs or are employed by YFVCs).
    b. Who are unable or not willing to provide voluntary consent to participate in this survey conducted in the UK.

9.2.3 Analysis population(s)

All eligible HCPs (physicians, nurses and pharmacists) and vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) who complete the web/paper questionnaires (totally or partially for the paper version) will be included for analysis.

9.2.4 Modalities of recruitment

All YFVCs will be included in the sampling plan so that the results of the survey are representative of all regions in the UK (England, Wales, Northern Ireland and Scotland).

9.2.4.1 *HCPs selection*

It is expected that nurses will represent the majority of HCPs in the YFVCs. Other HCPs to be included in the study will be general practitioners, and a minority will be pharmacists.[16]

The initial identification of participating HCPs will be based on the list of all YFVC practices as reported by the NaTHNaC[17] in each region and HPS[18]. The lists of YFVCs will be reconciliated

with OneKey lists (OneKey, IQVIA) in order to retrieve contact details for HCPs working in each YFVC. OneKey is an IQVIA managed database with information of HCPs in each of the relevant specialities in the targeted country. OneKey databases are constructed and updated through manual and automated means from various sources, including publicly available sources. Information collected includes HCP personal information (e.g. age, gender, contact details) and professional information (e.g. year of graduation, specialties, practicing status). These lists are widely used for the recruitment of HCPs in clinical trials, observational studies and surveys.21, [22]

Since the study objective is to determine the extent of HCPs' awareness and knowledge of the safety information in the aRMMs, only HCPs who have provided consultation for yellow fever vaccine administration and/or administered the yellow fever vaccine in the past 12 months will be selected. As this information is not available in the lists of HCPs, the survey will be preceded by a set of questions to check the eligibility of HCPs. Among these, it will be asked if the HCP has provided consultation to yellow fever vaccinees and/or administered the yellow fever vaccine in the past 12 months. If the answer is "no", the survey will not open to that HCP.

According to the Annual Return 2020[13] report, the number of HCPs administering yellow fever vaccines varied for each YFVC and around 89% of YFVCs had 1 to 3 HCPs administering yellow fever vaccines. Therefore, to limit selection bias, we will recruit a maximum of 3 HCPs per centre. However, in case the target sample size is not achieved, this cap may be lifted to a maximum of 5 HCPs per centre.

HCPs recruitment and survey will be conducted by the following process:

- HCPs will be invited to participate in the survey by email and/or phone. An email invitation will include a web link directing to the questionnaire. In the invitation, the survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the HCPs. Compensation will be compliant with the relevant guidelines and the fees will compensate for the actual effort and time needed to fill out the questionnaire.

- If the HCPs agree to participate in the survey, they can access the survey and the instructions for the web questionnaire by clicking on the email link.

- If the questionnaire is not completed in the first attempt, HCPs will receive a reminder email (first reminder) 1 week after the initial invitation.

- If the web questionnare remains incomplete, a second reminder will be sent about 2 weeks after the initial invitation.

- If the questionnaire still remains incomplete, a third (and final) reminder will be sent 3 weeks after the initial invitation.

An HCP will be considered unreachable if he/she has been contacted up to 5 times without an answer. For each recruited HCP, the number of times the HCP is contacted, as well as the date and time when he/she completes the web questionnaire, will be recorded. HCP recruitment will be competitive.

9.2.4.2 *Vaccinee selection*

Vaccinees will be primarily recruited by the qualified HCPs who will participate in the HCP survey. In the event that the target sample size of vaccinees is not achieved, then the possibility of recruitment by HCPs who have not participated in the HCP survey will be explored.

Each HCP who has agreed to recruit vaccinees will systematically distribute a kit containing a simplified guide for taking the web or paper questionnaire (as needed) to eligible vaccinees (or their parents/guardians if vaccinees are younger than 18 years old). To limit selection bias, an HCP will be requested to consecutively solicit vaccinees for participating in the survey and a maximum of 10 vaccinees per centre will be recruited.

Vaccinee anonymity will be maintained throughout the study. A unique number will be printed on each page of the questionnaire, which will link each questionnaire with the corresponding HCP who will distribute it. However, no log would be kept at the HCP level which would provide linkage between material for the web/paper survey distributed to the vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) and vaccinee identity. When a vaccinee (or their parent/guardian if vaccinee is younger than 18 years old) fills in the survey on the web/paper, the unique number for the vaccinee survey will ensure that no more than 10 vaccinee questionnaires originate from the same YFVC. Vaccinee recruitment will also be competitive.

Selection bias is reduced through 1) consecutive recruitment of vaccinees by each enrolled qualified HCP, 2) the cap on the number of vaccinees who could be recruited per centre, and 3) the recruitment through both participating HCPs and non-participating HCPs (if the target vaccinee sample size is not achieved) in the survey. As there will be no information linking the vaccinees' identities with the recruiting HCP, there would be no incentive for HCPs to recruit their best vaccinees. There will be incentive for the vaccinees. As there will be no information linking the vaccinees' identities with the recruiting HCP, vaccinees will be unlikely to worry about the answer they provide about the use of the checklist by their HCPs.

<u>Vaccinee recruitment by non-participating HCPs in the survey (if needed):</u>

Qualified HCPs who do not participate in the survey will be contacted and will be asked a few screening questions in order to confirm their eligibility to help with vaccinees' recruitment. Vaccinees will be recruited using the same methods, as used by the participating HCPs in the survey.

9.3 VARIABLES

9.3.1 HCP questionnaire

The following variables will be collected through the HCP survey:

- Variables related to HCPs' practice:
    - Demographic information (age range, gender and region)

- HCP profession (physician, nurse or pharmacist)
- Type of work setting (General Practice [National Health Service], General Practice [Private], pharmacy, travel clinic, occupational health department, hospital or other)
- Years of experience in the profession
- Prescriber administering STAMARIL® under a Patient Group Direction (PGD)[4]
- Experience with STAMARIL® (whether providing consultation and/or administering STAMARIL®, years of experience in providing consultation and/or administering STAMARIL® and number of patients administered with STAMARIL® and/or provided consultation for the administration of STAMARIL® in the past 12 months)
- Yellow fever training sponsored by NaTHNaC or PHS (HCP trained ≤12 months ago or >12 months ago)

- Variables related to the HCPs' awareness, utilisation, and distribution of the aRMM materials:
  - Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist by the HCPs
  - Use of the UK (STAMARIL®) yellow fever pre-vaccination checklist (Annex 3) by the HCPs
  - Use of the NaTHNaC/PHS yellow fever pre-vaccination checklist[5] by the HCPs (Annex 4)
  - Distribution of STAMARIL® PIL by the HCPs to yellow fever vaccinees
- Variables related to the knowledge and understanding of the key safety messages in any standardised yellow fever pre-vaccination checklist(s)
  - Indications (e.g. yellow fever activity at travel destination) and contraindications (e.g. hypersensitivity to vaccine components, immunosuppression [congenital or acquired], thymus dysfunction, thymoma, thymectomy, or age less than 6 months), or precautions

[4] Patient Group Directions (PGDs) provide a legal framework that allows some registered HCPs to supply and/or administer specified medicines to a pre-defined group of patients, without them having to see a prescriber (such as a doctor or nurse prescriber)

[5] Note: In addition to the checklist developed by MHRA, NaTHNaC/PHS has also issued a checklist which aligns with the Green Book (the Green book has the latest information on vaccines and vaccination procedures for all the vaccine preventable infectious diseases that may occur in the UK) and is intended for travellers to read and complete for yellow fever consultation with HCPs; both checklists are similar in content.

(e.g. infants from 6 up to 9 months of age, advanced age, pregnancies and breastfeeding)

- Possible side effects (including signs and symptoms of yellow fever vaccine-associated viscerotropic disease and yellow fever vaccine-associated neurotropic disease; hypersensitivity).

9.3.2 Vaccinee questionnaire

The following variables will be collected through the vaccinee survey:

- Variables related to vaccinees' demographic information (age range, gender, region and education level)
- Variables related to vaccinees' receipt of the STAMARIL® PIL

9.4 DATA SOURCES

This will be a primary data collection survey conducted through two questionnaires administered primarily by web; a paper version (*if required)* is intended only for vaccinees:

- An HCP questionnaire (administered by web only)
- A vaccinee questionnaire (administered mainly by web; paper questionnaire is a supplement to web questionnaire)

9.4.1 Questionnaire description

The questionnaires have a disclaimer and consent at the beginning. They are designed to collect information on the eligibility and demographics of the participants. The questionnaires include open and closed questions on the contents of the checklist and STAMARIL® PIL, and the questions are in the order of exploring knowledge to awareness. The language of both questionnaires (HCPs and vaccinees) will be English.

The questionnaires are designed to be nondirecting, to avoid inducement of social desirability bias, and without any self-evident answers. Also, to avoid information bias, the web questionnaires will be programmed in such a way that the participants cannot go back to the previous questions.

A brief overview of the contents in each of these questionnaires is as below:

***HCP questionnaire will include questions on*:**

- screening criteria, demographics
- awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist
- utilisation of any standardised yellow fever pre-vaccination checklist(s)
- distribution of the STAMARIL® PIL
- knowledge and understanding of key safety messages

Vaccinee questionnaire will include questions on:

- screening criteria, demographics

- receipt of the STAMARIL® PIL

9.4.2 Questionnaire pilot testing

The objective of each questionnaire will be tested among 3 HCPs and 3 non-HCPs, respectively, to make sure the right language and medical terms are used, and also to check the understandability of the language.

9.4.3 Time to completion

HCP questionnaire is estimated to take 10 to 15 minutes to complete. Vaccinee questionnaire is estimated to take up to 5 minutes to complete.

9.4.4 Approaches for increasing response rate

People are frequently contacted to participate in web or phone surveys. According to international studies, the overall response rate of participation remains low.[19-21] Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey.[21] Van Geest et al. conducted a systematic review of 66 published reports on efforts to improve response rates.[22] Two general strategies were explored: incentive-based approaches and survey design-based approaches. Financial incentives, even little ones, were reported to be effective in improving physician response rates, while non-monetary incentives were much less effective. These measures include the use of a short questionnaire, as well as questionnaires personalised and endorsed by professional associations.

In order to increase the response rate among HCPs in the present survey, a compensation fee will be proposed to HCPs for their participation in the survey and/or vaccinee recruitment. Also, to increase the response rate among vaccinees (or their parents/guardians if vaccinees are younger than 18 years old), they will be immediately provided with material for the web/paper survey after the receipt of the vaccine and an honorarium after they complete the survey.

9.5 STUDY SIZE

9.5.1 Determination of sample size

The sample size formula based on the normal approximation of the binomial distribution, for calculating the number of participants required for a proportion is as follows:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

where P is the expected proportion, e is one half the desired width of the confidence interval (CI), and $Z_{1-\alpha/2}$ is the standard normal Z value corresponding to a cumulative probability of $1 - \alpha/2$ (e.g., if $\alpha = .05$ then $Z = 1.96$). The following table provides the margin of error for 95% CI based on various sample sizes and proportions of interest.

Table 2 Margin of error for 95% CI based on various sample sizes and proportions of interest

Margin of error for 95% CI (absolute precision)					
Proportion of interest	**8%**	**7%**	**5.7%**	**5%**	**4%**
10%	54	71	106	139	216
30%	126	165	248	323	504
50%	150	196	295	384	600
70%	126	165	248	323	504
90%	54	71	106	139	216

As P is not known in advance, we consider it to be 50%. Such a hypothesis yields the most conservative i.e. the largest, sample size.

Based on 2019 figures,[23] a minimum sample size of 200 HCPs (a 7% precision) and 150 vaccinees (a 8% precision) are targeted assuming an expected proportion of interest of 50%. If the proportion of interest is greater than 50% which may be predicted from other sources such as an Annual Return Report, the precision could be further increased with the same sample size, or the sample size could be further decreased with the same precision. For example, based on the Annual Return 2020 report published by NaTHNaC, 90.7% of YFVCs supplied the yellow fever vaccine PIL routinely to travellers receiving yellow fever vaccination. In this case, a sample size of 200 HCPs will achieve a precision below 4%. If a similar proportion of vaccinees (or parents/guardians of minor vaccinees) can also confirm receipt of yellow fever vaccine PIL, a sample size of 54 vaccinees will achieve an 8% precision in this case.

9.5.2 Sample size feasibility

In 2019, there were 2,821 YFVC (5,474 HCPs) in England, Wales, and Northern Ireland.[23] However, the number of YFVCs and the frequency of travel, especially to endemic countries, have been significantly affected by the COVID-19 pandemic. There were 2,295 YFVC (3,763 HCPs) which remained designated in 2020,[13] suggesting a 19% decrease compared to 2019. The average number of yellow fever vaccine doses given per centre decreased from 47 (median: 22) in 2019 to 13 (median: 5) in 2020, which corresponds to a decrease of 72%. Sales of the yellow fever vaccine went from around [redacted] doses in 2019 in the UK, to around [redacted] doses in 2020, representing a 71% fall.

The dynamics of vaccine centres, vaccinees and number of doses administered are still not stabilised. Therefore, a sample size feasibility assessment will be done before the start of fieldwork to predict the likelihood of achieving the desired sample size and to eventually adjust the sample size.

For this assessment, the updated number of YFVCs, the number of vaccinees and the sales of the vaccine will be estimated. The YFVC will be matched with the OneKey database and HCPs will then be identified through OneKey as detailed in Section 9.2.4. This will provide an actualised number of identified HCPs.

The number of vaccinees will be estimated using the most recent sales data of STAMARIL® received by the MAH at the time of the feasibility assessment.

For HCP survey, the number of HCPs that will be included in the survey will be estimated based on a response rate of 5-10%. Therefore, for a sample size of 200 HCPs, between 2000 to 4000 HCPs will have to be contacted. Using the results of this assessment of the actual numbers of HCPs at the time of the survey will allow us to adjust the target sample size.

For vaccinee sample size assessment, the number of vaccinees who will complete the web/paper questionnaires will be estimated using a process as presented in Table 3. Participation rates may vary around the figures presented in this table. However, with a yearly population of vaccinees of around [redacted] (as presented for 2019) it is possible to recruit around 174 vaccinees, while only 37 could be recruited with a yearly population of [redacted] (as in 2020). Using the most recent numbers of vaccinees at the time of the survey will allow to adjust the target sample size.

In case the desired number of completed vaccinee questionnaires is not achieved during the 12-week period, the data collection period may be extended up to 24 weeks.

Table 3 Example of assumptions for calculation of expected sample size for patients during 12 weeks

Assumptions	2019[4]	2020 [4]
A/ Number of vaccines sold as a proxy for number of vaccinees for 12 weeks (from March to May) [1]	45,984	11,396
B/ Number of active YFVCs	2,989	2,418
C/ Number of HCPs involved in vaccinations	5,668	3,905
D/ Number of vaccinees per center per week ((A/B/12) [2]	1.28	0.39
E/ Number of HCPs who participate in the survey (10% participation rate based on IQVIA experience[3])	567	391
F/ Number of HCPs who agree to distribute material among vaccinees (assumption 10% based on IQVIA experience [3])	57	39
Vaccinees response:		
Number of vaccinees who actually receive the survey invitation during 12 weeks fieldwork (F*D*12)	872	184
20% response rate from vaccinees	174	37
10% response rate from vaccinees	87	18

1) The real number of vaccinees is smaller due to waste and stock.
2) Please note that there is a high variation between vaccine centres in practice concerning the number of vaccinees per week (please see Table 4 of NaTHNaC Annual Return 2019)[23], and seasonality of vaccination for yellow fever. Data collection from March to May is the highest probable period of vaccination as per sales data.
3) Based on similar design in UK
4) NaTHNaC Annual reports figures adjusted to include Scotland

9.5.3 Sample weighting

Since the relative weight of each region in the final sample will be different from its real relative weight in estimations, the extrapolation of the raw survey results to the overall target population would not be relevant without weighting. Thus, the survey results will be weighted to reflect the real proportion of the HCPs or vaccinees in participating regions. Both unweighted (i.e. raw data) and weighted results will be presented in the report.

A weight variable will be applied to each statistical unit during the results calculation in order to correct any over- or under-sampling that may have occurred for a region or a target population. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per region. The weights will be normalised to obtain a sum equal to the sample size.

The number of YFVCs as reported by NaTHNaC[17] and HPS[18] in each region and the median number of qualified HCPs per YFVC will be used to determine the universe, to weight back HCPs' samples. For vaccinees, an approximation of the vaccinees' universe will be obtained from the vaccine sales data of each region provided by the MAH.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

The data collection period will last about 12 weeks (fieldwork) or longer if needed (up to 24 weeks).

9.6.2 Data collected

Data related to the variables listed in Section 9.3.1 and 9.3.2 will be collected from the HCP and vaccinee questionnaires, respectively.

9.6.3 Survey questionnaire

The HCP and vaccinee questionnaires are separate stand-alone documents included in Annex 1 .

9.6.4 Participant tracking log

A fully anonymous tracking log will be used to collect HCP information.

9.7 DATA ANALYSIS

General statistical considerations

The statistical analysis will be conducted using the SAS® software V9.4 (SAS Institute North Carolina, USA), or R version 3.6 or higher on Windows™. All the analyses will be descriptive. Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, and median, Q1, Q3, minimum and maximum. Categorical variables will be described as the total number and relative percentage per category.

In case of multiple-choice questions, the frequency of each option provided by the HCPs/vaccinees will be reported as the total number and relative percentage per category. Different combinations of the answers provided (if any) will not be considered.

Wilson CIs of 95% will be evaluated on the overall result.

The participation rate will be analysed overall and per region for HCPs and vaccinees separately.

The proportion of correct and desirable answers to the selected questions asked in the questionnaire will be separately expressed for HCPs and vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) who provide answers to those questions (the missing data will not be counted as a denominator in proportions). Success indicators by objectives will be presented separately for HCPs and vaccinees.

In the first step, calculations will be performed overall and per region on raw data. In the second step, only overall results will be weighted according to the proportion of HCPs and vaccinees in each region in order to accurately reflect the population that the survey seeks to measure. Estimation of HCPs' universe will be determined using the number of YFVCs in each region and median of qualified HCPs in YFVCs obtained from the official websites of NaTHNaC[17] and HPS[18]. For vaccinees, approximation of vaccinees' universe will be obtained from the vaccine sales data of each region provided by the MAH.

The statistical results will be presented in the same report, as overall and per region for both of the questionnaires.

9.7.1 Primary analysis

The general statistical considerations described above will be applied to quantitative and qualitative variables. The number of missing data will be indicated. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data.[24] Confidence interval of 95% will be evaluated for endpoint variables.

For each question associated with an outcome included in the objectives, a criterion will be applied to separate participants with the correct and desirable answers (or at least one correct and desirable answer as a response if the corresponding question allows multiple answers/true-false or is an open-ended question). These proportions of correct and desirable answers to each question will be expressed for HCPs/vaccinees who answer that question. Analysis for the survey will be performed for HCPs and vaccinees separately for the endpoints described below:

Primary endpoints

- **Awareness of the UK (STAMARIL®) yellow fever pre-vaccination checklist** will be assessed through the percentage of qualified HCPs who are aware of the checklist.

- **Utilisation of any standardised yellow fever pre-vaccination checklist(s)** (UK (STAMARIL®) yellow fever pre-vaccination checklist or NaTHNaC/PHS yellow fever pre-vaccination checklist) will be assessed through the percentage of qualified HCPs who frequently or always use any standardised yellow fever pre-vaccination checklist(s).

- **Distribution of the STAMARIL® PIL by qualified HCPs to vaccinees** will be assessed through the percentage of qualified HCPs who frequently or always distribute it among yellow fever vaccinees.

- **Knowledge and understanding of the key safety messages** will be assessed through the percentage of qualified HCPs who provide desirable responses to the related question on key safety messages associated with yellow fever vaccination in any standardised yellow fever pre-vaccination checklist(s).

- **Receipt of the STAMARIL® PIL** will be assessed through the percentage of vaccinees who receive the PIL.

Secondary endpoint: None *Assessment of success*

In each survey, the proportion of correct or desirable responses across all questions related to the evaluation of the primary objectives of the surveys will be considered to assess the success.

The questions considered as complementary will not be included in the assessment of success. The details of the assessment of the success for each survey and each objective is described in Annex 6 .

Success at the HCP/vaccinee level will be defined for each primary objective based on the number of sub-questions related to that objective being completed with desirable responses. A HCP/vaccinee will be successful in each objective (except knowledge and understanding for HCPs) if all related questions, including sub-questions, will be completed with desirable responses (Annex 6). An HCP will be successful for knowledge and understanding of any standardised yellow fever pre-vaccination checklist(s), if at least 80% of the related questions, including sub-questions, are completed with desirable responses.

A threshold of 80% successful HCPs or vaccinees on each of the primary outcomes would be considered appropriate for assessing the effectiveness of an aRMM.

It should be noted that the selection of this threshold for success is subjective and not based on *a priori* knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. If additional information from published literature becomes available at the time of reporting, then the results will be discussed in the context of this new information. The methods of reporting and analysis of results obtained will be done as already described in this protocol and will be further detailed in the statistical analysis plan (SAP).

Description of characteristics of HCPs with desirable/undesirable responses

The charactertistics of HCPs with desirable and undesirable responses to questions related to each outcome will be described using all available and relevant participant information collected in the survey (i.e. region, HCP profession, gender, age range, duration of practice, type of setting, years of professional experience and experience with STAMARIL®). This will be further detailed in the SAP.

Description of characteristics of vaccinees with desirable/undesirable responses

The characteristics of vaccinees with desirable and undesirable responses to questions related to each outcome will be described using all available and relevant participant information collected

in the survey (i.e., age range, region, gender, and education level). This will be further detailed in the SAP.

9.7.2 Secondary analysis

Not applicable.

9.7.3 Early analysis

No early analysis is planned for this study.

9.7.4 Handling of missing data

The web questionnaire will be programmed in such a way that participants cannot skip questions. We thus do not expect missing values in submitted web questionnaires, and neither replacement nor imputation of missing data is expected to be required. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data in submitted paper vaccinee questionnaires.

9.7.5 Analysis of participation rate

9.7.5.1 *HCP survey*

The following different cases will be distinguished:

- HCPs who do not participate (R): HCPs who do not respond or that explicitly indicate their refusal to participate.
- HCPs with partially answered questionnaires (P): HCPs click on the link provided in the invitation email, and who begin answering the questionnaire but never submit it.
- Failed screening (F): HCPs who will not be eligible for the survey (HCPs who will not meet inclusion criteria and/or who will meet any of the exclusion criteria).
- HCPs with completed questionnaire (C): HCPs who complete the entire questionnaire and submit it.
- Contacted HCPs: HCPs who are contacted by phone or who receive a web link to the online survey via email = C+P+R+F.
- HCPs who agree to participate: HCPs willing to participate in the survey (e.g. by clicking on the link provided in the invitation email) = P+C.

The HCPs participation in the survey will be examined as follows:[25]

- Response rate $= \frac{C}{C+P+R}$

- Refusal rate $= \frac{R}{C+P+R}$

For HCPs, R, P, F, C and response and refusal rates criteria will be presented overall and by region.

9.7.5.2 *Vaccinees survey*

- Vaccinees with partially answered questionnaires (P):
    - For web survey: Vaccinees who click on the link provided and who begin answering the questionnaire but never submit it.
    - For paper survey: Vaccinees who return partially completed paper questionnaires directly to IQVIA in a prepaid envelope.
- Failed screening (F): Vaccinees who will not be eligible for the survey (vaccinees who will not meet inclusion criteria and/or who will meet any of the exclusion criteria).
- Vaccinees with completed questionnaire (C): Vaccinees who complete the entire questionnaire and submit it (for web) or return to IQVIA (for paper).

For vaccinees, only C, P and F criteria will be presented overall and by region.

9.8 QUALITY CONTROL

9.8.1 Data collection, validation, and data quality control

Data will be collected using a web/paper-administered questionnaire to HCPs and vaccinees. The survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

Data from the web-based questionnaire will be collected using an electronic data capture (EDC) system developed following a full validation process. Similarly, data from the paper questionnaire will be entered into the EDC and thereafter validated along with the data collected via the web-based questionnaire. A rigorous System Development Life Cycle that complies with IQVIA Primary Intelligence information technology SOPs will be used for validation. The programmed survey will be tested and validated in accordance with IQVIA SOPs, which cover validation for all clinical and risk management-related applications. The internet-based repository will be used to store survey data and other relevant programme information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead without answering the previous question. Response options presented in a list are randomised to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation. Collected data will be entered and stored in a database specific to the survey. The HCP-identifying information will be stored separately from survey data.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values
- Cross-check the consistency of data for related variables (if feasible).

The number of variables with missing values will be indicated. Missing values are excluded from the calculation of percentages. The study database will be locked once validated.

9.8.2 Data quality control at site level

Not applicable.

9.8.3 Safeguards, security, and traceability of contacts

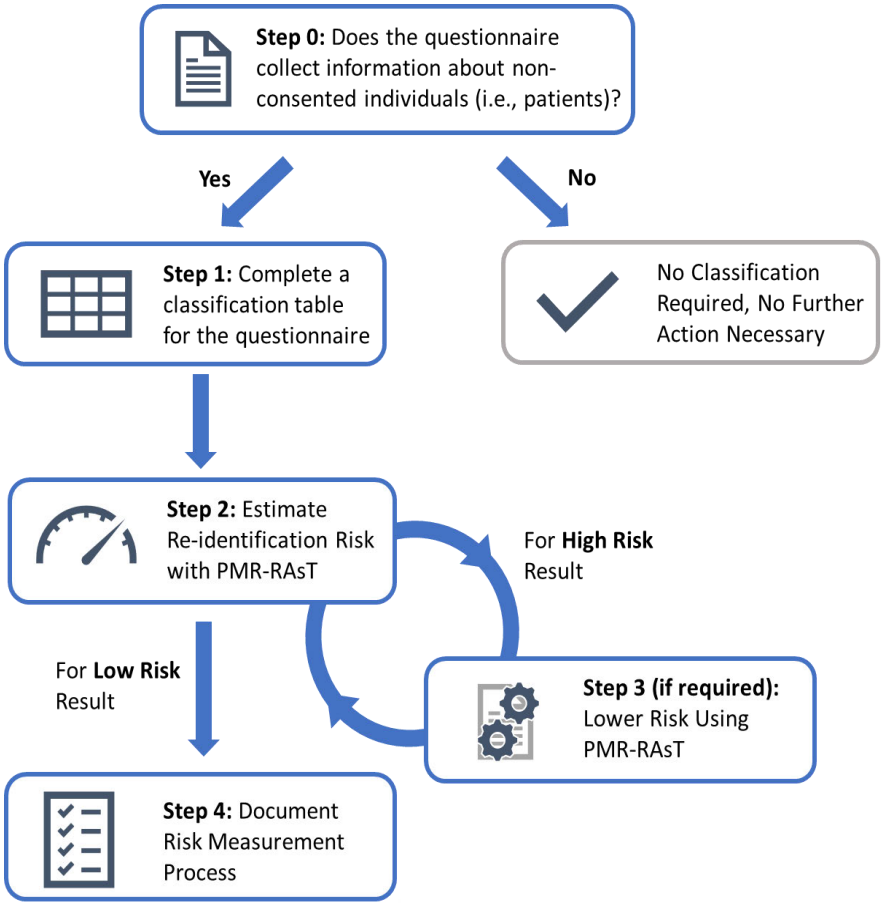
Operators of the call centre specialised in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts and phone calls will be traced using the management software. All survey aspects from protocol development to the reporting of the results will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions. These SOPs can be referred on site.[26]

9.8.4 Compliance to privacy regulations

To be compliant with the privacy regulations, the vaccinee questionnaire will be assessed with the IQVIA RAsT tool, which is developed to assess the risk of patient re-identification. The tool and attendant methodology meticulously check whether the project design and questionnaire could lead to patient identification, even before data collection has been initiated. Not only does the tool show the extent of project risk, but it also provides the researcher with the ability to check the variables that trigger the risk and recommends modifications to these variables.

The evaluation steps are depicted below:

Figure 1 Overview of Quality Control Process



Abbreviations: PMR-RAsT: Primary market research-risk assessment tool

The IQVIA Quality Management System (QMS) is built upon the quality and regulatory compliance principles established by the standards and guidelines from the International Standards Organisation and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The QMS encompasses all matters that individually or collectively influence the quality and regulatory compliance of the offerings in scope and defines systems, processes, and tools that enable the proposal to meet the appropriate quality standards and Good clinical practice compliance requirements. IQVIA has implemented an effective support network to ensure that the QMS is embedded across all projects.

1. At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA QMS and in accordance to the appropriate global procedures.

2. A Quality Control checklist will be developed and executed for the study, which will include Quality Control on study methodology, SAP, programming, data management and analysis, study results, conclusions, and study report.

3. Furthermore, the study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.

4. Individuals responsible for the execution of the specific Quality Control steps must have knowledge, capability, and experience which are adequate for the task.

5. The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required correction actions, if any.

6. The execution of any required corrective action will be documented.

Also, the Principal Investigator of the study will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure. Examples might be to check the following:

- The data are correctly anonymised
- The variables are in the expected format
- The range of each variable is as expected (e.g. no negative ages)

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Strengths

1. Questionnaire design and testing

- Both web questionnaires include general questions followed by specific ones. They include both open and closed questions. As the participants (HCPs and vaccinees) may understand the right answer in subsequent questions, it will not be possible to go back in the questionnaire and edit answers in former questions.
- Both questionnaires will be tested for their clarity. It will also be checked whether there are questions which would suggest a specific answer for any reason, for example social desirability.

2. Experience in drug safety and the evaluation of risk minimisation measures

The study will be conducted by an experienced team specialised in the design and conduct of such surveys in this safety area. It follows IQVIA SOPs, as well as the methodological guidelines from ENCePP and EMA GVP.

3. Quality control and compliance

The information contained in the file of each region of UK (which includes Wales, Scotland, Northern Ireland, England) is updated constantly with proactive updates. Quality controls are implemented on a regular basis by our teams.

In addition, IQVIA has developed a unique risk assessment tool, the IQVIA RAsT, to assess the risk of patient re-identification and ensure compliance with privacy regulations (please see Section 9.8.4).

9.9.2 Limitations

1. Bias

Selection bias

a. HCPs survey

The potential for selection bias of HCPs participating in a survey is an inherent limitation to any study based on volunteer participation. For instance, it is possible that HCPs willing to participate in the study will have the highest awareness of risks associated with use of STAMARIL®. In order to quantify any selection bias, the distribution of each stratification criterion of HCPs (region, HCP profession, and other demographic information collected) will be compared between participants and non-participants.

Non-response bias may also be introduced into the study if targeted HCPs have activated filters in their mailbox that block spam and unsolicited emails. If a very strict degree of message filtering is set, they may not even see the invitation to participate in the survey. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the HCPs do not check their emails frequently, they will not receive the invitation during the recruitment period. Some HCPs who are sent a letter may not receive it. This is one of the reasons why the HCPs will also be contacted by phone.

b. Vaccinee survey

For the vaccinees' recruitment by HCPs (who participate or do not participate in the HCPs' survey [in case the target vaccinee sample size is not achieved]), who are aware of the UK (STAMARIL®) yellow fever pre-vaccination checklist and provide the STAMARIL® PIL to the vacinees are more likely to participate in recruiting vaccinees for the patient survey.

HCPs will consecutively solicit vaccinees for participating in the survey. The recruitment of vaccinees will occur in the defined study period and until the limit of ten vaccinees per YFVC is reached. Although consecutive recruitment should minimise selection bias, HCP compliance to this approach cannot be verified. The characteristics of the vaccinees who will not fulfil eligibility criteria cannot be captured, so it is not possible to know the extent of the selection bias.

Information bias

Recall bias may lead to an underestimation of the HCP recalling having received aRMMs. To mitigate the risk of recall bias for HCPs, they will be recruited in the survey if they have provided consultation and/or administered yellow fever vaccines in the past 12 months. Also, to mitigate the risk of recall bias for vaccinees or their parents/guardians if vaccinees are younger than 18 years old, they will be immediately provided with material for the web/paper survey after receiving the vaccine/consultation.

Moreover, web surveys may promote social desirability bias, which refers to the tendency of HCP to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. physicians can copy-paste information gathered online instead of giving their own opinions.[27] Social desirability can affect the validity of survey research findings, but the use of prepopulated items in the questionnaire could/tends to reduce this bias. The access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once, and a traceability system. Thus, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

2. Generalisation of the survey results to the overall target population

In such surveys, the generalisation and external validity of the results is restricted to HCPs/vaccinees who can be reached and are willing (and able) to answer a questionnaire online or paper questionnaire (only for vaccinees). These HCPs/vaccinees may not be fully representative of the whole target population.[27]

Although the raw survey results cannot be generalised to the overall target population, a sample adjustment will be implemented to allow the generalisation of the results. For more transparency and accuracy, both unweighted (i.e. raw data) and weighted results by region will be presented in the report.

9.10 OTHER ASPECTS

9.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant independent ethics committee for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented only after approval or a favourable opinion has been obtained.

9.10.2 Study Management

This study will be performed by IQVIA, with guidance, input, review, and approval of MHRA, including development of materials, recruitment, training and management of sites, EDC, data management and analysis.

10 PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study Sponsor. Data collected will absolutely remain confidential, and only aggregated data will be analysed and communicated in a report.

HCPs and vaccinees (or their parents/guardians if vaccinees are younger than 18 years old) participating in the survey will be informed about the purpose of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data. IQVIA will ensure that the national and European data protection and ethical requirements are met for the HCPs and vaccinees, whenever applicable. This will be done electronically.

10.1 RESPONSIBILITIES OF THE INVESTIGATOR/HEALTHCARE PROVIDERS

Not applicable.

10.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH/MAH representative is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH/MAH representative is responsible for:

- Submission(s) to the MHRA complying with data protection rules.
- Any other local submission(s), *if applicable*.

10.3 ETHICAL, REGULATORY, AND ADMINISTRATIVE RULES

10.3.1 Laws and regulations

The survey will follow the regulatory and ethical requirements of the UK. This study will be conducted in accordance with the Module VIII of the GVP and Guidelines for Good Pharmacoepidemiology Practice (GPP).

As this survey is about the collection of opinions rather than healthcare data, it is technically considered as a market research in most countries. IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines.[28]

All necessary regulatory submissions (e.g., Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC), if applicable) are performed in accordance with local regulations, including local data protection regulations.

10.3.2 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable privacy & data protection laws and regulations, including the General Data Protection Regulation (GDPR).

Participants will access the website via a personal secure link. This link is unique to each participant.

Only aggregated data and presented as a synthesis will be transmitted to the MAH.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent others from accessing the data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. For the paper questionnaire, it will be stored at the IQVIA location where it is posted.

Description of all elements of security and traceability will be available upon request.

10.3.3 Dissemination of study data

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organisations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “The European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to HCPs and Healthcare Organisations”.

10.3.4 Insurance

No insurance is required, since this is a survey with no risk to the participants. The study will operate under real clinical practice conditions.

10.3.5 Secrecy agreement

Not applicable.

10.3.6 Record retention

The study documentation will be stored in the study master file. The web questionnaires data will be stored on the survey database for five years.

Data storage will be in line with national data protection requirements for the UK.

All documentation pertaining to the study, including paper and electronic records, will be retained for a minimum of five years after the end of the study, in accordance with IQVIA SOPs.

10.3.7 Discontinuation of the study

Sanofi can decide at any time and for any reason to discontinue the study.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC), and Competent Authorities should be informed.

10.3.8 MAH/MAH representative audits and inspections by competent authorities

Not applicable

10.3.9 Compensation

HCPs will be offered a compensation for the time they will spend while participating in this survey (which they may refuse). The time to complete the survey is estimated to be between 10 to 15 minutes. If at least one vaccinee, who is recruited by an HCP, completes the survey a fixed amount of compensation will be given to that HCP.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, which states:

“When it is necessary to compensate an HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCPs' participation in the survey. They must be declared to the tax authorities in accordance with applicable laws”.

Vaccinees will be offered an honorarium for the time they will spend while participating in this survey (which they may refuse). The time to complete the survey is estimated to be up to 5 minutes. The amount of the honorarium will be determined according to fair market value.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

It should be noted that this study is not designed to collect information on individual AEs. In the event any adverse reactions to STAMARIL® are identified during the study, IQVIA will report them using the MAH AE form (Annex 5) via email (*see* Section 11.1.3) within one working day from discovery as per Company policy on safety reporting and HCP guide.

Any AE information received will be documented and reported following the EMA Guideline on GPP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products[29] and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004).[30]

11.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations and Sanofi internal procedures.

11.1.1 Definitions of adverse event (AE) and serious adverse event (SAE)

An **AE** is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **SAE** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event.

Medical and scientific judgement should be exercised in deciding whether expedited 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 participant or may require medical or surgical intervention (i.e., specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

11.1.2 Adverse event of special interest

Not applicable.

11.1.3 Obligations of the Investigator regarding safety reporting

All adverse events must be reported by IQVIA to the MAH within one working day via email to uk-drugsafety@sanofi.com or fax to 0800 471 6122.

11.2 SAFETY OBSERVATIONS

Not applicable.

11.3 OBLIGATIONS OF MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH representative will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations.

The MAH will report all safety observations, if any, made during the conduct of the study in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorisation of the MAH/MAH representative conducting the study.

The survey will be registered in EU PAS register (currently the ENCePP e-register of studies) according to MAH preferences.

A survey report including the results of the study will be written in English, using MAH template which is based on the template included in the GVP module VIII and following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations in MS Word format.[31] The final survey report validated by the MAH will be communicated to health authorities.

An abstract of the study results may be also entered into the ENCePP database, according to MAH preferences.

12.2 PUBLICATIONS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the MAH is responsible for presentations and/or publications. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a steering committee/coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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ANNEXES

Annex 1 List of stand-alone documents

Number	Date	Title
1	10 October 2022	HCP questionnaire
2	31May 2023	Vaccinee questionnaire

Annex 2 ENCePP checklist for study protocols

Study title: Effectiveness evaluation of the local additional risk minimisation measures for STAMARIL® in the United Kingdom: a survey for healthcare professionals and vaccinees

EU PAS Register® number: **Study reference number : STA00059**

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
1.1.1	Start of data collection[6]	☒	☐	☐	
1.1.2	End of data collection[7]	☒	☐	☐	6
1.1.3	Progress report(s)	☐	☐	☒	
1.1.4	Interim report(s)	☐	☐	☒	
1.1.5	Registration in the EU PAS Register®	☒	☐	☐	
1.1.6	Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	
2.1.2	The objective(s) of the study?	☒	☐	☐	
2.1.3	The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4	Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5	If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[6] 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.

[7] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
4.2.1	Study time period	☒	☐	☐	
4.2.2	Age and sex	☒	☐	☐	9.2.2.1
4.2.3	Country of origin	☒	☐	☐	
4.2.4	Disease/indication	☐	☐	☒	
4.2.5	Duration of follow-up	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.2

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.2

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				9.4
9.1.1	Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2	Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3	Covariates and other characteristics?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:				
9.2.1	Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2	Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3	Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3	Is a coding system described for:				
9.3.1	Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.3.2	Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3	Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☒	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8	Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.1
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8.1
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	9.8.1

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias? 12.1.2 Information bias?	☒ ☒	☐ ☐	☐ ☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

There is no placeholder for deviation

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.2

Comments:

Name of the main author of the protocol: [redacted]

Date: 10 October 2022

Signature: _____

Annex 3 UK (STAMARIL®) yellow fever pre-vaccination checklist

CHECKLIST TO COMPLETE PRIOR TO ADMINISTRATION OF YELLOW FEVER VACCINE

This checklist is intended for use by registered healthcare professionals in the United Kingdom who have been designated in the administration of yellow fever vaccine (Stamaril) by the National Travel Health Network and Centre (NaTHNaC) in England, Northern Ireland and Wales or Public Health Scotland (PHS) in Scotland

This checklist must be used as part of the travel health consultation in order to determine:

- If yellow fever vaccination is indicated for the intended destination(s), based on WHO International Health Regulations[1]
- If there are any contraindications, warnings or precautions for use of yellow fever vaccine in the individual

This checklist should support appropriate evaluation of whether the benefit of vaccination outweighs the risk for the individual

This checklist is not a replacement for the full travel health risk assessment by a qualified practitioner[1]

Yellow fever vaccine must only be administered in a registered Yellow Fever Vaccination Centre by registered healthcare professionals who have completed the yellow fever training programme run by NaTHNaC in England, Wales and Northern Ireland or PHS in Scotland.

If there is any doubt to the Traveller's suitability for yellow fever vaccine, delay vaccination and seek expert advice from NaTHNaC (www.travelhealthpro.org.uk or 0845 602 6712) or Public Health Scotland (www.TRAVAX.nhs.uk or 0141 300 1164).

1.	**Gender (M/F):**
2.	**Traveller's age:**
3.	**Intended date of Travel:**
4.	**Travel destination(s) (please specify countries/areas to be visited, including during transit):** …… **Individuals should not receive the vaccine if they travel to a country without an ongoing risk of YF transmission at the time of travel.** **Is the need for YF vaccine supported by a current or periodic risk of yellow fever transmission?** **Yes ☐** **No ☐** **Is there a country requirement for an international certificate of vaccination or prophylaxis (ICVP)[2]?** **Yes ☐** **No ☐** **For details of recommendations and country requirement at entry please refer to:** • **England, Northern Ireland and Wales: TravelHealthPro (www.travelhealthpro.org.uk or 0845 602 6712)** • **Scotland: TRAVAX (www.travax.nhs.uk or 0141 300 1164)**

Contraindications: Stamaril must <u>not</u> be administered if 'yes' is ticked for any of these questions as these are likely to increase the risk of serious and/or life-threatening adverse reactions:	Please Tick	
	Yes	**No**
5. **Does the Traveller have any severe hypersensitivity to YF vaccine components, particularly to eggs or chicken protein?**		
6. **Has the Traveller ever experienced severe hypersensitivity reaction to a previous yellow fever vaccine or any of its components?**		

[1] For updated yellow fever vaccination requirements and recommendations consult the WHO dedicated website www.who.int/news-room/fact-sheets/detail/yellow-fever# or refer to resources provided by national health authorities. Country requirements are subject to change at any time; it is important for travellers to ensure that they know the requirements of the country to which they are travelling by checking with the relevant consulate or embassy.
[2] A registered healthcare professional who has completed the Yellow fever training programme

7. **Does the Traveller have any current or recent immunosuppression?** (e.g. primary immunodeficiency, symptomatic HIV infection, asymptomatic HIV infection accompanied by evidence of impaired immune function, leukaemia or lymphoma, recent bone marrow transplant, treatment with high dose systemic corticosteroids, or any other medicinal products including biologicals with known immunosuppressive properties, radiotherapy, cytotoxic drugs or any other condition which may result in immunocompromised status)		
8. **Does the Traveller have current or history of thymus dysfunction** (e.g. myasthenia gravis, Di George syndrome), **thymoma?**		
9. **Does the Traveller have a history of thymectomy (removal of thymus gland for any reason, including incidental thymectomy)?**		
10. **Is the Traveller currently experiencing a moderate/severe febrile illness or acute illness episode (temporary contraindication until illness resolves)?**		
11. **Is the Traveller aged less than 6 months?**		

Precautions: If any of the following apply, Stamaril should only be administered following a full evaluation of the specific risks and benefits and review of section 4.4 and 4.6 of the SmPC:	**Yes**	**No**
Age 1. **Is the Traveller aged 60 years or over?** There is an increased risk of serious and potentially fatal adverse reactions in persons aged 60 years and over (refer to Notes for further information). Stamaril should be administered only when there is a significant and unavoidable risk of acquiring yellow fever infection, such as travel to an area where there is an ongoing risk of yellow fever transmission at the time of travel - this excludes travel to areas in which vaccination is 'not generally recommended or not recommended by WHO. Refer to the WHO list of countries with risk of yellow fever transmission (https://www.who.int/publications/m) or to resources provided by national health authorities (as above). 2. **Is the Traveller aged 6-9 months?** Children aged from 6 months up to 9 months are at increased risk serious neurological adverse reactions and should only be vaccinated under special circumstances (e.g. during major outbreaks) and based on official advice. Expert advice should be sought on whether to vaccinate.		
Pregnant and breast-feeding women There is a probable risk of transmission of the vaccine virus to infants from breast-feeding mothers. Stamaril should not be given to nursing mothers unless when clearly needed such as during an outbreak control and following a full evaluation of the potential risks and benefits. There is insufficient information on the safety of administration during pregnancy. The vaccine should be given to pregnant women only when clearly needed and only after careful consideration of the potential risks and benefits: 3. **Is the Traveller breastfeeding and cannot discontinue for at least 14 days following vaccination?** 4. **Is the Traveller pregnant or planning a pregnancy within 1 month following vaccination?**		

Administration of Stamaril recommended?

☐ Yes (include rationale for vaccination if 'Yes' to any of the above):

Rationale:

☐ Was the traveller informed of risks associated with vaccination

☐ Was a patient information leaflet (PIL) provided

☐ No:

Name of registered healthcare professional: Date

Notes: (This checklist is not a replacement for a full travel health risk assessment)

- **For updated yellow fever vaccination requirements and recommendations consult the WHO dedicated website www.who.int/news-room/fact-sheets/detail/yellow-fever# or refer to resources provided by national health authorities (England, Northern Ireland and Wales: National Travel Health Network and Centre (NaTHNaC)** http://travelhealthpro.org.uk; Scotland: TRAVAX www.travax.nhs.uk) .
- The vaccine should be given at least 10 days before entering an endemic area since protective immunity may not be achieved until at least this time has elapsed.
  Those aged 60 years and older may have an increased risk of serious and potentially fatal adverse reactions (including systemic and neurological reactions persisting more than 48 hours, YEL-AVD and YEL-AND):
  Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD) which can result in multiorgan failure
  Yellow Fever Vaccine-Associated Neurotropic Disease (YEL-AND) which can affect the peripheral or central nervous systems[3]
  Revaccination is not generally recommended for most healthy travellers. The duration of protection following administration of one single dose of STAMARIL is expected to last at least 10 years and may be lifelong. However, revaccination may be required in certain groups.

[3] For further information refer to Commission on Human Medicines (CHM) report https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-benefit-risk-and-risk-minimisation-measures-of-the-yellow-fever-vaccine

Additional information resources include the Stamaril Summary of Product Characteristics, the yellow fever chapter in the online Green Book (Immunisation against infectious disease), and the World Health Organisation webpages on yellow fever.

Annex 4 NaTHNaC/PHS yellow fever pre-vaccination checklist (Traveller's checklist)[12]

NaTHNaC

Public Health Scotland

Checklist: yellow fever vaccine

This pre-vaccination checklist assists your healthcare professional to assess the risk of giving you yellow fever vaccine, **they must review the checklist** to ensure the vaccine is safe for you.

If you have any questions, concerns or do not understand anything please ask your healthcare professional to explain during your consultation.

If you answer 'yes' to any questions, you need to give more details during your consultation.
To read more about why these questions are important, please see **page 3** and **page 4** of this form.

Q1	How old are you?		
Q2	Are you feeling unwell today?	Yes ☐	No ☐
Q3	Do you have any allergies, particularly to eggs or chicken protein?	Yes ☐	No ☐
Q4	Have you ever reacted to a previous yellow fever vaccine?	Yes ☐	No ☐
Q5	Do you have cancer or have you had cancer in the past (even if it was a long time ago)?	Yes ☐	No ☐
Q6	Do you have any illness that might affect your immune system? For example, leukaemias, lymphoma, cellular immune deficiencies, chronic lymphoproliferative conditions, or if you have ever received a stem cell transplant.	Yes ☐	No ☐
Q7	Are you living with HIV?	Yes ☐	No ☐
Q8	Are you taking any medicines (now or within the last year) that affect your immune system? For example, steroids, biological or non-biological immune modulating medicines, treatment following an organ transplant.	Yes ☐	No ☐
Q9	Are you having chemotherapy or radiotherapy (now or within the last year)?	Yes ☐	No ☐

Q10	Have you ever been told that you may have a problem with your thymus gland (includes myasthenia gravis or a thymoma)?	Yes ☐	No ☐
Q11	Have you had an operation to remove your thymus gland (thymectomy) for any reason including during cardiac surgery?	Yes ☐	No ☐
Q12	Have you ever had open chest surgery?	Yes ☐	No ☐
Q13	Are you pregnant or planning a pregnancy?	Yes ☐	No ☐
Q14	Are you breast feeding?	Yes ☐	No ☐
Q15	Do you have a first-degree family relative (i.e. a blood relative – mother, father, full brother, sister or child) who has had a serious adverse reaction to yellow fever vaccine?	Yes ☐	No ☐

! **I have read the above and confirm that the questions have been answered to the best of my knowledge.**

Name of patient	Signature of patient	Date (dd/mm/yy)

If applicable

Name of parent/guardian	Signature of parent/guardian	Date (dd/mm/yy)

Form reviewed and risk assessment carried out by

Reviewed by	Qualifications	Date (dd/mm/yy)

Why are these questions important?

How old you are

Babies

- There is a greater risk of yellow fever vaccine related brain inflammation (encephalitis) in very young babies. Babies aged less than six months should not have yellow fever vaccine and babies aged six to nine months should only be given this vaccine if the risk of yellow fever at the destination to be visited is high, such as during epidemics/ outbreaks, and travel is unavoidable.

Aged 60 years or older

- You are at increased risk of developing serious side effects from the vaccine compared to younger travellers. If you are travelling to areas where yellow fever vaccine is 'generally not recommended' you should not receive vaccine. Further information is available in the **NaTHNaC Yellow Fever Information Leaflet for Travellers** and on the **FitForTravel Yellow Fever Vaccine page**.

How you are feeling today

- Minor illness without high temperature (fever) should not usually delay your yellow fever vaccination. However, vaccination may be postponed until you have fully recovered. This is to make sure any symptoms are not confused with possible reactions to the vaccine.

Your allergies and previous reactions to yellow fever vaccine

- This vaccine may contain traces of egg, chicken protein and other ingredients that some people are occasionally allergic to. If you have ever had a serious reaction (anaphylaxis) to any of the vaccine ingredients, you must tell your health professional; you will not usually be able to receive yellow fever vaccine.

Your general health and any condition or treatment that may affect your immune system

- This vaccine contains live yellow fever virus that has been weakened. Your response to the vaccine may not be so good if your immune system is weakened by certain illnesses or treatments, but occasionally the vaccine can still be given. However, if your immune system is very weak you must not receive yellow fever vaccine as you are at risk of developing serious side effects from the vaccine, including death.

If you have ever been told that you may have a problem with your thymus gland (includes myasthenia gravis or a thymoma), or if you ever had open chest surgery

- The thymus gland is part of your immune system and sometimes does not work properly or has been removed (thymectomy). Myasthenia gravis is a disease that may involve your thymus gland. If you have a history of any of these conditions, you must not receive yellow fever vaccine as you are at risk of developing serious side effects, including death.
- The thymus gland may be removed during chest surgery. Yellow fever vaccine can still be given in some instances following chest surgery.

If you are planning a pregnancy, pregnant now or breast-feeding

- If you are planning a pregnancy, it is recommended to wait until 28 days after yellow fever vaccination before getting pregnant (conceiving).
- Safety of yellow fever vaccine during pregnancy is not clear, although increased complications for mother or baby have not been reported when the vaccine was given during pregnancy. Discussion with a health professional about the risks and benefits of this vaccine during pregnancy will help you decide whether yellow fever vaccination is right for you at this time.
- You are encouraged to continue breast-feeding during your trip. Several very young (less than two months old) breast-fed babies developed brain inflammation shortly after their mothers' yellow fever vaccination. Discuss with a health professional whether the risk of yellow fever at your travel destination is sufficiently high for yellow fever vaccination to be recommended.

If you have a first-degree family member who has had a serious adverse reaction to yellow fever vaccine

- If such a reaction was not due to a known medical risk factor, it is possible that you may be susceptible to developing a serious adverse reaction due to an unidentified genetic reason.

If you cannot have the yellow fever vaccination, and travel to areas where yellow fever occurs cannot be avoided, you still need advice about yellow fever certificate requirements and how to avoid mosquito bites.

Please check the following websites for further information and updates:

- **TravelHealthPro** – **www.travelhealthpro.org.uk/countries**
- **Fit for Travel** – **www.fitfortravel.nhs.uk/yellow-fever-vaccine**

For healthcare professionals:

- **TravelHealthPro** – **www.travelhealthpro.org.uk**
- **TRAVAX** (Scotland) – **www.travax.nhs.uk/yellow-fever**

Annex 5 AE Form

Unsolicited Individual Safety Information (ISI) Report Form

Grey fields are for Sanofi use only

1 ADMINISTRATIVE SECTION FOR AFFILIATE/PARTNER ONLY

Company contact date: Click or tap to enter a date. Local PV receipt date: Click or tap to enter a date.

Country of Occurrence: Click here to enter text.

Social Media case: Yes ☐ No ☐ If Yes: Name of the social media: Click here to enter text.

☐**INITIAL** ☐ **FOLLOW-UP** Global Safety Database ID: Click here to enter text.

Local Reference ID: Click here to enter text. Local PTC ID: Click here to enter text. Global PTC ID: Click here to enter text.

2 PATIENT

Title, Name (first, middle, last)/Initials: Click here to enter text. Gender: F ☐ M ☐ Unk ☐

Address, city, postal code, state: Click here to enter text.

Country: Click here to enter text. Phone: Click here to enter text.

Email address: Click here to enter text.

2 PATIENT

Date of Birth (DD/MM/YYYY): Click or tap to enter a date. Age or Age Group (at time of the reaction)**:** Click here to enter text.

Height: Click here to enter text. cm/feet & inches Weight: Click here to enter text. kg/lb Registry ID #: Click here to enter text.

3 REPORTER

First Name: Click here to enter text. Last Name: Click here to enter text.

Occupation: Click here to enter text.

Address: Click here to enter text.

Zip / Postal Code: Click here to enter text.

Country: Click here to enter text.

Phone: Click here to enter text.

Fax: Click here to enter text.

E-mail address: Click here to enter text.

If the primary reporter is a consumer, is contact information provided for a HealthCare Professional? *Yes ☐ No ☐ NA ☐

If your country requires patient consent to contact the HCP, has the patient given their consent? *Yes ☐ **No ☐ NA ☐

*If YES, attempts should be made to contact the HCP **If NO, do not contact the HCP and document the exchange

Was FU request sent to reporter? Yes ☐ No ☐ NA ☐

3 REPORTER

The reporter will not have any further information ☐

The reporter does not wish to be contacted by the Pharmacovigilance Department ☐

4 SUSPECT MEDICATION / MEDICAL DEVICE (MD) / VACCINE (V)

Brand Name /INN	Indication	Dosage/ Unit/ Frequency/ Amount	Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO)	Start Date (DD/MM/YYYY)	Stop Date or duration (DD/MM/YYYY)	Route of Administration	Company product (Yes/No)	Primary/Booster (V)	Site of Injection (V)	Side (V)
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										

Is medical device available for evaluation (MD)? ☐Yes ☐No *Did the problem occur with initial use or during re-use of the medical device (MD)?* ☐Yes ☐No
For company suspect product inappropriately used as per local Marketing Authorization: *Is it intentional?* ☐Yes ☐No ☐Unk *at the initiative of* ☐HCP ☐Consumer ☐Unk *for a therapeutic purpose?* ☐Yes ☐No ☐Unk
Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions): Click here to enter text.

5 CONCOMITANT MEDICATION / MEDICAL DEVICE / VACCINE

Brand Name /INN	Indication	Dosage/ Unit/ Frequency/ Amount	Batch Number	Start Date (DD/MM/YYYY)	Stop Date or duration (DD/MM/YYYY)	Route of Administration	Company product (Yes/No)	Primary/ Booster (V)	Site of Injection (V)	Side (V)
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										

5 CONCOMITANT MEDICATION / MEDICAL DEVICE / VACCINE

Click here to enter text.										
Click here to enter text.										

Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions): Click here to enter text.

6 REACTION DESCRIPTION

Reaction	Date of Onset (DD/MM/YYYY)	Stop Date or Duration (DD/MM/YYYY)	Outcome	Corrective Treatment	Action Taken	Did reaction abate after product was stopped?	Did reaction recur after product was started again?	Kind of Reaction (V)	Lack of efficacy / failure (V)
Click here to enter text.									
Click here to enter text.									
Click here to enter text.									
Click here to enter text.									
Click here to enter text.									

7 DESCRIPTION OF THE CASE *(signs & symptoms, possible causes, progression, treatments, relevant medical history, investigations, severity ….)*

Click here to enter text.

8 ONGOING ILLNESS / MEDICAL HISTORY / RISK FACTORS

Personal *(if relevant for the reaction described in this form)*: Click here to enter text.

Family *(if relevant for the reaction described in this form)*: Click here to enter text.

9 HISTORY OF ADVERSE REACTION TO PREVIOUS ADMINISTRATION OF VACCINE (V)

Product Name / Therapeutic Class	Date of Occurrence (DD/MM/YYYY)	Reaction	Duration
Click here to enter text.			
Click here to enter text.			
Click here to enter text.			

Comments: Click here to enter text.

10 COMPLEMENTARY INVESTIGATIONS Type / Results *(indicate unit / attach photocopies if relevant. If patient died please specify if autopsy was performed and what was result)*

Click here to enter text.

11 SERIOUSNESS

☐**Non-Serious** ☐ **Serious (select at least one criteria below)**

☐Death *Date of Death:*Click or tap to enter a date. *Autopsy performed*: Yes ☐ No ☐ Unk ☐

☐Life threatening

☐Medically Significant (as per HCP)

☐Hospitalization or prolongation of hospitalization *Duration of hospitalization:* Click here to enter text.

☐Persistent or significant disability or incapacity

☐Suspected transmission of infectious agent

☐Congenital anomaly, birth defect

Was this reaction reported to Regulatory Authority? Yes☐ No ☐

NAME & SIGNATURE:

Annex 6 Assessment of success

6.1 Assessment of success (HCP questionnaire)

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
Knowledge and Understanding (5 questions)	Q1. According to your knowledge about the conditions of use for STAMARIL® (yellow fever vaccine), which of the following statements do you agree/disagree with? *Please select all options that apply*	Yes	Question completed correctly [5 points (3 True and 2 False)]	An HCP is considered successful for knowledge and understanding when he/she provides at least 22 out of 27 (80%) correct/desirable responses. Success for knowledge if ≥80% of HCPs are successful.
	Q2. According to your knowledge about the risks associated with STAMARIL® (yellow fever vaccine) administration, which of the following statements do you agree/disagree with? *Please select all options that apply*	Yes	Question completed correctly [4 points (2 True and 2 False)]	
	Q3. According to your knowledge about STAMARIL® (yellow fever vaccine), this vaccine is contraindicated in the following circumstances: *Please select all options that apply*	Yes	Question completed correctly [10 points (7 True and 3 False)]	
	Q4. According to your knowledge about the risks associated with STAMARIL® (yellow fever vaccine) administration, which of the following are the possible side effects of this vaccine? *Please select all options that apply.*	Yes	Question completed correctly [5 points (4 True and 1 False)]	

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
	Q5. According to your knowledge about STAMARIL® (yellow fever vaccine) administration to pregnant/breastfeeding women, which of the following statements do you agree/disagree with? *Please select all options that apply*	Yes	Question completed correctly [3 points (2 True and 1 False)]	
Awareness (2 questions)	Q6. Please select the option that best describes your experience with the standardised yellow fever pre-vaccination checklist(s).	Yes	Question completed desirably [Answers: 1 or 2 are desirable]	An HCP is considered successful for awareness when he/she is aware of the UK (STAMARIL®) yellow fever pre-vaccination checklist Success for awareness if ≥80% of HCPs are successful.
	Q7. Please select which of the following standardised yellow fever pre-vaccination checklist(s) you have received or are aware about: *Please select all options that apply*	Yes	Question completed desirably [Answer: 1 is desirable]	
Utilization (7 questions)	Q8. Please select the option that best describes your experience with the use of the yellow fever pre-vaccination (STAMARIL®) checklist issued by the Medicines and Healthcare products Regulatory Agency (MHRA)	Yes	Question completed desirably [Answers: 1 or 2 are desirable]	An HCP is considered successful for utilization when he/she utilizes either the UK (STAMARIL®) yellow fever pre-vaccination checklist or traveller checklist Success for utilization if ≥80% of HCPs are successful.
	Q9. Please select the option(s) that best describes why you never/rarely/sometimes use the yellow fever pre-vaccination (STAMARIL®) checklist issued by the Medicines and Healthcare products Regulatory Agency (MHRA)**:** *Please select all options that apply*	No	Complementary question	

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
	Q10. Please select the option(s) that best describes the challenges you face while using the yellow fever pre-vaccination (STAMARIL®) checklist issued by the Medicines and Healthcare products Regulatory Agency (MHRA): *Please select all options that apply*	No	Complementary question	
	Q11.Please select the option that best describes your experience with the use of the yellow fever pre-vaccination checklist (i.e. traveller checklist) issued by the National Travel Health Network and Centre (NaTHNaC) and Public Health Scotland (PHS)	No	Question completed desirably [Answers: 1 or 2 are desirable]	
	Q12. Please select the option(s) that best describes why you never/rarely/sometimes use the yellow fever pre-vaccination checklist (i.e., traveller checklist) issued by the National Travel Health Network and Centre (NaTHNaC) and Public Health Scotland (PHS): *Please select all options that apply*	No	Complementary question	
	Q13. Please select the option(s) that best describes the challenges you face while using the yellow fever pre-vaccination checklist (i.e., traveller checklist) issued by the National Travel Health Network and Centre (NaTHNaC) and Public Health	No	Complementary question	

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
	Scotland (PHS): *Please select all options that apply*			
	Q14. Please provide any additional comment you may have on the checklist(s).	No	Complementary question	
Distribution of the STAMARIL® PIL (2 questions)	Q15.Please select the option that best describes your experience with the delivery of the STAMARIL® (yellow fever vaccine) Patient Information Leaflet (PIL)	Yes	Question completed desirably [Answers: 1 or 2 are desirable]	An HCP is considered successful for delivery of the STAMARIL® PIL when he/she always/frequently distributes the STAMARIL® PIL
	Q16. Please select the option(s) that best describes why you never/rarely/sometimes deliver the STAMARIL® (yellow fever vaccine) Patient Information Leaflet (PIL): *Please select all options that apply*	No	Complementary question	

6.2 Assessment of success (Vaccinee questionnaire)

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
Awareness of STAMARIL® PIL (2 questions)	Q5. Please select the option that best describes your experience with the Patient information Leaflet for the yellow fever vaccine	Yes	Question completed desirably [1 point 1 or 2 is desirable]	A vaccinee is considered successful for receipt of STAMARIL® PIL information when he/she receives the yellow fever pre-vaccination checklist. Success for receipt if ≥80% of vaccinees are successful.
	Q6. Please provide any additional comment you may have on the Patient Information Leaflet for the yellow fever vaccine	No	Complementary question	