PASS INFORMATION

Title:	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Protocol version identifier:	203153 (EPI-PERTUSSIS-037 VS BR)
Date of last version of the protocol:	Final Version 1: 11 September 2015
EU PAS Register No:	To be determined.
Active substance:	Diphtheria toxoid, Tetanus toxoid, *Bordetella pertussis* antigens (Pertussis toxoid, Filamentous Haemagglutinin and Pertactin)
Medicinal product:	GlaxoSmithKline (GSK) Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine (Refortrix™) (263855)
Product reference:	DE/H/0210/001-002
Procedure number:	To be allocated.
Marketing Authorisation Holder (MAH):	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	To assess the risk of a series of pre-defined safety outcomes following routine vaccination with *Refortrix* in a cohort of pregnant women compared to a historical cohort of unvaccinated pregnant women in Brazil
Country of study:	Brazil
Authors:	**Contributing authors:** • [redacted] Director, Epidemiology • [redacted] Director, Epidemiology • [redacted] Epidemiologist • [redacted] Epidemiology Scientist • [redacted] Epidemiology Analyst • [redacted] Regional Epidemiology Director, LATAM • [redacted] Senior Epidemiologist, LATAM • [redacted] Project Statistician, Ningyang Group Co., for GSK Biologicals • [redacted] Lead Statistician • [redacted] Study Delivery Lead • [redacted] Local Delivery Lead, Quintiles, for GSK Biologicals • [redacted] Clinical Safety

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MARKETING AUTHORISATION HOLDER

MAH:	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person:	[redacted] Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium

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2. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ATP Cohort	According-To-Protocol Cohort
CARS	Computer Aided Regulatory Submission
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CONEP	Comissão Nacional de Ética em Pesquisa
D-Rh	Rhesus factor
eCRF	electronic Case Report Form
EMA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorisation Holder
MoH	Ministry of Health
OR	Odds Ratio
PAHO	Pan American Health Organization
PASS	Post-Authorisation Safety Study
PII	Personally Identifiable Information

PNI	National Immunization Program (Brazil)
QC	Quality Control
SAE	Serious Adverse Event
SDD	Statistical Analysis System Drug Development
TC	Total Cohort
Tdap	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine
TSS	Targeted Safety Study
UK	United Kingdom
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

[redacted] (Director, Epidemiology) is the GSK Biologicals designated contact person for this study.

Refer to Annex 4 for the list of principal and coordinating investigators.

4. ABSTRACT

Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Version and date of the protocol	Final Version 1: 11 September 2015
Main author	[redacted] GlaxoSmithKline Biologicals
Rationale and background	Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority of cases occurred in infants. The increased fatality rate in this group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started implementation of the maternal immunization program, administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date). The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under/over reporting, reporting bias and quality issues. Therefore, studies using appropriate designs that focus on regions where the maternal immunization program is starting can provide valuable information.
Research question and objectives	The aim of this retrospective study is to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates following the routine maternal *Refortrix* vaccination during pregnancy. The AEs identified for this study are those considered important in the context of maternal immunization [Zheteyeva, 2012; Kharbanda, 2014] and for which it would be feasible to obtain the required data (refer to section 10.1.2). The diagnosis of pregnancy-related AEs will follow the international case definitions (refer to Annex 7) and will be

obtained directly from the medical records. Since the vaccine is routinely administered in the third trimester of pregnancy, the events that are more commonly reported during this period have been chosen as primary endpoints.

Co-primary objectives:

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* as part of the maternal immunization program in Brazil (Exposed cohort) with a historical cohort of unvaccinated pregnant women before the implementation of this immunization program (Unexposed cohort).
- To compare the risk of preterm birth and small for gestational age in neonates born to subjects in the Exposed cohort and to subjects in the Unexposed cohort.

Secondary objectives:

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischaemic encephalopathy) in the Exposed and Unexposed cohorts.
- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.
- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Study design

- Type of design: An observational, retrospective, cohort, single-centre study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study population will consist of two cohorts:
  - Exposed Cohort (cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil)
  - Unexposed Cohort (historical cohort of unvaccinated pregnant women before the implementation of the immunization program)
- Data collection: electronic Case Report Form (eCRF) based on medical chart data.
- Period of data collection: The minimum period of the data collection is expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 will be included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects will be collected once the maternal immunization program is well implemented in Brazil and the inclusion of data will start from May 2015 till the Exposed cohort is enrolled completely.
  - Epoch 001: Retrospective data collection.

Population

The study population will consist of pregnant women aged between 18 and 45 years, who are residing in the study area (city of São Bernardo do Campo) and delivered in the 2 years before or during the period following the implementation of the PNI. The subjects who delivered in the study centre from May 2015 will be considered as potentially exposed subjects who had opportunity to receive vaccine and those who delivered before implementation of the PNI (September 2014) will be considered as potentially unexposed subjects. Subjects meeting all the inclusion/exclusion criteria will be eligible for enrolment in the study.

Variables

Co-primary endpoints:

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.

  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum).

- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.
  - Preterm birth
  - Small for gestational age

Secondary endpoints:

- Occurrence of pregnancy-related AEs of interest/ neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes.
  - Preterm premature rupture of membranes.
  - Premature uterine contraction.
  - Neonatal death.
  - Maternal death.
  - Still birth.
  - Neonatal hypoxic ischaemic encephalopathy.
- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Data sources

This retrospective study will use the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynaecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation will be done on the diagnosis or evaluation of these events and only the final diagnosis as described in the source document will be included in the study.

To evaluate the vaccination exposure, the information in the anamnesis and pregnancy card archived in the medical files will be used as the only source.

Study size

The planned sample size of this study is 2400 subjects. Using a two-sided (alpha = 0.01) test assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [1200 subjects in each cohort], will be needed to have more than 80% power to

detect a relative risk of 2 or higher.

Data analysis

The main analysis for co-primary objectives will contain only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects have missing vaccination date in the Exposed cohort, a sensitivity analysis will be performed with the imputed vaccination date to 27 completed weeks of gestational age.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy haemorrhage, preterm birth and small for gestational age) will be calculated. For each specific endpoint, the number of subjects where the event occurred (between the index date and the date of the delivery) will be divided by the total number of subjects at risk for both the Exposed and Unexposed cohorts respectively, together with its exact 95% confidence interval (CI).

The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage) will be pooled together as well as the birth outcomes (preterm birth and small for gestational age). The analysis of the risk for the pooled endpoints will be performed using the same method as for the separate co-primary endpoints.

The comparison of the risk with its two sided 95% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression. Univariate analysis will describe the association between Tdap vaccination status, maternal age, parity and gestational age.

A multiple logistic regression model will be fitted with a backward selection to identify the possible confounding factors for each of the primary outcomes using an alpha level of 0.1. Potential confounders will be parity, age of the mother at the start of the pregnancy and congenital anomalies (in parents or first degree relatives). Adjusted odds ratio (OR) and its 95% CI will be derived from the final model.

Milestones

Data collection is planned to start in Quarter 2-2016 and end in Quarter 4-2016. The final report of study results is planned in Quarter 2-2017.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	Quarter 2 2016
End of data collection	Quarter 4 2016
Final report of study results	Quarter 2 2017

7. RATIONALE AND BACKGROUND

7.1. Background

Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority of cases occurred in infants [WHO, 2014]. The increased fatality rate in this group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started implementation of the maternal immunization program [MoH, 2014], administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date).

Although the Tdap maternal immunization strategy has been implemented in the United Kingdom (UK), the United States of America (USA) and other countries, only limited data on the safety of *Refortrix* in pregnant women is available. The data from the Vaccine Adverse Event Reporting System (VAERS), pregnancy registries and case series have concluded that there is no indication of any safety concern about maternal, foetal and infant outcomes following vaccination during pregnancy with Tdap [Healy, 2006; Murphy, 2008; Gall, 2011; Zheteyeva, 2012; ACIP, 2013; CDC, 2015].

Immunization with inactivated vaccines during the last trimester of pregnancy can be beneficial because maternal antibodies can be transferred efficiently to the foetus across placenta, thus providing indirect protection to infants for the first months of life [Keller-Stanislawski, 2014]. Additionally, the risk of abnormal organogenesis is minimal at that gestational age.

7.2. Rationale

The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under/over reporting, reporting bias and quality issues. Therefore, observational studies using appropriate designs that focus on regions where the maternal immunization program is starting can provide valuable information.

A retrospective cohort study in this country will present a unique opportunity to continue monitoring the safety of this vaccine in a large population of vaccinated pregnant women, especially in the immediate period after introduction at the end of 2014 of this maternal immunization program. This study will generate safety data that could be used to complement other data generated by the Ministry of Health (MoH) in Brazil. Together, these should provide a comprehensive evaluation of routine maternal Tdap vaccination in Brazilian women.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this retrospective study is to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates. The AEs identified for this study are those considered important in the context of maternal immunization [Zheteyeva, 2012; Kharbanda, 2014] and for which it would be feasible to obtain the required data (refer to section 9.1.2).

The diagnosis of pregnancy-related AEs will follow the international case definitions (refer to Annex 7) and will be obtained directly from the medical records. The list of outcomes as potential pregnancy-related AEs of interest is derived from literature. Since the vaccine is routinely administered in the third trimester of pregnancy, the events that are more commonly reported during this period have been chosen as primary endpoints. Refer to Annex 2 for the definition of each of these events.

8.1. Co-primary objectives

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* as part of the maternal immunization program in Brazil (Exposed cohort) with a historical cohort of unvaccinated pregnant women before the implementation of this immunization program (Unexposed cohort).
- To compare the risk of preterm birth and small for gestational age in neonates born to subjects in the Exposed cohort and to subjects in the Unexposed cohort.

8.2. Secondary objectives

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischaemic encephalopathy) in the Exposed and Unexposed cohorts.

- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.

- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

9. RESEARCH METHODS

9.1. Study design

- Type of design: An observational, retrospective, cohort, single-centre study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study population will consist of two cohorts:
  - Exposed Cohort (cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil)
  - Unexposed Cohort historical cohort of unvaccinated pregnant women before the implementation of the immunization program)

  Refer to Section 9.3.1 for definition of the study cohorts.
- Data collection: electronic Case Report Form (eCRF) based on medical chart review.
- Period of data collection: The minimum period of data collection is expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 will be included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects will be collected once the maternal immunization program is well implemented in Brazil and the inclusion of data will start from May 2015 till the Exposed cohort is enrolled completely.
  - Epoch 001: Retrospective data collection.

The study cohorts and epoch foreseen in the study are presented in Table 1.

Table 1 Study cohorts and epoch foreseen in the study

Study Cohorts	Approximate number of subjects	Age (Min/Max)	Epochs
			Epoch 001
Exposed cohort	1200	18 years-45 years	x
Unexposed cohort	1200	18 years-45 years	x

Refer to Section 9.3.2 for definition of the endpoints.

9.1.1. Discussion of study design

Considering that *Refortrix* is now routinely recommended for all pregnant women in Brazil through the maternal immunization program, randomised controlled trials are not considered ethical. Therefore, an observational cohort study provides the opportunity to evaluate the safety of this routinely used vaccine.

The feasibility assessment (refer to section 9.1.2 for details) indicated that adequate and appropriate data exist and are available to allow a retrospective cohort design to be used, with the further advantage of being time efficient.

As maternal immunization with *Refortrix* is recommended by the Ministry of Health (MoH) and vaccine uptake is expected to be high with limited possibility to recruit contemporary unvaccinated pregnant women, the comparative cohort (Unexposed) will comprise a historical cohort of pregnant women who delivered in the same hospital (study centre) in the two years before implementation of the maternal immunization program with *Refortrix* (started in end of 2014) in Brazil.

Considering that more than 20% of the pregnant population in this area in Brazil are classified as high risk pregnancies (refer to Annex 6), excluding this group from the study would represent an important selection bias and it would decrease the representativeness of the study population. In addition, high risk pregnancy is not an exclusion criterion to receive the Tdap vaccination according to the maternal immunization guidelines in Brazil [ESC, 2014]. Therefore the study will include both low and high risk pregnancy women as determined and defined by local guidelines [MoH, 2010; MoH, 2012].

9.1.2. Feasibility assessment

A feasibility assessment was conducted in seven potential study centres from south-east Brazil during September 2014-November 2014.The objective was to assess the research capabilities and availability of data for the collection of pregnancy-related AEs and vaccination data, as well as to identify the most adequate study design for this setting. These sites were pre-selected based on their capacity to perform clinical research and with an available population of pregnant women that could be enrolled in the study. The results of this exercise demonstrated that at least three out of the seven centres evaluated have the potential to perform the study and have appropriate data available. The final decision to opt for a single centre was due to its recruitment capacity, completeness of records of the pregnancy-related AEs/birth outcomes and transcript information from antenatal care visits on vaccination exposure for the Exposed cohort. Refer to Annex 6 for details on the feasibility assessment.

9.2. Setting

9.2.1. Number of subjects/centres

The study will be conducted in a single centre in south-east Brazil. The subjects who delivered in the study centre from May 2015 will be considered as potentially exposed and those who delivered before September 2014 will be considered as potentially unexposed (the data of Unexposed subjects will be included for the period of September 2012 – August 2014). The estimated number of subjects to be included in each cohort (Exposed and Unexposed) is 1200 (total 2400 subjects). Refer to Section 9.5 for a detailed description of the criteria used in the estimation of sample size.

The study centre was selected based on the accuracy and completeness observed in the medical records. The selected study centre receives approximately 300 pregnant women per month for delivery. Refer to Section 9.2.5.1 for details on screening of the subjects.

9.2.2. Inclusion criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study or regulatory acceptability. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects between 18 and 45 years of age at the time of pregnancy under consideration for the study, who deliver in the study centre.

  Note: Only the latest pregnancy in the specified period will be included (to avoid multiple pregnancies from the same mother).

- Residents of the study area (city of São Bernardo do Campo).
- Subjects who were compliant with the routine antenatal care [Gestacao de Alto Risco, 2010; Cadernos de Attencao Basica, 2012], including at least one ultrasound assessment report early in the pregnancy.
- Subjects with the complete and relevant medical records available.

Inclusion criteria for the Exposed cohort:

- Subjects who received one dose of *Refortrix* vaccine in the recommended time period between 27 and 36 completed weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil, and according to the program recommendations from May 2015 onwards.
- Subjects with appropriate vaccination records.

Inclusion criteria for the Unexposed cohort:

- Subjects who had delivered in the same hospital (study centre) before 01 September 2014 (September 2012-August 2014) and who did not receive Tdap vaccination during pregnancy to the best knowledge of the investigator.

9.2.3. Exclusion criteria

The following criterion should be checked at the time of study entry. If the exclusion criterion applies, the subject must not be included in the study:

- Subjects who have been transferred to other specialised centres, where their medical records would be inaccessible for the study (private clinics, psychiatric or prison hospitals, other state hospitals, etc).

9.2.4. Outline of the study procedures

The study procedures consist only of the collection of retrospective data from the source documents (refer to section 9.4 for data sources) available at the study centre.

Table 2 represents the list of procedures in the study.

Table 2 List of study procedures

Epoch 001: Retrospective data collection from medical files	
Screening	○
Check inclusion/exclusion criteria	●
Allocate subject number	●
Obtain demographic data	●
Obtain medical history and gynaecological history	●
Obtain data on vaccination during the pregnancy (Exposed cohort)	●
Record any risk factor of interest *	●
Record clinical data on pregnancy relevant to the specified study period**	●
Record data from physical examination of the neonate	●
Record adverse pregnancy outcome and follow-up	●
Record intercurrent medical conditions and/or medications***	●
Study conclusion	●

● is used to indicate a study procedure that requires documentation in the individual eCRF. Details of the data to be collected in eCRF are presented in Annex 8.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
*Risk factors of interest: Refer to Section 9.3.3 for details.
**In case of multiple pregnancies, details of the latest pregnancy in the specified period will be included.
***The intercurrent medical conditions and/or medications reported at the time of delivery will be recorded.

The events of interest to be collected from the medical files are presented in Table 3.

Table 3 Events of interest to be collected from the medical files

Events*	Time point
Gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum)	After week 27
Preterm birth	After week 27 up to week 37
Small for gestational age	After week 27
Premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth, neonatal hypoxic ischaemic encephalopathy	After week 27
Congenital anomalies	After week 27 up to birth.

*For definitions, refer to Annex 2.

9.2.5. Detailed description of study procedures

9.2.5.1. Screening

Potential subjects in the age range for the study will be identified using the electronic admission listings at the centre. This will provide a list of total candidate subjects eligible for the study. For the Unexposed cohort, to reach an equal number of subjects who delivered in each of the two years, a random sample of subjects will be selected each month (using Microsoft Excel or equivalent application). This will enable identification of 50 eligible subjects per month to reach the required number of 600 subjects per year. In contrast, for the Exposed cohort, all subjects who delivered from May 2015 onwards will be considered sequentially for enrolment until the total number of 1200 is reached. This will facilitate investigating any trends over time in AE reporting.

Only the medical files from those candidate subjects will be evaluated to determine if they qualify for the study.

9.2.5.2. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.2 and 9.2.3 before enrolment.

9.2.5.3. Allocate subject number

Subject numbers will be allocated sequentially to the medical file of each subject who has been included in the study.

9.2.5.4. Obtain demographic data, medical and gynaecological antecedents

Age of the subject in years and area of residence will be obtained from the medical file. Medical history including diabetes, hypertension and haemorrhage in previous pregnancies will be obtained. The gynaecological history including parity, type of

delivery, pre-vaccination ultrasound report and delivery month/year will be obtained if applicable.

9.2.5.5. Obtain concomitant vaccination history (Exposed cohort)

The information on *Refortrix* vaccination during pregnancy including gestational age when the vaccination was administered and date of administration will be obtained from the vaccination section in the medical file. Also, the information on any concomitant vaccination administered during the pregnancy will be obtained.

9.2.5.6. Record risk factors

All the available data on risk factors will be obtained from medical file (refer to Annex 8).

9.2.5.7. Record clinical data of pregnancy

All the events of interest (refer to Table 3) diagnosed and recorded in the medical file in the period after 27 completed weeks of the pregnancy will be included. Other pregnancy events will not be evaluated.

9.2.5.8. Record data from physical examination of neonate

Height, weight, head circumference, Apgar scores and birth complications will be obtained from medical file of the mother.

9.2.5.9. Record adverse pregnancy outcome

Adverse pregnancy outcomes and pregnancy-related or neonate-related events of interest will be recorded.

9.2.5.10. Record intercurrent medical conditions/medications

Intercurrent medical conditions and medications reported at the time of delivery, if any, will be recorded.

9.2.5.11. Study conclusion

The investigator will:

- review all the data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

The information on pregnancy-related AEs/outcomes and birth outcomes will be obtained from medical file according to the details on final visit available in the medical file.

9.3. Variables

9.3.1. Study cohort definitions

- Exposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study centre) from May 2015 and who received one dose of *Refortrix* during 27 to 36 weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil. The index date will be considered as the date of *Refortrix* administration or where not specified, as 27 completed weeks of gestation.
- Unexposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study centre) before implementation of the maternal immunization program in Brazil in September 2014 and who did not receive Tdap vaccination during pregnancy as per information of the investigator. The Unexposed cohort will include those subjects who had delivered in the period during September 2012-August 2014. This period was chosen because Tdap vaccine was not administered to pregnant women before the maternal immunization program was implemented in the country.

9.3.2. Endpoints

9.3.2.1. Co-primary endpoints

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum).
- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.
  - Preterm birth.
  - Small for gestational age.

9.3.2.2. Secondary endpoints

- Occurrence of pregnancy-related AEs of interest/neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes.
  - Preterm premature rupture of membranes.
  - Premature uterine contraction.

  - Neonatal death.
  - Maternal death.
  - Still birth.
  - Neonatal hypoxic ischaemic encephalopathy.

- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

9.3.3. Potential confounding factors

Age of the mother and high risk pregnancy are considered as important confounding factors for the occurrence of pregnancy-related AEs of interest, so they will be controlled in the analysis.

Other potential important confounding factors associated with onset of the outcomes of interest will also be collected: smoking, multiparity, multiple births, assisted fertilisation, congenital anomalies (in parents or first degree relatives), alcohol consumption and recreational drug use. Antecedents of previous pregnancies would be predictive factors for the development of a pregnancy-related AE and where available, they will be described. These are: history of spontaneous abortion/ miscarriage, preterm delivery, preterm premature rupture of membranes (P-PROM), red blood cell isoimmunisation [e.g., D-Rh (Rhesus factor) sensitised], pre-eclampsia, eclampsia and major congenital anomalies during previous pregnancies. Other conditions of interest to record are hypertension, diabetes and anaemia.

Further, confounders may include multi-foetal gestation, diagnosis of a foetus with aneuploidy or a major congenital anomaly, cervical insufficiency or incompetent cervix, premature contractions, bleeding throughout the gestation, gestational hypertension, maternal immunization with diphtheria, hepatitis B or other vaccines [Exposed cohort (refer to section 9.2.5.5)] and an active infection (treated or untreated).

The study will start monitoring for pregnancy outcomes on the day of vaccine administration for the Exposed cohort and at 27 completed weeks of gestation for the Unexposed cohort, and end at the date of delivery. Only the outcomes of interest diagnosed and described in the medical files during the risk period will be included in the study. For details, refer to Table 3. The study outcomes would be accounted in the same risk period for both the Exposed and Unexposed cohorts.

9.4. Data sources

This retrospective study will use the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynaecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation will be done on the diagnosis or evaluation of

these events and only the final diagnosis as described in the source document will be included in the study.

To evaluate the vaccination, the information in the anamnesis and pregnancy card archived in the medical files will be used as the only source.

9.5. Study size

The background proportions of different safety outcomes from publications [Munoz, 2005; Zheteyeva, 2012; Goldfarb, 2014; Passini, 2014] and as reported in the feasibility assessment from Brazil are summarised in Table 4 below.

Table 4 Background proportions of different safety outcomes

Safety Outcome	MUNOZ 2005 (Influenza Vaccination) - Proportion		GOLDFARB 2014*-Proportion		Feasibility assessment-Proportion (Brazil local data)
Exposure	VAC	UNVAC	VAC	UNVAC	UNVAC
Co-Primary endpoints					
Gestational Diabetes	2.2%	1.7%			2.95% (2.53-3.64)
Pre-eclampsia	4.8%	3.9%			1.6%
Vaginal or Intrauterine haemorrhage					16.4%
Preterm Delivery			7.8%	21.2%	Around 10%
Secondary endpoints					
Congenital Anomalies					0.79%
Transient Hypertension	6.7%	2.9%			14.3%
Eclampsia					1.6%
Premature Rupture of Membranes	2.6%	2.4%			3.53%
Still Birth					0.31%

VAC: Vaccinated group
UNVAC: Unvaccinated group
* Tdap vaccine coverage of 81.6%

Sample size:

The background proportions from the feasibility reports and literature for some of the co-primary endpoints ranged from 1.6% - 16.4%, from 0.79% - 10% for some of the secondary endpoints and unknown for the rest of the endpoints (refer to Table 4), besides the power estimation for each endpoint were assessed in Table 5**.** Therefore, a conservative proportion of 3% was chosen for the sample size calculation.

Using a two-sided (alpha = 0.01) test, assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [(1200 subjects in each cohort] will be needed to have more than 80% power to detect a relative risk of 2 or higher.

The power estimation of each safety outcome with background proportions is presented in Table 5.

Table 5 Power estimation of each safety outcome with background proportions from the feasibility assessment without multiple adjustment and sample size of 1200 subjects in each cohort

Safety outcome	Assumed background proportion	Alpha level Two-sided	Ratio between vaccinated and control	Power for RR=2(%)*
Co-primary endpoints				
Gestational Diabetes	0.0295	0.05	1:1	94.0
Pre-eclampsia	0.016	0.05	1:1	72.6
Vaginal or intrauterine haemorrhage	0.164	0.05	1:1	>99.9
Preterm Delivery	0.1	0.05	1:1	>99.9
Secondary endpoints				
Congenital anomalies	0.0079	0.05	1:1	43.2
Transient Hypertension	0.143	0.05	1:1	>99.9
Premature Rupture of Membranes	0.0353	0.05	1:1	>99.9
Still birth	0.0031	0.05	1:1	20.0

Two independent proportions were used for the sample size calculation in PASS.
*RR: Relative risk

The sample size and power estimation is presented in Table 6.

Table 6 Sample size and power estimation without and with multiple adjustment for background proportions of 3% and 5% and relative risk of 2

Assumed background proportion	Multiple comparisons	Alpha level Two-sided	Number of vaccinated subjects	Ratio between vaccinated and control	Total Number of subjects needed	Power (%)
0.03	1	0.05	749	1:1	1498	80
0.05	1	0.05	435	1:1	870	80
0.03	5	0.01	1114	1:1	2228	80
0.05	5	0.01	647	1:1	1294	80

Two independent proportions were used for the sample size calculation in PASS.
Bonferroni adjustment was used for adjustment of alpha level.

9.6. Data management

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, Personally Identifiable Information (PII) will not be collected nor transmitted to GSK (refer to Annex 2 for definition). Subject data necessary for analysis and reporting will be entered into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate

clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data. Refer to Annex 8 for details.

Once the database is archived and the study report is complete and approved by all parties, the participating investigator will be provided with a CD-ROM of the final version of the data generated from the investigational site.

9.7. Data analysis

All the statistical calculations will be done in SAS 9.2 or higher.

In case of multiple pregnancies, only the latest pregnancy in the specified period will be included in the study to avoid correlation of the safety endpoints from different pregnancies for one subject. The latest pregnancy will be considered in the study and the analysis.

9.7.1. Cohorts for analyses

9.7.1.1. Total Cohort (TC)

The TC will include all subjects enrolled in the study. All the information for these subjects will be entered in the eCRF.

9.7.1.2. According-To-Protocol (ATP) Cohort

The ATP cohort will include all the evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol).

9.7.2. Analysis of demographics and baseline characteristics

The baseline and demographic characteristics of the Exposed and Unexposed cohorts will be tabulated in a summary of statistics (mean, median, standard deviation and range) including age and gestational age.

9.7.3. Analysis of co-primary endpoints

The main analysis for co-primary objectives will contain only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects have missing vaccination date in the Exposed cohort, a sensitivity analysis will be performed using the imputed vaccination date to 27 completed weeks of gestational age to evaluate if this has any potential impact on the results.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy haemorrhage, preterm birth and small for gestational age) will be calculated. For each specific endpoint, the number of subjects where the event occurred [between the index date (refer to Annex 2 for definition of index date) and the date of the delivery] will be divided by the total number of subjects at risk for both the Exposed and Unexposed

cohorts respectively, together with its exact 95% confidence interval (CI).The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage) will be pooled together and of birth outcome (preterm birth and small for gestational age) will be pooled together in addition. The analysis of the risk for the pooled endpoints will be performed using the same method as for the separate co-primary endpoints.

The comparison of the risk with its two sided 95% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression model, using the exposure status as a binary independent variable in the model. Absence of increased risk will be concluded if this CI contains 1.

Univariate analysis will describe the association between Tdap vaccination status, maternal age, parity and gestational age.

A multiple logistic regression model will be fitted with a backward selection to identify the possible confounding factors for each of the primary safety event using an alpha level of 0.1. Potential confounders will be parity, age of the mother at the start of the pregnancy and congenital anomalies (in parents or first degree relatives). Adjusted odds ratio (OR) and its 95% CI will be derived from the final model.

9.7.4. Analysis of secondary endpoints

The risk for each secondary endpoint (pregnancy-related AEs and birth outcomes) will be calculated by the number of subjects with at least one of the each event occurring between the index date (refer to Annex 2 for definition of index date) and the date of the delivery, corresponding to that endpoint divided by the total number of subjects at risk for both the Exposed and Unexposed cohort, together with its exact 95% CI. If more than 10% of subjects have missing vaccination date in the exposed cohort, a sensitivity analysis will be performed as for the co-primary endpoints.

In addition, the risk of all the co-primary and secondary endpoints will be calculated by calendar year as well to evaluate the comparability among the Exposed and Unexposed cohorts.

9.7.5. Handling of missing data

Missing or non-evaluable primary and secondary outcome measurements will not be replaced. Therefore, the main analysis will exclude subjects with missing or non-evaluable data.

A sensitivity analysis will also be performed if more than 10% of the measurements are missing for each endpoint. In the first instance, missing outcomes will be imputed with a value of ‘0’. In the second instance, all missing outcomes will be imputed with a value of ‘1’. The risk for each endpoint will then be analysed using similar methods as mentioned in sections 9.7.3 and 9.7.4 for all the co-primary and secondary endpoints.

For subjects in the Exposed cohort whose date of the vaccination is not available, it will be imputed to the completed 27th gestational week as the recommended start time for the vaccination for the sensitivity analysis.

9.7.6. Conduct of analysis

9.7.6.1. Sequence of analyses

The statistical analyses will be performed when all data are available. All analyses will be performed on final and clean data.

9.7.6.2. Statistical considerations for interim analyses

No interim analyses are planned for this study.

9.8. Quality control

GSK will monitor the study to verify that the data are authentic, accurate, and complete. Direct access to all study-site related and indirect access to source data is mandatory for the purpose of monitoring review.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The final study dataset will be archived and stored on a secured, access limited, computer platform SAS Drug Development (SDD) according to GSK Biological Standard Procedures. Specific statistical programs will be written in SAS 9.2 (or higher) and validated according to the GSK standard procedures. The validation of the quality control (QC) of the statistical analysis will be documented. All statistical programs, output files and QC documentation will be saved as read-only files on SDD.

The final study protocol and possible amendments, the final statistical report and the QC document, and the final study report(s) will be archived on a Document management system based on the Documentum platform: Computer Aided Regulatory Submission (CARS).

9.9. Limitations of the research methods

There is a possibility that timing of events with respect to the exposure may not always be captured with appropriate accuracy, particularly with retrospective studies which make use of the existing data (which may be limited). However, considering that the antenatal

care visits at regular intervals are standard of care in Brazil [MoH, 2010; MoH, 2012], the e appropriate documentation of vaccination and pregnancy events for the Exposed cohort, and pregnancy events for the Unexposed cohort is expected. This will allow the determination of the timing of the events as compared to the moment of the exposure. The availability of these data was checked during the feasibility assessment (refer to Annex 6).

Incomplete and imprecise medical records could lead to bias and misclassification of the events. To minimise this, the feasibility assessment was performed in the study centre selected to determine the quality and completeness of the medical records for both vaccination exposure and pregnancy outcomes. The pregnancy outcomes diagnosed at the study centre during the pregnancy are recorded. However, for some of the outcomes this may be the earliest date of diagnosis at the site rather than the actual date of onset. Therefore, date of diagnosis will be used based on the assumption that it is the date of onset, although this may not be the case in some instances and is recognised as being a limitation of the study.

The information on concomitant vaccinations administered during pregnancy will not be available for the Unexposed cohort, but this information can be retrieved for the Exposed cohort. This will prevent formal quantitative comparison with the Unexposed cohort and is a limitation of the study. However, the availability of information on other vaccines given to pregnant women who received Tdap will enable some insight and comment on whether any increased safety signal observed may be solely attributed to *Refortrix*.

Congenital anomalies diagnosed at birth will be used as there will be no post-delivery follow-up visit. Therefore, anomalies which may manifest at a later stage will not be captured.

For vaccinated subjects, whilst the date of *Refortrix* vaccination is being systematically collected, there is a possibility that it may not always be available with the appropriate level of accuracy needed. For example, index date (refer to Annex 2 for definition) may not always be available from the medical files with no feasible means of subsequently obtaining this information. The potential lack of the date of *Refortrix* vaccination for every subject in the Exposed cohort is therefore considered as a study limitation. Since the subjects will not be contacted during the study, the assumption will therefore be made that the index date is 27 completed weeks of gestation, which is the earliest time point to receive the vaccination from the maternal immunization program in Brazil. The number of women without the date of *Refortrix* administration will therefore be assessed following the data collection, if more than 10% of them are without the date of *Refortrix* administration, a sensitivity analysis will be performed on top of the primary analysis (refer to section 9.7.3 for details) (as this could create a potential selection bias in the Exposed cohort compared to the Unexposed cohort).

Another potential limitation is the possibility that the maternal Tdap vaccination program itself may have influenced the attitude of pregnant women towards attending antenatal care or medical consultation. This could potentially lead to an increased frequency of reporting of pregnancy-related AEs. However, the evaluation done during the feasibility assessment that was confirmed by other studies performed at the study centre indicated a high acceptance of vaccination in the study population with no changes in the reporting or ascertainment of the expected pregnancy-related AEs. Therefore, the Exposed and Unexposed cohorts are assumed to be comparable.

When using a historical cohort as the unexposed comparison group, caution is required due to potential bias from changes over time and confounding factors including differences in standard of care and pregnancy management practices (from the perspective of both the pregnant woman and the health care professional). Using a comparative cohort collected over two calendar years will provide some capacity to identify any such potential differences in relation to the Exposed cohort.

9.10. Other aspects

Not Applicable.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), applicable local guidelines in Brazil, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study prior to a site initiating the study in that country or will document that neither a favourable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- Independent Ethics Committee (IEC)/ Comissão Nacional de Ética em Pesquisa (CONEP) review and favourable opinion/approval of study protocol and any subsequent amendments.

As this study will be based on a retrospective analysis from medical records, informed consent will not be requested from the subjects in this study [PAHO, 2005] and a waiver from this process will be requested by the investigator from the IEC and CONEP.

No contact will be established with the subjects to obtain, clarify or record information and anonymisation of source data will be guaranteed.

10.1. Data Privacy

Data privacy will be protected by using anonymised individual data (refer to Annex 2 for definition of anonymised data). No Personally Identifiable Information (PII) will be collected in the study, including date of birth. No GSK Biologicals personnel or delegates will have the ability to link data to an identifiable individual.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the 06 June 2013 European Medicines Agency (EMA) - EMA/873138/2011 Guideline on Good Pharmacovigilance Practices (GVP) [EMA, 2013], the sponsors of

non-interventional studies based on secondary data sources are not required to report suspected adverse events or adverse reactions as Individual Case Safety Reports (VI.C.1.2.1).

Only the pregnancy and birth outcomes related to primary and secondary objectives (refer to section 8) will be recorded and collected retrospectively from the subjects participating in the study. Other post-vaccination AEs or Serious Adverse Events (SAEs) have been collected and reported to the national pharmacovigilance system Notivisa, [Notivisa, 2015] as per the country regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers following finalisation of the protocol and, whenever possible, before initiation of the data extraction/ analysis.

Summary results of observational studies that are designed to inform the safety, effectiveness, including cost-effectiveness, of GSK vaccines/products (and other informative studies) are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed.

12.2. Provision of study results to investigators

Where required by applicable regulatory requirements, the investigator signatory will be requested for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreed location.

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	203153	21 Jul 2015	List of stand-alone documents
2	203153	21 Jul 2015	Glossary of terms
3	203153	21 Jul 2015	Trademarks
4	203153	21 Jul 2015	List of principal and coordinating investigators
5	203153	21 Jul 2015	Sponsor Information
6	203153	19 Jan 2015	Feasibility assessment
7	203153	21 Jul 2015	Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from [Munoz, 2013])
8	203153	21 Jul 2015	Planned variables to be collected in electronic Case Report Form (eCRF)
9	203153	21 Jul 2015	Recommendations for *Refortrix* vaccine in Brazil
10	203153	21 Jul 2015	Protocol Sponsor Signatory Approval
11	203153	21 Jul 2015	Protocol Investigator Agreement
12	203153	21 Jul 2015	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Anonymised data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual, or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymised Information
Cohort study:	A form of epidemiological study where subjects in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
Congenital anomalies:	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC, 2015] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the foetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious conditions or biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognised congenital birth defect.

Eclampsia:	Features of pre-eclampsia are accompanied by new onset generalized seizures. See more at Pregnancy-related hypertension.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Section 9.7.1.2 for details on criteria for evaluability).
Gestational Age:	Gestational age is based on first day of the last menstrual period (LMP) OR the first trimester ultrasound, if no known date of LMP OR known date of fertilisation; with the second trimester beginning at week 14 0/7, and the third trimester beginning at week 28 0/7.
Gestational diabetes:	Onset or first recognition of abnormal glucose tolerance during pregnancy (the diagnosis is based on administration of glucose challenge test at 24-28 weeks of gestation). Includes Class A1: Euglycaemia achieved with diet and/or exercise and Class A2: Euglycaemia achieved with medication. Refer to Annex 7 for details on diagnosis.
HELLP syndrome:	Form of severe pre-eclampsia with associated laboratory abnormalities including haemolysis (H), elevated liver (EL) function tests and low platelets (LP) with or without proteinuria. Refer Pregnancy-related or gestational hypertension for more details. Patients are classified as having partial HELLP syndrome when one or two laboratory abnormalities of HELLP occur.

High-risk pregnancy:	Pregnancy that threatens the health or life of the mother or her fetus. Risk factors for a high-risk pregnancy can include existing health conditions such as high blood pressure, diabetes, being Human Immunodeficiency Virus (HIV)-positive, overweight, obesity, multiple births and young or old maternal age.
Index date:	For the Exposed cohort, the index date will be the date of *Refortrix* vaccination given as part of the maternal immunization program in Brazil. For the Unexposed cohort, the gestational age of 27 completed weeks will be considered as the index date. Only the events for each endpoint occurring after the index date for both groups will be considered.
Key coded information:	Refers to encoded or otherwise pseudo-anonymised Personally Identifiable Information (PII) from which direct identifiers have been removed and replaced by a unique identifier or random code. Key coded PII shall not be considered anonymised information.
Last Menstrual period (LMP):	Considered as the first day of the LMP before conception (fertilisation) onset. The first day of LMP is equal to first day of gestation. The estimated day of conception (fertilisation) is calculated as the first day of LMP plus 14 days.
Live birth:	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement.
Maternal death:	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
Neonatal death:	Death of neonate at any time from birth to 28 days of life, regardless of gestational age.
Neonatal hypoxic ischaemic encephalopathy:	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty in initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or due to another cause.

Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Personally Identifiable Information (PII):	Information which directly (e.g. by name) or indirectly (e.g. by one or more identifiers such as height, weight, date of birth, initials etc) is considered, either individually or in combination, to have the potential to allow identification of named individuals. Different jurisdictions apply varying criteria to define 'personally identifiable data'. In the case of data collected during GlaxoSmithKline (GSK) sponsored clinical trials and processed via Biometrics and Data Sciences (BDS), the true identity of the data of the subject is substituted by a code and the "key" linking the code with the true identity is held by a third party outside GSK (the investigator). These data are generally considered not to be personally identifiable.
Placental abruption:	Partial or total placental detachment prior to delivery of foetus.
Placenta previa:	Presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to haemorrhagic shock.
Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase ‘In accordance with the terms of the European marketing authorisation’ means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).

Post-partum haemorrhage:	Excessive blood loss after delivery i.e. estimated blood loss in excess of 500 ml after vaginal delivery and estimated blood loss in excess of 1000 ml after Caesarean delivery. The other symptoms are ≥10% drop in haematocrit, need for blood transfusion, symptomatic hypotension, dizziness, pallor and oliguria.
Pre-eclampsia:	An acute pregnancy related hypertensive condition characterised by hypertension (>140 and/or >90 mmHg) and/or proteinuria (>300 mg in a 24 hour urine specimen) occurring after the 20th week of gestation and resumes after delivery
Pregnancy/gestational duration:	Pregnancy duration will be classified using the gestational age according to the duration of pregnancy in number of completed weeks: • Preterm will be defined as birth before 37 weeks of gestation. • Full term will be defined as birth between 37 and 41 weeks of gestation. • Post-term will be defined as birth after 41 weeks of gestation.
Pregnancy-related hypertension:	Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least two separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of pre-eclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks post-partum. For this study, this will include pre-eclampsia, eclampsia and HELLP Syndrome.
Premature rupture of membranes (PROM):	Spontaneous rupture of foetal membranes that occurs before the onset of labour.
Premature uterine contraction:	Uterine contractions without cervical change.
Preterm birth:	Birth before 37 weeks of gestation.
Preterm Premature rupture of membranes (P-PROM):	Spontaneous rupture of foetal membranes that occurs before the onset of labour before 37 weeks of gestation.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.

Retrospective study: A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.

Self-contained study: Study with objectives not linked to the data of another study.

Serious Adverse Event (SAE): A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or

prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.

Small for gestational age (SGA): Birth weight less than 10% for infants of same gestational age and gender in same population.

Still birth: Death of the foetus(es) at ≥22 weeks of gestation, occurring antepartum or intrapartum.

Study population: Sample of population of interest.

Subject: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.
Vaginal or intrauterine haemorrhage:	Vaginal or intrauterine haemorrhage which may be caused due to partial or total detachment of placenta or due to presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to haemorrhagic shock. This includes the following diagnosis- placental abruption and placenta previa.

Annex 3 Trademarks

The following trademark is used in the present protocol.

Note: In the body of the protocol (including the abstract), the name of the vaccine will be written without the superscript symbol ™ and in *italics*.

Trademark of the GlaxoSmithKline group of companies	Generic description
Refortrix™	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine

Annex 4 List of principal and coordinating investigators

The contact details and list of all investigators are available upon request.

Annex 5 Sponsor Information

Sponsor:

GlaxoSmithKline Biologicals
Rue de l'Institut, 89
1330 Rixensart, Belgium

Sponsor Study Monitor:

Refer to the local study contact information document.

Annex 6 Feasibility assessment

The details on feasibility assessment are available upon request.

Annex 7 Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from Munoz, 2013)

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PREGNANCY RELATED TERMS				
GESTATIONAL AGE ESTIMATES: Dating of Pregnancy	Dating from: -first day of last menstrual period (LMP), OR -1st trimester ultrasound if no known LMP or the ultrasound is not consistent with LMP, OR -known date of fertilization (e.g. by Assisted Reproductive Technology or Intrauterine Insemination). [ACOG, 2014]		Test for urine or serum β-HCG -urine test: positive about 10-12 days after conception. -serum test: positive about 5-7 days after conception. The estimated date of conception or pregnancy onset is calculated as the last menstrual period plus 14 days. Ultrasound (US): Gestational age is assessed in the 1st trimester (< 14 weeks) by measurement of crown-rump length. In the second trimester (14 to 20 weeks), the biparietal diameter is used (accuracy is within +/- 10 days up to 34 weeks, then +/- 3 weeks). At term, abdominal circumference and femoral length are used. US limited by: insufficient standardization, operator variability and expertise, lack of large population based reference, assumption that all fetuses with the same measurements have the same gestational age without accounting for true differences in fetal growth in early gestation or genetic and other familiar factors.	-The Committee on Obstetric Practice, American Institute of Ultrasound in Medicine and Society for Maternal-Fetal. Committee Opinions: Method for estimating Due Date. Number 611, October 2014 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Method-for-Estimating-Due-Date).

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
TRIMESTER OF GESTATION	Pregnancy is divided in three trimesters: -First trimester: up to and including 13 6/7 weeks of gestation. -Second trimester: 14 0/7 weeks to 27 6/7 weeks of gestation. -Third trimester: 28 0/7 weeks of gestation and beyond.			
LENGTH OF PREGNANCY	Preterm: up to and including 36 6/7 weeks of gestation. Term: 37 0/7 weeks through 41 6/7 weeks of gestation [ACOG, 2013]. Early term: Birth at 37 0/7 to <39 weeks of gestation. Post-term (S: post-mature): 42 0/7 weeks of gestation and beyond.		Estimated Date of Delivery (EDD)= 40 0/7 weeks (280 days) from the first day of the last menstrual period or by Ultrasound examination.	The American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Committee Opinions: Definition of Term Pregnancy. Number 579, November 2013 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Definition-of-Term-Pregnancy)
PREGNANCY OUTCOMES				
LIVE BIRTH S: Live born	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
SPONTANEOUS ABORTION S: miscarriage, pregnancy loss	Pregnancy ending spontaneously before 22 weeks of gestation (i.e. up to and including 21 6/7 weeks of gestation) [EMEA, 2005]. Includes death of embryo/ fetus in utero (missed abortion), or blighted ovum /anembryonic pregnancy (i.e. fertilized ovum whose development has ceased at an early stage). Subgroups: -Early miscarriage if it occurs during the first trimester. -Late miscarriage when it occurs during the second trimester.	Overall rates: The prevalence of spontaneous abortion reported by several authors among clinical pregnancies (i.e. recognized pregnancies following a missed menstrual period) for all age groups combined is about 12-18% of all pregnancies in first or second trimester. -Early miscarriage: Up to 20%of pregnancies. -Late miscarriage: Up to 2% of pregnancies. Risk factors: Studies have shown that approximately 50% of spontaneous abortions are associated with fetal chromosome abnormalities [Brown 2008]. Many studies have shown that maternal age is one of the strongest and most consistent risk factor.	Note: case definitions vary between countries, as definition of viability is varied between resource settings (e.g. 20-24 weeks versus 28 weeks and corresponding fetal weight of 500 mgr. vs. 1000 mgr). Document circumstances of fetal loss, physical exam/estimated gestational age of the product if feasible and/or collect results of available studies including pathology report of fetus and placenta to establish a possible etiology, association/causality. Genetic testing if available; a karyotype may or may not be performed as part of routine clinical care. Of note, it may not be possible to perform evaluation if the subject does not seek medical attention.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - Brown S. Miscarriage and its associations. Seminars in Reproductive Medicine 2008; 26(5): 391-400. - Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE,et al. Incidence of early loss of pregnancy. New England Journal of Medicine1988;319: 189–94. - Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 1980; 2:173–6.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
STILLBIRTH S: Stillborn, Fetal Demise/Death, Deadborn	Delivery of a death fetus after 22 0/7 weeks of gestation [EMEA, 2005]. Categories: - During pregnancy or antepartum. - Intrapartum. Subgroups: -Early Stillbirth: Delivery 22 0/7 – <28 weeks and/or ≥500 -1000 grams. -Late Stillbirth: Delivery ≥ 28 0/7 weeks and/or >1,000 grams	Overall rates [ACOG, 2009]: 6.2/1,000 births or 1 in 160 deliveries. -Early stillbirth: 3.2/1,000 births. -Late stillbirth: 3.1/1,000 births. Risk factors: Non-Hispanic black race, nulliparity, maternal age >35 years, hypertension, diabetes, obesity BMI >30, multiple gestations, smoking, drug and alcohol use, infections, growth restriction, and placental anomalies.	Includes macroscopic examination for fetal anomalies, and if available, autopsy and karyotype; cord and placental examination and pathology. Document antepartum events: maternal factors, fetal factors (e.g., IUGR), external factors (e.g., trauma), and peripartum events such as preterm premature rupture of membranes (PPROM), infection, abruption, cord events.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - American College of Obstetricians and Gynecologists. Management of stillbirth. ACOG Practice Bulletin Number 102. Obstetrics and Gynecology2009; 113: 748–61. (accessed on-line on 13/Oct/2014 at: https://stillbirthmatters.files.wordpress.com/2014/05/acog-management-of-stillbirth1.pdf)
CONGENITAL ANOMALIES S: Birth defects, Malformations	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC,2007] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious	Minor anomaly: Rates vary widely depending on study. Minor malformations and developmental variants occur in 14 - 40% of otherwise normal newborns [Leppig, 1987]. Major anomaly: Apparent at birth in approximately 3% of population [CDC, 2013].	An exact cause or mechanism for a major defect can be determined in less than 50% of the cases. Some agents cause major defects if exposure occurs during a specific critical period of gestation, but not at other times. After organogenesis has been completed (about 8 weeks after conception or 10 weeks after last menstrual period), the observable effect may be limited to fetal growth restriction or functional rather than gross structural defects [Sadler,2009]. The primary outcomes relative to stage of exposure are as follows: Pre-implantation: embryonic lethality	Centers for Disease Control. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007.(accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf) - Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, MooreCA. Guidelines for case classification for the National Birth Defects Preven-tion Study. Birth Defects Research Part A: Clinical and Molecular Teratology2003;

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	conditions or certain biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect. Morphological anomalies: Abnormalities of body structure or function that are present at birth and are of prenatal origin. Categories: Minor anomaly: Anatomic variant or defect that do not have serious medical, functional or cosmetic consequences for the child. Includes those found in association with major anomalies. Major anomaly: Structural or functional defect that require surgical/medical treatment, have serious adverse effects on health or development (functional), or have significant cosmetic impact. [Rasmussen, 2003].		Implantation to time of organogenesis: morphological defects. Fetal → neonatal stage: functional disorders, growth retardation, Carcinogenesis. A certain pattern of minor malformations may have important predictive value in identifying more serious associated problems, some of which may be unrecognizable at an early age. Specific patterns of multiple minor malformations may be presenting signs of a genetic condition or malformation syndrome.	67:193–201. - Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. Association with major malformations. Journal of Pediatrics1987; 110: 530–7. -Sadler TW. Langman's medical embryology. 11th ed. Lippincott Williams and Q4Wilkins; 2009. - Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects-Atlanta, Georgia, 1978–2005. MMWR; 2013. (accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm)
ELECTIVE OR THERAPEUTIC TERMINATION OF PREGNANCY S: Induced abortion	Expulsion of products of conception with medical or surgical assistance. The termination of the pregnancy can be elective or therapeutic. -Elective: performed for personal choice/socio-economic reasons, excluding maternal or fetal health reasons. -Therapeutic: performed to preserve the health or save the life of a			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	pregnant woman.			
ECTOPIC PREGNANCY S: Extra-uterine pregnancy	Condition in which a fertilized ovum implants outside the uterine cavity, most often in the fallopian tube (97%).	Affects 1.5% to 2% of all pregnancies and poses a significant threat to women of reproductive age. It is the leading cause of maternal death during the first trimester of pregnancy. Risk factors: tubal surgery, genital tract infections leading to pelvic inflammatory disease, previous ectopic pregnancy, and in utero exposure to diethylstilbestrol [ACOG, 2008].	Diagnosis is generally based on: clinical symptoms/signs, diagnostic transvaginal ultrasonography, abnormal serum progesterone level of less than 5 ng/mL and/or an inappropriate increase in hCG.	- Kurt T. Barnhart. Ectopic pregnancy. N Engl J Med 2009; 361:379-87. - American College of Obstetricians and Gynecologists. Medical Management of Ectopic Pregnancy. ACOG Practice Bulletin Number 94. Obstetrics and Gynecology Jun 2008; 111(6): 1479–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
MOLAR PREGNANCY S: gestational trophoblastic neoplasia, gestational trophoblastic tumor	Pregnancy marked by a neoplasm within the uterus, whereby part or all of the chorionic villi are converted into a mass of clear vesicles. Histologically distinct disease entities encompassed by this general terminology include: complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.	The incidence is estimated at 1-3 per 1000 pregnancies for partial or complete hydatidiform moles. The malignant invasive moles (choriocarcinoma and placental site trophoblastic tumour/epithelioid trophoblastic tumour) are very rare, 0.2% of the gestational trophoblastic disease cases [ESMO, 2013; ACOG, 2004]. Risk factors: extremes of maternal age and prior molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population.	The disease is most frequently diagnosed on the basis of increasing or plateauing hCG values. Patients should be monitored with serial determinations of quantitative hCG values. A baseline post-evacuation chest X-ray should be considered.	- American College of Obstetricians and Gynecologists. Diagnosis and Treatment of Gestational Trophoblastic Disease. ACOG Practice Bulletin Number 53. Obstetrics and Gynecology June 2004; 103 (6):1365-77. - M. J. Seckl, N. J. Sebire, R. A. Fisher, F. Golfier, L. Massuger & C. Sessa, on behalf of the ESMO Guidelines Working Group. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (Supplement 6): vi39–vi50.
PREGNANCY RELATED ADVERSE EVENTS OF INTEREST				
VAGINAL OR INTRAUTERINE HEMORRHAGE S: Obstetric Hemorrhage, Major obstetric hemorrhage	Vaginal or intrauterine hemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours post-delivery). A major obstetric hemorrhage is defined as blood loss from uterus or genital tract >1500 mL or a decrease	Antepartum hemorrhage: has an incidence of 2–5% of all pregnancies beyond 24 weeks [Walfish, 2009]. Infrequent (14% of cases occur before 32 weeks gestation) and up to 60% between 32-37 weeks gestation [Munoz, 2013]. Risk factors for placenta previa:	Given the wide range of definitions applied to maternal hemorrhage, it is important to combine the clinical presentation and objective data, while keeping in mind the probability of concealed bleeding within the uterus, peritoneal cavity, and retroperitoneal space, and the relative masking of haemodynamic signs of haemorrhagic	- American College of Obstetricians and Gynecologists. Cervical insufficiency. ACOG Practice Bulletin No. 76, Postpartum Haemorrhage International Journal of Gynecology and Obstetrics Oct 2006: 108 (4): 1034-47 (accessed on-line on 13/Oct/2014 at:

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	in hemoglobin of >4 gr/dl or acute loss requiring transfusion of >4 units of blood, or signs or symptoms of hypovolemia. Common causes of blood loss: - Antepartum hemorrhage: placenta previa (presence of placental tissue overlying or proximate to the internal cervical os), placental abruption (partial or total placental detachment prior to delivery of fetus), uterine rupture, bleeding from vaginal or cervical lesions, etc. - Postpartum Hemorrhage: uterine atony, retained products of conception, abnormal placentation (abnormal attachment of the placenta to the uterine wall and includes accreta, increta, and percreta, depending on the extent of uterine invasion), genital tract trauma, uterine inversion, puerperal sepsis, uterine pathology such as fibroids, etc.	prior uterine trauma, multiparity, advanced maternal age, previous C-section or other uterine surgery, and prior placenta previa. Risk factors for placental abruption: hypertension, pre-eclampsia, advanced maternal age, multiparity, maternal/paternal tobacco use, cocaine use, trauma, premature rupture of membranes, chorioamnionitis, and prior abruption. Risk factors for uterine rupture: prior uterine surgery, trauma, uterine anomalies, dystocia, use of uterotonic drugs, and abnormal placentation. Post-partum hemorrhage: Primary postpartum hemorrhage, which occurs in 4–6% of pregnancies, is caused by uterine atony in 80% or more of cases [ACOG,2006]. Risk factors for Postpartum Hemorrhage: Prolonged labor, Augmented labor, Rapid labor, History of postpartum hemorrhage, Episiotomy, especially mediolateral, Preeclampsia, Overdistended uterus (macrosomia, twins, hydramnios), Operative delivery, Asian or Hispanic ethnicity, Chorioamnionitis. Risk factors for abnormal	shock due to the physiological adaptations of pregnancy. Diagnosis is based on clinical presentation; ultrasound and placental pathology if available.	https://www.acog.org/~/media/Districts/District%20II/PDFs/Final_Hemorrhage_Web.pdf - Walfish M et al. Maternal haemorrhage. Br. J. Anaesth. (2009) 103 (suppl 1): i47-i56. -Munoz et al. Research on vaccines during pregnancy: Protocol design and assessment of safety, Vaccine, (2013): 31 (40): 4274-4279, Appendixes

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		placentation: placenta previa with or without previous uterine surgery, prior myomectomy, prior cesarean delivery, Asherman's syndrome, submucous leiomyomata, and maternal age older than 35 years.		
PREMATURE RUPTURE OF MEMBRANES (PROM) AND PRETERM PREMATURE RUPTURE OF MEMBRANES (P-PROM)	PROM: Spontaneous rupture of fetal membranes that occurs before the onset of labor. Preterm PROM (P-PROM): Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks gestation.	Term PROM may occur in 8% of pregnancies, P-PROM in approximately one-third of all preterm births or 4% of all births [ACOG, 2007]. Risk factors: Numerous maternal and fetal factors involved, particularly infection, obstetric factors including abruption placenta, as well as previous P-PROM or premature delivery. Recurrence for P-PROM is 16-32%.	Assessment of gestational age and assessment of maternal and fetal risks, including intrauterine infection, labor, fetal compromise.	-American College of Obstetricians and Gynecologists. Premature rupture of membranes. ACOG Practice Bulletin Number 80. Obstetrics and Gynecology2007;109:1007–20.
PREMATURE UTERINE CONTRACTIONS AND PREMATURE LABOR	Premature uterine contractions: Uterine contractions without cervical change. Premature labor: Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.	Refer to incidence of preterm delivery: 12% of all live births [ACOG, 2012].	Collect any clinical and laboratory information that is available. Standard work-up may include: vaginal examination, uterine monitoring, and fetal monitoring. Work-up to determine etiology or association to study product may include: evaluation for infections (urine culture, Group B streptococcus, Chlamydia, gonococcus, *Trichomonas vaginalis*, bacterial vaginosis), drug screen, and ultrasound to rule out abruption, cord prolapse, oligo/polyhydramnios.	- American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 127. International Journal of Gynecology and Obstetrics 2012 Jun; 19(6):1308-17.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
INTRAUTERINE GROWTH RESTRICTION / POOR FETAL GROWTH S: IUGR S: Fetal growth retardation	Estimated or actual birth weight below the 10th percentile for gestational age.	10% of live births [ACOG, 2013]. Risk factors: Numerous, classified as maternal, placental, fetal.	May include ultrasound (specific biometric parameters and estimated fetal weight), umbilical artery Doppler velocimetry, amniocentesis, chromosomes, and assessment of maternal risk factors (infection, hypertension, etc.). NOTE: curves used to determine %iles should account for gender and race/ethnicity	- American College of Obstetricians and Gynecologists. Fetal Growth Restriction. ACOG Committee Opinion Number 134. Obstetrics and Gynecology May 2013;121: 1122–33.
GESTATIONAL HYPERTENTION, PREECLAMPSIA AND ECLAMPSIA S: Pregnancy Related Hypertension, Pregnancy Induced Hypertension (PIH), Toxemia	Gestational hypertension: Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least 2 separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of preeclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks postpartum Pre-eclampsia: Hypertension (>140 and/or >90 mmHg) occurring after the 20th week of gestation, and up to 6 weeks postpartum, combined with other abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen). HELLP syndrome: Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests, and low platelets (LP), with or without proteinuria. Eclampsia: If the features of pre-	Hypertensive disease occurs in 12-22% of pregnancies [ACOG, 2001; ACOG, 2002]. As many as 25% of women with gestational hypertension will develop preeclampsia. The reported incidence of preeclampsia is 5-8% of pregnancies, usually first pregnancies. Risk factors: First pregnancy, multiple gestation, preeclampsia in previous pregnancy, chronic hypertension, pre-gestational diabetes, vascular and connective tissue disorders, nephropathy, antiphospholipid antibody syndrome, obesity, age >35 years, non-Hispanic black race.	Blood pressure elevation should be sustained and documented in two independent measurements. Additional assessments include a random or 24-hour urine protein determination of 300 mg/dL, other laboratory testing to establish severity and collection of available data on fetal well-being.	- American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin Number 33.Obstetrics and Gynecology 2002; 99:159–67. - American College of Obstetricians and Gynecologists. Chronic hypertension in pregnancy. ACOG Practice Bulletin Number 29. Obstetrics and Gynecology2001; 98:177–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	eclampsia are accompanied by new onset generalized seizures. Chronic Hypertension with superimposed preeclampsia: Chronic hypertension definition PLUS preeclampsia definition			
GESTATIONAL DIABETES MELLITUS S: Diabetes of pregnancy	Onset or first recognition of abnormal glucose tolerance during pregnancy (old definition still used by ACOG). Diagnosis based on administration of glucose challenge test at 24-28 weeks gestation	1% to 14%, with 2-5% being the most common figure [ACOG, 2001].	Includes urine glucose measurement during routine prenatal care visits; a fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or A1C ≥6.5 percent using a standardized assay, or a random plasma glucose ≥200 mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above. Glucose tolerance screening is universal at 24-28 weeks of gestation.	- American College of Obstetricians and Gynecologists. Gestational diabetes. ACOG Practice Bulletin Number 30. Obstetrics and Gynecology2001;98: 525–38.
MATERNAL DEATH	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Direct obstetric death: death of the mother resulting from conditions or complications which are unique to pregnancy and occur during the antepartum, intrapartum, or postpartum period. Indirect obstetric death: A maternal death that is not directly due to obstetric cause (such as from	The global maternal mortality rate is estimated to be about 210 maternal deaths per 100,000 live births [WHO,2013]. Indirect causes and obstetric hemorrhage are the largest causes of maternal death worldwide. Of the direct causes of death, hemorrhage is the leading cause of maternal death, followed by hypertensive disorders and sepsis. Regional estimates varied substantially [Say, 2014].		- Trends in Maternal Mortality: 1990 to 2013. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. (accessed on-line on 13/Oct/2014 at: http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf?ua=1) -Lale Say et al, Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2: e323–33

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	previously existing disease, or disease developing during pregnancy, labor, or the puerperium but that was not unique to pregnancy.) Late Maternal Death: Death of woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.			
NEONATAL RELATED EVENTS				
BIRTH WEIGHT (BW)	Small for gestational age (SGA): Birth weight < 10% for newborns of same gestational age and gender in same population (<2500g at term). Low birth weight: BW <2500 g (5.5 lb). Very low birth weight : BW <1500 g (3.3 lb) Extremely low birth weight: BW <1000 g (2.2 lb). Large for gestational age (LGA): Birth weight > 90% for newborns of same gestational age in same population (>4000g at term). High Birth Weight (Macrosomia): BW >4000 g (8.13 lb).	SGA newborns are predisposed to complications, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, and neonatal death. One of the primary risk factors of LGA is poorly-controlled maternal diabetes (pre-existing diabetes mellitus/gestational). Other risk factors in decreasing order of importance, are as follows: a history of macrosomia, maternal weight before pregnancy, weight gain during pregnancy, multiparity, male fetus, gestational age more than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years and a positive 50g glucose screen with a negative result on	Birth weight: Objective is measurement of weight on the day of delivery (OR first weight obtained). Varies with singleton vs. multiple gestation, gestational age, gender, race, ethnicity, maternal nutritional status (BMI), and maternal health status. Birth weight is one of the most sensitive – and also one of the most important – measures of the well-being of children. Weight at birth is directly influenced by the general level of health status of the mother. Assessment of Birth Weight is in relation to Gestational Age (BW/GA): -Gestational age should be based on best obstetric estimate, usually prenatal ultrasound or first day of last menstrual period if ultrasound not available; or neonatal physical exam. -Weight should be based on objective measurement on the day of birth. -Estimate of BW/GA should be based on population specific curves	

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		the three-hour glucose tolerance test.		
PRETERM BIRTH	Birth before 37 weeks of gestation. Late Preterm: 34 to <37 weeks Moderate Preterm: 32 to <34 weeks Very Preterm: 28 to < 32 weeks Extreme Preterm: < 28 weeks	10-15% of all pregnancies, with most recent National Vital Statistics Report showing a decline to 11.72% in recent years. Extreme preterm birth occurs in less than 1% of live births [ACOG, 2003].	Includes physical examination and determination of gestational age, and evaluation for maternal or infant causes of premature delivery. Assessment requires gestational age assessment by best available obstetric estimate, usually prenatal ultrasound or first day of the last menstrual period if ultrasound not available. Also assessed by pediatric estimate through physical and neurological examination of newborn at birth. This is less desirable as this assessment is affected by abnormal fetal growth, placental anatomic and functional anomalies, maternal nutrition, racial and ethnic background, population and genetic factors, and birth weight for GA.	-American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 43. International Journal of Gynaecology and Obstetrics 2003;82: 127–35.
NEONATAL DEATH	Death of newborn at any time from birth to 28 days of life, regardless of gestational age. Subgroups: Very early neonatal death: < 24hrs Early neonatal death: from birth to < 7 days Late neonatal death: 7 to < 28 days Intrapartum-related neonatal death (previously called: asphyxia deaths): neonatal death of term babies with	The early neonatal death rate is estimated to be 8.4 per 1000 liveborns; 67.1% occur by day 3 of life [Vogel, 2014]. Prematurity is the main cause of early neonatal deaths (~62%).	Causes of death and rates may vary according to whether the birth setting was in a hospital or in the community	- Vogel JP et al, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 76–88.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	neonatal encephalopathy or who cannot be resuscitated (or for whom resuscitation is not available). Also includes babies who die from birth injury without hypoxic brain injury)			
NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) S: HIE, Birth Asphyxia, Perinatal Asphyxia, Neonatal encephalopathy	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or be due to another cause.	Rates may vary widely. The incidence of HIE in developed countries is estimated to be 1.5 per 1,000 live births [Kurinczuk, 2010]. Estimates in developing countries range from 2.3–26.5 per 1,000 live births [Horn,2013].	Assessed by clinical and laboratory findings: 5 minute Apgar score of 0-3, Respiratory distress and Acidosis (pH < 7.0), altered tone, depressed level of consciousness, seizures, multiorgan involvement. Diagnostic tests: - MRI is preferred imaging study. - CT can identify focal lesions, hemorrhage, diffuse cortical injury - EKG (ECG) and continuous EKG (ECG) May result in neonatal death or permanent damage to the brain and other organs. May be associated with perinatal events, rarely to prenatal events.	- Kurinczuk JJ, White-Koning M, Badawi N: Epidemiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy. Early Hum Dev 2010, 86(6):329-338. - Horn AR, Swingler GH, Myer L, Harrison MC, Linley LL, Nelson C, Tooke L, Rhoda NR, Robertson NJ: Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. J Perinat Med 2013, 41(2):211-217.
FAILURE TO THRIVE OR GROWTH DEFICIENCY	Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.	Failure to thrive (FTT) is a common problem, however precise epidemiological data is lacking. The population prevalence of FTT has been found to range anywhere between 1.3% and 20.9% depending on the definition of FTT that is used. FTT accounts for 1–5% of paediatric hospital admissions under 2 year of age [Sullivan, 2004]	Normal newborn weight gain includes weight loss of up to 10% of birth weight in the first 1-2 weeks of life, with steady, predictable weight gain thereafter. Progress varies by gestational and post-natal age, genetic and environmental factors. Definitions vary. Fall of weight below 5th percentile for age often used. Olsen et al have described multiple different anthropometric criteria for failure to thrive. These criteria include signs of	- Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child. February2007; 92(2):109-114. - Peter B Sullivan. Commentary: The epidemiology of failure-to-thrive in infants. Int. J. Epidemiol. (2004) 33 (4): 847-848.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
			failure to gain weight (weight < 75% of median weight for chronological age, weight for chronological age < 5th percentile, weight deceleration crossing > 2 major percentile lines, etc), failure to grow (length for chronological age < 5th percentile), and failure to grow and gain weight (weight < 80% of median weight for length, body mass index < 5th percentile) [Olsen, 2007]	

Annex 8 Planned variables to be collected in electronic Case Report Form (eCRF)

Demographic data:

Age (in years)

Resident

Medical antecedents:

Chronic hypertension

Diabetes mellitus

Anaemia

Nutritional disorders: Malnutrition , overweight, obesity

Infectious diseases (e.g.: Chagas disease, Malaria, HIV, Hepatitis, Tuberculosis)

Other Chronic Diseases: Heart disease, rheumatic disease, epilepsy, renal disease, thyroid and other endocrine diseases

Blood transfusion

Accidents

Major surgeries

Neurologic diseases

Gynaecological history

Menstrual cycles: Duration in days, interval in days and regular

Prior use of contraceptive methods

Sexually transmitted diseases

Gynaecological surgeries (at what age, diagnosis)

Breast problems

Obstetric Antecedents:

Number of pregnancies :including miscarriage, ectopic pregnancy

Number of deliveries

Type of deliveries: forceps, Caesarean, spontaneous, vaginal

Number of miscarriages including spontaneous, induced, therapeutic

Number of live births

Interval between pregnancies

Number of newborns: Preterm (before 37 weeks), Post tem (> 42 weeks)

Rh isoimmunization

Number of newborns of low birth weight (less than 2,500 gm) and more than 4000 gm

Early neonatal deaths (if during hospitalisation): Up to seven days of life

Late neonatal deaths (if during hospitalisation): Between 7 and 28 days

Stillbirth (intrauterine foetal death) and gestational age at which the event occurred

Newborns with jaundice, transfusion, hypoglycaemia

Events or complications in previous pregnancies : Haemorrhage, pre-eclampsia, other

Complications in puerperium: Haemorrhage, infections, other

Current Pregnancy History:

Date (first day/month/year) of the last menstrual period

Weight

Ultrasound scan result

Lab tests: Blood group, Rh, haemoglobin, glycaemia, other

Vaccination(s)

Concomitant medications reported at the time of delivery

Hospitalisation during this pregnancy

Habits: Smoking, alcohol and illicit drugs

Pregnancy events

Gestational diabetes

Pre-eclampsia

Eclampsia

HELLP Syndrome

Placenta abruption

Placenta previa

Vaginal haemorrhage

- Ante-partum
- Intra-partum
- Post-partum

Birth Outcomes

Pre term birth (weeks of gestation)

Small for gestational age (birth weight in grams)

Apgar score

Other events

Premature rupture of membranes

Preterm premature rupture of membranes

Premature uterine contraction

Premature labour

Neonatal death

Maternal death

Still birth

Neonatal hypoxic ischaemic encephalopathy

Congenital anomalies

Annex 9 Recommendations for *Refortrix* vaccine in Brazil

The recommendation for *Refortrix* vaccine in Brazil is available upon request.

Annex 10 Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
Date of protocol	Final Version 1: 11 September 2015
Detailed Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Sponsor signatory	[redacted] Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Signature	_____
Date	_____

For internal use only

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24bb8f87799044d934087a90fddf4e667f64f8f7 1.0 9/18/2015 9:30:58 AM - -
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Annex 10 Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
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Sponsor signatory	[redacted] Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Signature	[redacted]
Date	21 Sept. 2015

For internal use only

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Annex 11 Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP), other applicable guidelines and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
Date of protocol	Final Version 1: 11 September 2015
Detailed Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Investigator name	_____
Signature	_____
Date	_____

For internal use only

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Annex 12 ENCePP Checklist for study protocols

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	15

Comments:

The EU PASS registration will be updated in the final version.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16 16-17
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)	☒	☐	☐	15-17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	27
2.1.5 If applicable, that there is no a priori				

[1] 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.

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16-18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	24-25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	23-24

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.5 Co-morbidity?	☒	☐	☐	17
4.2.6 Seasonality?	☐	☐	☒	
	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	19-24
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	29
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	23 and 24
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	29

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	24
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	24
8.1.3 Covariates?	☒	☐	☐	24
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	25-26

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	27-28
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27-28
10.3 Are descriptive analyses included?	☒	☐	☐	27-28
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	28
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	28
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29
12.1.2 Information biases?	☒	☐	☐	29
(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. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18
12.3 Does the protocol address other limitations?	☒	☐	☐	30

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	31

Comments:

The study still has to be submitted to EC/IRB.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	32

Comments:

Name of the main author of the protocol: [redacted] Director, Epidemiology, GlaxoSmithKline Biologicals

Date: / /

Signature: _____