Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

1. PASS INFORMATION

Title	Boostrix Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix during pregnancy or within 28 days preceding conception.
Protocol version identifier	201327 (EPI-PERTUSSIS-028 VS US PR)
Date of last version of the protocol	Amendment 1 Final: 05 October 2017
EU PAS Register No	Not applicable
Active substance	J07AJ52, bacterial vaccine, pertussis vaccines
Medicinal product	Boostrix, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Product reference	Not applicable
Procedure number	Not applicable
Marketing Authorization Holder	GlaxoSmithKline (GSK) Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	**Co-primary objectives** • To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.

	• To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.
Country of study	United States
Authors (Amended on 05 October 2017)	Coordinating author: • PPD, Scientific Writer, Keyrus Biopharma, contractor for GSK Biologicals GSK contributors: • PPD, Senior Manager, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • PPD, Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • PPD, Director, Director, Head of Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance (Therapeutic) • PPD, Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • PPD, Director, Head of Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance (Prophylactic) • PPD, Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • PPD, Senior Manager, Vaccine Value & Health Science Epidemiology • PPD, Director, Global Regulatory Affairs • PPD***, Safety Scientist, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance*** • PPD***, Safety Physician, Safety***

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2. MARKETING AUTHORIZATION HOLDER

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

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
DLP	***Data Lock Point***
DTaP	Diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP	Diphtheria and tetanus toxoids and whole cell pertussis vaccine
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	International Conference on Harmonization
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorization Safety Study
PT	Pertussis Toxin
Td	Tetanus and diphtheria toxoid vaccine
Tdap	Combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
UK	United Kingdom
US	United States

3. RESPONSIBLE PARTIES

GlaxoSmithKline (GSK) Biologicals has the overall responsibility for the conduct of the study.

4. ABSTRACT

Title	Boostrix Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix during pregnancy or within 28 days preceding conception. 201327 (EPI-PERTUSSIS-028 VS US PR), Amendment 1 Final: 05 October 2017
Main author	PPD, Senior Manager, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance, GSK Biologicals
Rationale and background (Amended on 05 October 2017)	***In the US,*** *Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in individuals 10 years of age and older. The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies ***in the US***. The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced Pharmacovigilance. Following new European Union pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry ***is*** therefore converted into a PASS ***in Q1 2014***. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy. Retrospective reports will be captured by the Registry but will not be included in the analyses of prospective reports.

Research question and objectives	**Co-primary objectives** • To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes. • To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.
Study design (Amended on 05 October 2017)	• This study is a transition of an ***US*** ongoing pregnancy registry (starting on 03 May 2005) into a PASS. • This is a prospective*, observational, exploratory, cohort study. The *Boostrix* pregnancy registry study requires voluntary, prospective reporting of eligible pregnancies by patients and healthcare professionals (HCPs). Data such as vaccination with *Boostrix* during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively**. ** Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.* *** Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.* • Study population: pregnant women, residing in the United States (US), vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception volunteering to take part in the study. • Type of study: self-contained. • Data collection: initial and follow-up data will be collected using questionnaires. Follow-up of cases is performed within ***2*** months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6 months and 12 months after the EDD (for all live births ***for whom the contact details of their HCP will be available***) to ascertain the presence of birth defects not diagnosed before.

- After transition of the ongoing pregnancy registry into a PASS, data will be collected for a minimum of 5 years, starting Q1 2014.

Population, including the setting and study population

In the US, *Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis. Originally licensed for persons aged 10 through 18 years, the vaccine was approved by the Food and Drug Administration (FDA) for use in persons aged 19 through 64 years in 2008, and in persons aged 65 years and older in 2011. The study population includes women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

Size of the potential "at-risk" population

The US Census Bureau estimates that, as of 1 July 2012, the resident US female population was 62,744,930 between the ages of 15 and 44 years old [US Census Bureau, 2013]. The provisional fertility rate in the US in 2012 was 63.2 births per 1000 women aged 15-44 years and the provisional count of births was 3.96 millions [CDC, 2012].

Number of pregnant vaccinees

Boostrix is classified as FDA Pregnancy Category B since September 2012. Since February 2013, *Boostrix* vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) in each pregnancy.

More than 20 million doses of *Boostrix* were distributed in the US between May 2005 and July 2011. Experiences with the ongoing *Boostrix* pregnancy registry (391 exposed pregnancies reported prospectively and 5 exposed pregnancies reported retrospectively between 03 May 2005 and 02 August 2013) and other vaccine pregnancy registries indicate that it is likely that fewer than 100 pregnancies per year will be registered.

Variables

Primary endpoint

Occurrence of any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

Data sources (Amended on 05 October 2017)

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP. ***Follow-up from the HCP of the infant post birth 6 and 12 months will be performed when the contact details are available and***

	with consumer's permission. A toll-free telephone number for reporting adverse events (AEs) and vaccine-exposed pregnancies to the Registry will be listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary information.
Study size	No minimum sample size is required for this descriptive study. Refer to Abstract Section "Study population" above for the size of the potential "at-risk" population and the number of pregnant vaccinees.
Data analysis (Amended on 05 October 2017)	Pregnancy outcomes include spontaneous abortion (pregnancy loss before ***22*** weeks gestation), fetal deaths/stillbirths (loss at or after ***22*** weeks gestation), elective/***induced*** abortions and live births. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories. Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation. Spontaneous abortions without birth defects are excluded from the risk calculations. All defects regardless of trimester of vaccine exposure will be included in the periodic summary reports of this Registry and stratified by trimester of exposure. A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.
Milestones (Amended on 05 October 2017)	The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and ***is*** converted into a PASS ***in Q1 2014***. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. Summary reports ***with cumulative analysis*** will be written annually. A final

cumulative report will be written and submitted ***within one year of completion of the five-year period***. After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

References

Centers for Disease Control and Prevention (CDC). Recent Trends in Births and Fertility Rates Through December 2012. http://www.cdc.gov/nchs/data/hestat/births_fertility_december_2012/births_fertility_december_2012.htm. Accessed: 27 November 2013.

United States Census Bureau (US Census Bureau), Population Division. Annual Estimates of the Resident Population for Selected Age Groups by Sex: April 1, 2010 to July 1, 2012. Release date June 2013. http://www.census.gov/popest/data/national/asrh/2012/index.html. Accessed: 27 November 2013.

5. AMENDMENTS AND UPDATES

The summary of the amendment is provided in Annex 4.

6. MILESTONES (AMENDED ON 05 OCTOBER 2017)

Milestone *(Including Data Lock Point (DLP) of each report)*	**Planned *Submission* date**
Start of data collection	Q1 2014[a]
End of data collection	***2 August 2019***[b]
Annual report 1 ***(DLP: 2 August 2015)***	***Q2 2016***
Annual report 2 ***(DLP: 2 August 2016)***	***Q2 2017***
Annual report 3 ***(DLP: 2 August 2017)***	***Q2 2018***
Annual report 4 ***(DLP: 2 August 2018)***	***Q2 2019***
Annual report 5***/Final report (DLP: 2 August 2019)***	***Q2 2020***[c]
Registration in the EU PAS register	Q1 2014

[a] The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry will therefore be converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. ***Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report (PBRER) and the Development Safety Update Report (DSUR) for Boostrix.***

[b] After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

[c] ***Since the annual reports also contain cumulative data, the last annual report (with DLP: 2 August 2019) will serve the purpose of the Final report.***

7. RATIONALE AND BACKGROUND

7.1. Background

7.1.1. *Boostrix* vaccine

Boostrix is a vaccine indicated for active booster immunization against tetanus, diphtheria, and pertussis. It contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin). Each 0.5-mL dose is formulated to contain 5 Lf of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 µg of inactivated PT, 8 µg of FHA, and 2.5 µg of pertactin (69 kD outer membrane protein). Each antigen is individually adsorbed onto aluminium hydroxide.

7.1.2. Animal studies/human exposure

No published or unpublished clinical data on immunogenicity, efficacy, or effectiveness in pregnant women are available since pregnant women have been routinely excluded from clinical trials. However, there are no specific safety concerns or expectations of harm, and use in pregnancy is not contraindicated.

There are two non-clinical studies performed recently:

1. HLS HEY0017: A study of effects on fertility, embryo-fetal and prenatal and post-natal development in rats by intramuscular administration (including pre-mating immunization phase) with *Boostrix*, *Boostrix* (United States [US] formulation), and *Boostrix IPV* (study report dated 2012, [GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0017]).
2. HLS HEY0018: A study of effects on female fertility and embryo-fetal development in rabbits by intramuscular administration (including pre-mating immunization phase) with *Boostrix* and *Boostrix IPV* (study report dated 2013, [GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0018]).

These studies have shown that there are no key safety findings after the use of *Boostrix* in rats and rabbits. The first study was mainly focused on the reproductive profile in rats and the other study explored the developmental toxicity in rabbits. In the reproductive toxicity study with rats, it was concluded that female rats did not develop important pre- and post-natal adverse effects and that *Boostrix* did not affect the growth or development of the offspring studied. In the developmental toxicity study with rabbits, it was concluded that female rabbits adequately tolerate *Boostrix* and that the vaccine did not adversely affect embryo-fetal development or survival.

In order to generate data on pregnancy outcomes, GSK closely monitored outcomes of unplanned pregnancies in clinical trials, and established a pregnancy exposure registry in the US on 03 May 2005.

Up to 02 August 2013, 10 pregnancy reports were received from clinical trials. Three pregnancies were exposed within 28 days prior to conception; these three pregnancies resulted in three infants without birth defects. Four pregnancies were exposed during the first trimester. Of these, three were lost to follow-up and one resulted in spontaneous abortion in a vaccinee with epilepsy, who was taking lamotrigine prior to and during the pregnancy. Two pregnancies were exposed during an unspecified trimester; both of which were lost to follow-up. The remaining one pregnancy involved exposure to *Boostrix* during an unspecified time prior to conception and no follow-up information has been received until now.

The *Boostrix* pregnancy registry was originally initiated as part of a program of enhanced pharmacovigilance. As of 02 August 2013, 391 pregnancies involving exposure to *Boostrix* in the US had been prospectively reported since the initiation of the pregnancy registry. Among these, 153 (39%) were lost to follow-up and 200 (51%) were ongoing at the time of last contact, including one report from a physician of an unspecified ‘congenital anomaly’ and one report from a healthcare provider regarding a defect noted from an abnormal prenatal screening test (left ventricular echogenic intracardiac focus) in a 22-year-old woman who was exposed to *Boostrix* during the third trimester. Outcomes were reported for 38 (10%) pregnancies, and consisted of 35 live infants born without birth defects, one spontaneous abortion at seven weeks gestation with exposure to *Boostrix* vaccine during the first trimester, and two live infants with birth defects exposed during the second trimester (plagiocephaly in a female diagnosed at two months of age, family history of occipital deformational plagiocephaly) and third trimester (mild left foot ligament laxity in a male diagnosed at birth). Five retrospective pregnancy reports were received up to 02 August 2013. Two pregnancies resulted in a live infant. The outcome of

one pregnancy was unknown. The remaining two reports pertained to one spontaneous abortion at eight weeks of gestation with exposure during the first trimester and one infant who was delivered at an unspecified gestational age and who was diagnosed at birth with pulmonary hypertension and arterial venous malformation (exposure during an unspecified trimester to both *Boostrix* and *Adacel,* on the same day). The infant died while hospitalized; the cause of death was not provided and it was unknown whether an autopsy was performed.

Since 2005, 60 prospective spontaneous reports and two retrospective spontaneous reports were received from outside the US. Among the pregnancies reported prospectively, 12 were reported to be ongoing, 28 were lost to follow-up and 19 had an outcome reported as normal delivery. One subject delivered a live infant with a congenital anomaly (trigonocephaly) approximately 5 days after vaccination. One out of the two pregnancies reported retrospectively resulted in the birth of a live infant without congenital anomaly, the other pregnancy with exposure during the third trimester resulted in the birth of a live infant with fetal pleural effusion and cardiomegaly. These events were considered as unlikely related to vaccination by the reporting physician.

In 2011, the Advisory Committee on Immunization Practices (ACIP) reviewed published and unpublished data from the Vaccine Adverse Event Reporting System, Sanofi Pasteur (*Adacel*) and GSK (*Boostrix*) pregnancy registries, and small studies [Talbot, 2010; Gall, 2011] investigating the administration of combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnancy [Centers for Disease Control and Prevention (CDC), 2011a]. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events (AEs) in pregnant women who received Tdap and that the few serious AEs reported were unlikely to have been caused by the vaccine. Both tetanus- and diphtheria-toxoid vaccines (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic [Silveria, 1995; Czeizel, 1999]. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks gestation is preferred to minimize the risk for any low-frequency AEs and the possibility that any spurious association might appear causative [CDC, 2013a; Terranella, 2013].

Pregnancy and birth outcomes in infants born to women who did or did not receive Tdap vaccine during pregnancy were assessed in a retrospective cohort study [Shakib, 2013]. The study, ending in 2009, was performed before Tdap administration during pregnancy was recommended. From May 2005 through August 2009, 138 women 12-45 years of age with documented Tdap administration during pregnancy (cases) were identified at Intermountain Healthcare facilities; 552 pregnant women without documentation of Tdap immunization were randomly selected as controls. The mean age of pregnant women was 27 years for both cases (range: 14-40) and controls (range: 14-43) ($p = 0.735$). Of the immunized women, 63% received Tdap in the first trimester and 37% in the second or third trimester. The incidence of spontaneous or elective abortion was not higher in cases than in controls. There were no significant differences in pre-term delivery, gestational age, or birth weight between both groups. At least one congenital anomaly was identified in 3.7% infants in the exposed group and 4.4% infants in the control group ($p = 0.749$). In

infants of exposed women, 3.6% had International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnoses consistent with complex chronic conditions within 12 months compared with 10.4% of infants in the control group (p = 0.054). The authors concluded that there was no increase in adverse outcomes in infants born to women receiving Tdap compared to infants of women in the control group.

7.1.3. Medical conditions for use

Though the incidences of diphtheria, tetanus and pertussis during childhood have decreased with immunization programs, immunity to each of these diseases gradually decreases in the absence of administration of booster vaccine doses.

Pertussis is highly contagious (greater than 90% risks of infection have been reported among unvaccinated household contacts) and can cause severe disease, particularly among very young children. During the pre-vaccination era, pertussis was one of the most common childhood diseases and a major cause of infant mortality. Following the introduction of vaccines, the number of cases fell dramatically. In the US, the annual number of reported cases of pertussis decreased from an average of 175,000 per year between 1940 and 1945, to 2900 per year between 1980 and 1990 [CDC, 2012a]. Since the 1990s, the number of cases has been gradually increasing [WHO, 2012]. Despite high vaccination coverage, outbreaks have been reported in numerous countries including the US since 2004. In 2012, 48,277 cases of pertussis were reported in the US, but many more go undiagnosed and unreported. In recent years, adolescents and adults have accounted for a large proportion of cases of pertussis. In Europe, between 1998 and 2002, disease incidence remained steady among infants < 1 year of age; whereas the rate doubled in adolescents and adults, from 16% to 35% [Celentano, 2005]. Between 2008 and 2010, adolescents and adults accounted for more than 50% of all cases in Europe [EUVAC.NET, 2008; EUVAC.NET, 2009; EUVAC.NET, 2010]. A similar shift has been reported in the US [Murphy, 2008].

Pertussis can be severe in infants and children, but in adults the symptoms tend to be mild and indistinguishable from those of other respiratory infections [CDC, 2012a]. However, infected adults can still transmit the disease to susceptible individuals, including infants who have not completed the full vaccination course. It has been established that siblings and adolescent or adult family members with unrecognized pertussis represent the primary source of infection to infants [Bisgard, 2004; Jardine, 2009]. The majority of patients with pertussis will gradually recover; however, some develop potentially life-threatening complications, including pneumonia, neurological complications, otitis media, anorexia and dehydration. Young infants are most at risk of complications; CDC data from 1997 to 2000 found that pneumonia occurred in 5.2% of pertussis cases, but in infants younger than 6 months of age it occurred in 11.8% of cases [CDC, 2012a].

The occurrence of **diphtheria** is currently rare in the US primarily because of the high level of appropriate vaccination among children and because of an apparent reduction in the circulation of toxigenic strains of *Corynebacterium diphtheriae*. Between 2000 and 2012, 5 cases of diphtheria were reported in the US. The overall case fatality risk for diphtheria is 5-10% with higher risk in persons less than 5 years and older than 40 years of age (up to 20%), and has changed very little in the last 50 years [CDC, 2012b].

Tetanus is the only vaccine-preventable disease that is infectious, though not contagious. The incidence of tetanus increases with age due to inadequate booster vaccination in countries where immunization programs are implemented [CDC, 2011b]. In the US, tetanus has become a disease primarily affecting older adults. Vaccinated mothers confer protection to their infants through transplacental transfer of maternal antibody. Neonatal tetanus, which is fatal in 25% of affected neonates, occurs among infants born under unhygienic conditions to inadequately vaccinated mothers [Hackley, 1999]. In the US, 233 tetanus cases were reported between 2001 and 2008; among the 197 cases with known outcomes, the case-fatality rate was 13.2%. Among all persons with reported tetanus, the risk for fatal disease was greater among those aged ≥ 65 years than those aged < 65 years [CDC, 2011b].

Originally, *Boostrix* was licensed in 2005 for persons aged 10 through 18 years. In 2008, the US Food and Drug Administration (FDA) approved an expanded age indication for *Boostrix* to include persons aged 19 through 64 years. In 2011, the indicated age range was further expanded to include persons aged 65 years and older. *Boostrix* is now licensed in the US for use in persons aged 10 years and older as a single-dose booster vaccination. For prevention of tetanus, diphtheria, and pertussis, ACIP recommends that adolescents and adults receive a one-time booster dose of Tdap. Adolescents aged 11 through 18 years who have completed the recommended childhood diphtheria and tetanus toxoids and whole cell pertussis/ diphtheria and tetanus toxoids and acellular pertussis (DTP/ DTaP) vaccination series should receive a single dose of Tdap instead of Td vaccine, preferably at a preventive-care visit at the age of 11 or 12 years. For adults aged 19 through 64 years who previously have not received a dose of Tdap, a single dose of Tdap should replace a single decennial Td booster dose [CDC, 2011c]. Vaccination with Tdap is recommended for all adults aged 65 years and older [CDC, 2012c]. Tdap can be administered regardless of interval since the last tetanus- or diphtheria-toxoid containing vaccine. After receipt of Tdap, persons should continue to receive Td for routine booster vaccination against tetanus and diphtheria, in accordance with previously published guidelines [CDC, 2012c].

In response to pertussis epidemics, several Health Authorities from different countries (US, United Kingdom [UK], New Zealand, Argentina, etc.) recommended Tdap vaccination in pregnancy in order to indirectly protect newborns that are more at risk of acquiring pertussis, before they begin the primary vaccination series. In the US, ACIP voted on 24 October 2012 to recommend Tdap vaccination in each pregnancy. Maternal vaccination programs with Tdap vaccines have also been recommended by Public Health Authorities in a number of other countries (Switzerland, Mexico, Brazil, Argentina, Ireland, UK, and Pan American Health Organization) [CDC, 2013a; HPA, 2013a]. The UK Health Protection Agency is currently evaluating the effectiveness of maternal immunization. A pertussis vaccination program for pregnant women was introduced on 01 October 2012 and pregnant women were offered a 5-component acellular pertussis containing vaccine (diphtheria-tetanus-acellular pertussis-inactivated polio) between 28 and 38 weeks of gestation. Between October 2012 and June 2013, the uptake of pertussis vaccine in pregnant women in the UK was approximately 50%; there has been a slight decline in uptake during 2013 [HPA, 2013b]. Surveillance data captured until end of July 2013, 9 months after initiation of the vaccination program, were presented recently. These data show that the target population of women is strongly supportive of

immunization against pertussis in pregnancy. Since October 2012 pertussis activity has fallen, especially in infants aged less than 3 months of age. Early calculations of programme effectiveness are high and safety data are reassuring [Campbell, 2013].

7.1.4. Characteristics of exposure

Women can be intentionally or unintentionally exposed to vaccines during pregnancy. In general, the women are closely monitored throughout the remainder of the pregnancy.

Refer to Section 9.2.1.2 for potential annual exposure in pregnant women.

7.1.5. Potential benefits of product

No clinical data on the safety or immunogenicity of the use of *Boostrix* during pregnancy or lactation have been generated. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating woman [CDC, 2011d]. In the absence of supporting data, *Boostrix* should only be administered to pregnant women when clearly needed, and when the possible benefit outweighs the possible risks to the fetus. In the US, Tdap vaccination is recommended by ACIP in each pregnancy ([CDC, 2013a], see Section 7.1.3).

7.2. Rationale (Amended on 05 October 2017)

The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies ***or within 28 days preceding conception.*** The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as PASS. The ongoing Registry ***is*** therefore converted into a PASS ***in Q1 2014***.

The Registry requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Patient confidentiality is strictly maintained. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.
- To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.

Refer to Section 9.3.1 for the definition of the primary endpoint.

9. RESEARCH METHODS

9.1. Study design

9.1.1. Overview (Amended on 05 October 2017)

- This study is a transition of an ongoing pregnancy registry (starting on 03 May 2005) into a PASS.
- This is a prospective*, observational, exploratory, cohort study. The *Boostrix* pregnancy registry study requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Data such as vaccination with *Boostrix* during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively**.

  ** Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.*
- *** Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.*
- Study population: pregnant women, vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception, volunteering to take part in the study.
- Type of study: self-contained.
- Data collection: initial and follow-up data will be collected using questionnaires. ***Data for enrollment will be collected using the Initial Notification Form***. Follow-up of cases is performed within ***2*** months of the estimated date of delivery (EDD) to ascertain ***pregnancy*** outcome ***(through the Pregnancy Outcome Form)*** and approximately 6 months and 12 months after the EDD (for all live births ***for whom the contact details of their HCP will be available***) to ascertain

the presence of birth defects not diagnosed before ***(through the 6- and 12-month post-delivery Follow-Up Form)***.

- After transition of the ongoing pregnancy registry into a PASS, data will be collected for a minimum of 5 years, starting Q1 2014.

9.1.2. Rationale for study design

This prospective cohort study is designed as a Registry. After market authorization, AEs that occur after administration of the vaccine can and should always be reported. In that case, however, there is no clear group in which the events occur and so a proper rate of occurrence cannot be estimated. In this pregnancy registry, participants are recruited between administration of the vaccine and the potential occurrence of an AE (i.e., a teratogenic effect in the offspring). This allows for a more proper estimation of the rate of occurrence of these events. Nevertheless, the results of this study still need to be regarded with caution as the exact number of women exposed during pregnancy is unknown. Incidences of events can therefore not be calculated from the study data.

Furthermore, it is likely that pregnant women who accept vaccination may differ from those who refuse vaccination in underlying health status, propensity to seek medical care, propensity to report AEs and differences in access to medical care in general. The differential response/participation by vaccinated versus unvaccinated pregnant women in a pregnancy registry could significantly bias risk estimates and possibly in unpredictable ways, because of the inability to collect adequate data to characterize the non-responders. Therefore, the risks of any identified birth defects will be compared to those in the general population, such as that defined by the Metropolitan Atlanta Congenital Defects Program (MACDP).

9.2. Setting

9.2.1. Study population

9.2.1.1. Patient population

In the US, *Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis. Originally licensed for persons aged 10 through 18 years, the vaccine was approved by the FDA for use in persons aged 19 through 64 years in 2008, and in persons aged 65 years and older in 2011.

The study population includes women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

9.2.1.2. Potential annual exposure

Size of the potential "at-risk" population

The US Census Bureau estimates that, as of 1 July 2012, the resident US female population was 62,744,930 between the ages of 15 and 44 years old [US Census Bureau, 2013]. The provisional fertility rate in the US in 2012 was 63.2 births per 1000 women aged 15-44 years and the provisional count of births was 3.96 millions [CDC, 2012d].

Number of pregnant vaccinees

Boostrix was originally classified as FDA Pregnancy Category C, which was changed to Category B in September 2012, as a study of developmental toxicity in female rats showed no key safety concerns. Pregnancy Category B means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Since February 2013, *Boostrix* vaccination is recommended by the ACIP in each pregnancy.

More than 20 million doses of *Boostrix* were distributed in the US between May 2005 and July 2011. Experiences with the ongoing *Boostrix* pregnancy registry (391 exposed pregnancies reported prospectively and five exposed pregnancies reported retrospectively between 03 May 2005 and 02 August 2013) and other vaccine pregnancy registries (e.g., smallpox vaccine [CDC, 2003], varicella vaccine [Shields, 2001], and *Twinrix*) indicate that it is likely that fewer than 100 pregnancies per year will be registered.

9.2.2. Patient recruitment (Amended on 05 October 2017)

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Since the initiation of the Registry in 2005, GSK has taken several measures to increase the rate of pregnancy registration (accrual). A GSK Registry web page has been created with instructions for enrolling patients in the Registry and GSK has requested that the FDA post a link to this web page on their Pregnancy Registry Website. ***The forms for enrolling and reporting outcomes are also accessible to healthcare providers through the GSK Registry web page.*** In response to a 2008 request from the FDA to facilitate enrollment, GSK initiated a dedicated toll-free telephone number (PPD), at which US-based callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the US Prescribing Information in early 2009. The Prescribing Information and GSK Registry website each give a brief summary of the purpose and intent of the Registry, along with telephone contact information. ***Fax contact information is available on the GSK Registry web page***.

9.2.3. Selection of a comparison group

This registry study is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal

warranting further investigation. Background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) will be used.

9.2.4. Study period (Amended on 05 October 2017)

The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and converted into a PASS ***in Q1 2014***. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

9.2.5. Inclusion criteria

A subject will be included in the Registry if all of the following criteria are met:

- Exposure to vaccine occurs during pregnancy or within 28 days preceding conception.
- Subject is a US resident.
- A HCP is identified (name, address and phone number).
- Subject can be identified (by GSK or HCP).

Data from registered subjects will be included in the analyses if the following criterion is met:

- Pregnancy is ongoing and the outcome is unknown.

9.2.6. Exclusion criterion

Data from registered subjects will not be included in the analyses if the following criterion is met:

- Outcome of pregnancy is known at the time of initial report. Types of known outcomes include prenatal testing reports in which the results are abnormal or outside the reference range, indicating possible abnormality in the fetus. Typically, pregnancies > 16 weeks gestation will have undergone prenatal testing that can identify whether a child has congenital abnormalities.

9.3. Variables

9.3.1. Primary endpoint

- Occurrence of any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

9.3.2. Data to be collected (Amended 05 October 2017)

Initial and follow-up data will be collected using questionnaires. ***Data for enrollment will be collected using the Initial Notification Form. Follow-up of cases is performed within 2 months of the estimated date of delivery (EDD) to ascertain pregnancy outcome (through the Pregnancy Outcome Form) and approximately 6 months and 12 months after the EDD (for all live births for whom the contact details of their HCP will be available) to ascertain the presence of birth defects not diagnosed before (through the 6- and 12-month post-delivery Follow-Up Form).*** The following data will be collected:

- Patient identifier.
- Maternal data, including date of birth, date of last menstrual period (LMP), EDD.
- Maternal relevant medical/family history.
- Paternal relevant medical/family history.
- Type of conception.
- Prenatal testing.
- Maternal prenatal drug/vaccine exposure, including drug/vaccine name, date of administration, route of administration, dose, lot number, indication.
- Pregnancy outcome.
- Method of delivery.
- Infant/fetal information, including gestational weeks at birth/miscarriage/ termination, gender, length, weight, Apgar score.
- Description of birth defects, if applicable.
- AEs experienced by the fetus/infant or the mother.
- Reporter information.
- Any additional data that seems relevant for this study.

9.4. Data sources (Amended on 05 October 2017)

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP. ***Follow-up from the HCP of the infant post birth 6 and 12 months will be performed when the contact details are available and with consumer's permission***. A toll-free telephone number for reporting AEs and vaccine-exposed pregnancies to the Registry is listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary information.

9.5. Study size

No minimum sample size is required for this descriptive study.

Refer to Section 9.2.1.2 for the size of the potential "at-risk" population and the number of pregnant vaccinees.

9.6. Data management

9.6.1. Data collection (Amended on 05 October 2017)

Initial and follow-up data will be collected using questionnaires. Initial data will be collected before the outcome is known. Follow-up of cases will be performed at the following timepoints:

- ***For consumer reports:***
  - ***At initial notification of pregnancy exposure: 2 attempts at 4-6 week intervals will be made to obtain more information about the pregnancy (e.g. estimated time of delivery (EDD) and/or last menstrual period (LMP) and to obtain permission to contact the patient's HCP***
  - ***Within 2 months after EDD, 1 additional attempt is made if permission to contact the patient's HCP has not already been granted to obtain more information about the pregnancy and obtain the permission to contact the patient's HCP.***
  - ***Within 2 months after EDD (and if the patient has not previously provided the contact information for the infant's HCP): 2 attempts at 4-6 week intervals will be made for the prospective cases reporting a live birth to obtain the contact information of the HCP supervising the health of the infant.***

- ***For the HCP reports:***
  - ***At initial notification of pregnancy exposure or once permission has been granted for reports initially received from a consumer, two attempts at 4-6 week intervals will be made to obtain more information via pregnancy follow-up form.***
  - Within ***2*** months of the EDD, to ascertain outcome. ***Two follow-up*** attempts to obtain outcome information will be made before any case is considered lost to follow-up.
- An additional follow-up ***attempt*** will be done for ***the*** live births approximately 6 months and 12 months after the EDD to ascertain the presence of birth defects not diagnosed at the time of the initial ***pregnancy outcome***. ***This follow-up will be done for the prospective reports if the consumer has granted the permission and when the contact details of the HCP attending the infant are available.***

9.6.2. Processing of reports (Amended on 05 October 2017)

Reports are entered into the GSK safety database by ***GSK Case Management Group (CMG)*** using existing mechanisms and practices. Medical Dictionary for Regulatory Activities (MedDRA) is used in the database to code AEs.

Follow-up is conducted by ***CMG***. The HCP is contacted if she/he requests or if initial information is insufficient or needs clarification. ***The follow-up of cases is performed as described in section 9.6.1.***

9.6.2.1. Solicitation of outcome (Amended on 05 October 2017)

As explained in section 9.6.1, within ***two*** months after the EDD and if the HCP has not already provided the ***pregnancy*** outcome, she/he is sent an outcome form (questionnaire). The mode of communication is ***generally via standard letter***.

Two attempts are made to secure the outcome information from the HCP ***via standard letter***. ***For the live births*** and with the mother's permission, attempts are made to solicit information from the pediatrician and/or other specialists who have provided healthcare/consultation to the child ***until 12 months of age***.

9.6.2.2. Classification of outcomes (Amended 05 October 2017)

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. For purposes of analysis, pregnancy outcomes are dichotomized according to the presence or absence of birth defects. ***Pregnancy outcomes are*** further categorized as: 1) live births, 2) spontaneous abortions (i.e., pregnancy losses), 3) ***Elective/***induced abortions ***and 4) Fetal deaths/Stillbirths***.

This Registry adopts a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects.

To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor, 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC inclusion list may be classified as birth defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

9.7. Data analysis (Amended on 05 October 2017)

Pregnancy outcomes include spontaneous abortion (pregnancy loss before ***22*** weeks gestation), fetal deaths/stillbirths (loss at or after ***22*** weeks gestation), elective/***induced*** abortions and live births. Gestational weeks are counted from the date of the LMP. The second trimester is considered to begin at week 14 and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy (i.e., multiple administrations of *Boostrix*) are classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. ***Given the descriptive nature of this study, confidence intervals will not be calculated***. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation.

The majority of spontaneous abortions occur early in pregnancy [Wilcox, 1981; Wilcox, 1983; Ellish, 1996]. If spontaneous abortions were to be evaluated as an outcome of interest, it would be essential to enroll pregnancies as soon as possible after vaccination with *Boostrix*. Because enrollment and recognition of pregnancy would occur at various times, it would be virtually impossible to meaningfully evaluate the effects of *Boostrix* on pregnancy loss [Kennedy, 2004]. Therefore, spontaneous abortions without birth defects are excluded from the risk calculations.

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (1 of 33) of live births [CDC, 2013b]. The estimated risk cited in the medical literature varies because of differences in case definitions, populations sampled and ascertainment methods. The Collaborative Perinatal Project, using a broader case

definition and prospective ascertainment, reports a frequency of 5% to 7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis [CDC, 2013b]. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness and to enable the assessment of possible increases in the frequency of birth defects, all defects will be included in the periodic summary reports of this Registry.

Criteria for review of a specific individual report include:

- Is the timing of the vaccination with *Boostrix* commensurate with the ontogenetic development of the organ(s) affected by the abnormalities?
- Is there another known or likely cause (e.g., pre-existing genetic or chromosomal defect or exposure to a known teratogen)?
- Is the congenital abnormality not previously described (i.e., is it new to medical science)?
- Is there a unique constellation of defects (i.e., is there a new syndrome)?

Criteria for review of aggregate data include:

- Is there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects?
- Is there a deviation from the expected frequencies of individual defects?
- Is there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology?

Studies have shown that the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10% to 22% [Wilcox, 1981; Wilcox, 1983; Wilcox, 1988; Fenster, 1997; Windham, 1997; Khattak, 1999; Anderson, 2000; Osborn, 2000].

While the Registry is to be limited to prospective reports, some pregnancy exposures are reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports. In general, retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases and is not reflective of the general experience with the drug. Information about the total number of exposed pregnancies, i.e., the pool of exposures from which the retrospective reports arise, is unknown; therefore, incidences of outcomes cannot be calculated from these data. A series of reported birth defects, however, can be analyzed to detect patterns of specific congenital abnormalities and can identify early signals of new vaccine-associated risks. A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.

Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.

9.8. Quality control

Data will be recorded using questionnaires. Subject data necessary for analysis, follow-up and reporting will be entered/transmitted into a validated database or data system. Data management will be performed in accordance with applicable GSK standards.

To ensure compliance with Good Clinical Practice (GCP) and all other applicable guidelines and 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.

9.9. Limitations of the research methods

This Registry is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. Therefore, background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) are used. The potential limitations of comparisons between Registry and background data depend upon the event(s) being compared and will be discussed on an *ad hoc* basis in the relevant periodic Registry reports.

Potential sources of biases are described below:

- As reporting of pregnancies is voluntary, it is possible that even among prospectively reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.
- The calculation of risk, which does not include spontaneous abortions or voluntary terminations for which no defects have been reported, may introduce bias. It is unknown what proportions of these pregnancies consist of potentially normal outcomes versus congenital abnormalities. GSK attempts to obtain information on anomalies detected at the time of the outcome, but this may not be known to the reporting physician.
- Those pregnancies that have reached EDD but for which outcome information was unobtainable are considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. All attempts are made to minimize this potential source of bias.

Refer to Section 9.1.2 for other potential limitations of the study.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the International Conference on Harmonization (ICH) Guideline for GCP or other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favorable opinion/approval to conduct the study prior to study start or will document that neither a favorable opinion nor an approval to conduct the study is needed.

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

- Institutional Review Board review and favorable opinion/approval of study protocol and any subsequent amendments;
- Institutional Review Board review and favorable opinion/approval of waiver for documentation of informed consent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. All reports received by the Registry will be entered into the GSK safety database and reported to regulatory authorities according to applicable regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS (AMENDED ON 05 OCTOBER 2017)

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

GSK plans to continue the Registry for 5 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report ***and the DSUR*** for *Boostrix*. A final report will be written and submitted ***within one year of completion of the five-year period as described in Section 6***. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within ***12*** months of completion of the analysis. GSK also aims to publish the results of these studies in the ***indexed***, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

13. REFERENCES (AMENDED ON 05 OCTOBER 2017)

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	List of stand-alone documents
2	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	ENCePP Checklist for study protocols
3	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Glossary of terms
4	201327 (EPI-PERTUSSIS-028 VS US PR)	05-OCT-2017	Amendments and administrative changes to the protocol
5	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Trademarks
6	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Protocol Sponsor Signatory Approval

Annex 2 ENCePP Checklist for study protocols

Annex 2 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]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☐	☐	☒	See comments
1.1.4 Interim progress report(s)	☒	☐	☐	13, see comments
1.1.5 Registration in the EU PAS register	☒	☐	☐	13, see comments
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

For 1.1.3: no progress reports are planned for this study For 1.1.4: five annual reports are planned for this study For 1.1.6: the EU PAS register number will be generated at the time of the final version of the protocol.

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)	☒	☐	☐	13-18
2.1.2 The objective(s) of the study?	☒	☐	☐	19

[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)**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	20-21
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori 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, randomized controlled trial, new or alternative design)	☒	☐	☐	19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22
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)	☒	☐	☐	25-27

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	23
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	21

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.2 Age and sex?	☒	☐	☐	20, 22
4.2.3 Country of origin?	☒	☐	☐	20, 22
4.2.4 Disease/indication?	☒	☐	☐	16-18
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	22

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)	☒	☐	☐	23-24
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)	☒	☐	☐	19, 26
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	25-26
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?	☒	☐	☐	19, 22
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)	☒	☐	☐	19, 20, 27

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)	☒	☐	☐	22, 23
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	19, 25, 26

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.)	☒	☐	☐	23, 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.)	☒	☐	☐	23, 24
8.1.3 Covariates?	☒	☐	☐	23, 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)	☒	☐	☐	23, 24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23, 24
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23, 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)	☒	☐	☐	24
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?	☐	☒	☐	See comments

Comments:

For 9.1: This is an exploratory/descriptive study. No minimum sample size is required. Reference pages 20 and 24 of the protocol.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25-26
10.3 Are descriptive analyses included?	☒	☐	☐	25-26
10.4 Are stratified analyses included?	☒	☐	☐	25-26
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	25-26
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?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24, 27, 28
11.3 Are methods of quality assurance described?	☒	☐	☐	27

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
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?	☒	☐	☐	20, 27
12.1.2 Information biases?	☒	☐	☐	20, 27
(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)	☒	☐	☐	20, 21, 23
12.3 Does the protocol address other limitations?	☒	☐	☐	20, 27

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?	☒	☐	☐	27, 28
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.3 Have data protection requirements been described?	☒	☐	☐	27, 28

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13

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)?	☒	☐	☐	28
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	28

Comments:

Name of the main author of the protocol: PPD

Date: / /

Signature: _____

Annex 3 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
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).
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
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.
Post-Authorization Safety Study (PASS):	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized 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 authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).

Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations and organization 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.
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.

Annex 4 Amendments and administrative changes to the protocol

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 1

eTrack study number and Abbreviated Title:	201327 (EPI-PERTUSSIS-028 VS US PR)
Amendment number:	Amendment 1
Amendment date:	05 October 2017
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

The current protocol is being amended to correct the protocol deviations identified, and describe the data collection and management process to be followed. A summary of the amendments done to the protocol is provided below:

Number of Follow -up attempts:

According to the initial version of the protocol, outcomes will be solicited within 3 months after the expected delivery date (EDD) and "at least 3 attempts to obtain outcome information will be made before any case is considered lost to follow-up".

For this study, two attempts had been made before any case was considered lost to follow-up instead of the 3 attempts described in the protocol. The two-attempt follow-up process is consistent with the GSK standard operating procedures for spontaneous pregnancy reports received worldwide. This is considered an acceptable standard practice in attempting to obtain follow-up information.

Considering the above rationale, this amendment will reduce the requirement of 3 follow-up attempts to 2 follow-up attempts to obtain pregnancy outcome data in order to reflect current practices. Also, follow-up retrospectively on subjects who have already been lost to follow-up after two consecutive attempts to obtain outcome data is also not recommended in this amendment. By not pursuing a third follow-up attempt among lost to follow-up patients, the data collected before and after the deviation was consistent and comparable to one-another. Furthermore, the risk of recall bias via retrospective data collection is also avoided.

Additionally, data collection section has been updated to describe in more detail the initial and follow-up process of data collection for the reports received from consumers and HCPs.

Additional Follow up at 6 and 12 months after EDD:

According to the initial version of the protocol, additional follow-up questionnaires should be sent for all live births approximately 6 months and 12 months after EDD to ascertain the presence of birth defects not diagnosed at the time of the initial follow up. However neither of these follow-up questionnaires were implemented as of this protocol amendment.

GSK Biologicals acknowledges the importance of this information and intends to implement both 6- and 12-month follow-up attempts prospectively. The data collection form for 6- and 12-month follow-ups will be developed in parallel to this protocol amendment. For the subjects already enrolled, there will be no attempt to collect the 6 and 12-month data as the likelihood of having appropriate contact details and/or receiving reliable data is low and such practice is likely to introduce recall bias, hence compromising the validity of the results.

Hence, the above proposed changes will only be applicable for patients to be enrolled after the approval of this protocol amendment (and the related documents/forms) when the pregnancy outcome is a live birth, the contact details of the HCP attending the infant are available and with the consumer's permission.

Originally, a signed consent form from pregnant subjects was only requested when these registered themselves into the registry, and to allow GSK to contact their HCPs. GSK will now also encourage HCPs who register their patients to provide these with the consent form. This consent will also allow to contact the HCP supervising the health of the infant up until 12 months after delivery (the updated consent form will now request contact information from HCP supervising the health of infant). This new consent form will be implemented for all prospective reports after the protocol amendment approval.

Gestational age cut-off for spontaneous abortions and stillbirths:

The 20 weeks' cut-off in gestational age has been replaced by 22 weeks based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006], as per the standard definition used by GSK Biologicals. It is recognized that national regulations might be different.

Exclusion Criteria section:

The following sentence have been deleted from the exclusion criteria section *"Pregnancies in which prenatal testing indicates a normal pregnancy would also be excluded because inclusion of such pregnancies could potentially bias results toward a lower overall estimate of risk for defects*"

It is important to notice that besides the presence of that wording in the initial version of the protocol, normal pregnancies have not been excluded from the registry since the beginning. The prenatal routine testing is non-invasive and is performed during prenatal visits (usually at least one by pregnancy trimester). The routine screening includes, blood serum assessment, ultrasound undertaken in first and second trimester, nuchal translucency measurement and serum screening for alpha-fetoprotein. Neither of the prenatal testing (regardless if it is routine or specific targeted) do not diagnose 100% of the cases. Thus, by excluding the pregnancies with normal prenatal screening, part of the anomalies will be excluded as well. Additionally, considering that most pregnancies in the US go through foetal ultrasounds by the first trimester of gestation, this exclusion criterion will limit the number of subjects who enrol into the registry and enrich for subjects with low prenatal care coverage.
Hence, the exclusion criterion is being amended not to exclude the pregnancies with normal prenatal screening, in line with the process followed on this pregnancy registry, where the reported pregnancies with normal prenatal testing were always included.

Pregnancy registry reports Milestones:

The table summarizing the dates for submission of the annual reports has been updated to reflect the data lock point and the updated submission dates of each report.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Cover page:

Authors	• PPD, ***Safety Scientist, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance***
	• PPD, ***Safety Physician, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance***
	• PPD, ***Safety Evaluation & Risk Management Team Leader, Vaccine Clinical Safety and Pharmacovigilance***
	• PPD, ***Head, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance***
	• PPD, ***Clinical and Epidemiology Project Lead, DTP Polio Hib – containing vaccines***
	• PPD, ***Regulatory Affairs***
	• PPD, ***Study Delivery Lead***
	• PPD, ***Manager, CMG US***

	• PPD , ***Director, CMG US*** • PPD , ***Clincial Safety Associate, CMG*** • PPD , ***Director CMG***

List of abbreviations:

DLP	***Data Lock Point***

Abstract:

Rationale and background

In the US*, Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in individuals 10 years of age and older.

The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies ***in the US***. The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced Pharmacovigilance. Following new European Union pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry ~~will~~ ***is*** therefore ~~be~~ converted into a PASS ***in Q1 2014***. ~~Timelines for collection of follow-up data will be adapted in order to correspond to the follow-up timelines of other GSK pregnancy registries.~~

The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy. Retrospective reports will be captured by the Registry but will not be included in the analyses of prospective reports.

Study design

- This study is a transition of an ***US*** ongoing pregnancy registry (starting on 03 May 2005) into a PASS.
- This is a prospective*, observational, exploratory, cohort study. The Boostrix pregnancy registry study requires voluntary, prospective reporting of eligible pregnancies by patients and healthcare professionals (HCPs). Data such as vaccination with Boostrix during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively**.

* Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.

** Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.

- Study population: pregnant women, residing in the United States (US), vaccinated with Boostrix during pregnancy or within 28 days preceding conception volunteering to take part in the study.
- Type of study: self-contained.
- Data collection: initial and follow-up data will be collected using questionnaires. Follow-up of cases is performed within ***2*** ~~3~~ months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6 months and 12 months after the EDD (for all live births ***for whom the contact details of their HCP will be available***) to ascertain the presence of birth defects not diagnosed before.
- After transition of the ongoing pregnancy registry into a PASS, data will be collected for a minimum of 5 years, starting Q1 2014.

Data sources	• Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP, ***follow-up from the HCP of the infant post birth 6 and 12 months will be performed when the contact details are available and with consumer's permission***. A toll-free telephone number for reporting adverse events (AEs) and vaccine-exposed pregnancies to the Registry will be listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary information.
Data analysis	• Pregnancy outcomes include spontaneous abortion (pregnancy loss before ***22*** ~~20~~ weeks gestation), fetal deaths/stillbirths (loss at or after ***22*** ~~20~~ weeks gestation), elective/~~therapeutic~~ ***induced*** abortions and live births. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories. • Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation. • Spontaneous abortions without birth defects are excluded from the risk calculations. • All defects regardless of trimester of vaccine exposure will be included in the periodic summary reports of this Registry and stratified by trimester of exposure. • A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.
Milestones	• The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and ~~will now be~~ is converted into a PASS ***in Q1 2014***. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. Summary reports ***with cumulative analysis*** will

be written annually. A final ***cumulative*** report will be written ~~and submitted 18 months after the last annual report~~ ***within one year of completion of the five year period***. After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

Section 6 Milestones

Milestone ***(Including Data Lock Point (DLP) of each report)***	**Planned *Submission* date**
Start of data collection	Q1 2014[a]
End of data collection	***2 August 2019***[b] ~~Q4 2018~~[b]
Annual report 1 ***(DLP: 2 August 2015)***	***Q2 2016***
Annual report 2 ***(DLP: 2 August 2016)***	***Q2 2017*** ~~Q1 2016~~
Annual report 3 ***(DLP: 2 August 2017)***	***Q2 2018*** ~~Q1 2017~~
Annual report 4 ***(DLP: 2 August 2018)***	***Q2 2019*** ~~Q1 2018~~
Annual report 5/***Final report (DLP: 2 August 2019)***	***Q2 2020***[c] ~~Q1 2019~~
Registration in the EU PAS register	Q1 2014
~~Final report~~	~~Q2 2020 (18 months after the last annual report)~~

[a] The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry will therefore be converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014.***Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report (PBRER) and the Development Safety Update Report DSUR) for Boostrix.***

[b] After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

[c] ***Since the annual reports also contain cumulative data, the last annual report (with DLP: 2 August 2019) will serve the purpose of the Final report.***

Section 7.2 Rationale

The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies ***or within 28 days preceding conception.*** The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as PASS. The ongoing Registry ~~will now be~~ ***is*** therefore ~~be~~ converted into a PASS ***in Q1 2014***. ~~Timelines for collection of follow-up data will be adapted in order to correspond to the follow-up timelines of other GSK pregnancy registries. The *Boostrix* pregnancy registry was and will be maintained by Vaccine Clinical Safety and Pharmacovigilance.~~

The Registry requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Patient confidentiality is strictly maintained. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy.

Section 9.1.1 Study design overview

- Data collection: initial and follow-up data will be collected using questionnaires. ***Data for enrollment will be collected using the Initial Notification Form***. Follow-up of cases is performed within ***2*** ~~3~~ months of the estimated date of delivery (EDD) to ascertain ***pregnancy*** outcome ***(through the Pregnancy Outcome Form)*** and approximately 6 months and 12 months after the EDD (for all live births ***for whom the contact details of their HCP will be available***) to ascertain the presence of birth defects not diagnosed before ***(through the 6- and 12-month post-delivery Follow-Up Form)***.

Section 9.2.2 Patient recruitment

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Since the initiation of the Registry in 2005, GSK has taken several measures to increase the rate of pregnancy registration (accrual). A GSK Registry web page has been created with instructions for enrolling patients in the Registry and GSK has requested that the FDA post a link to this web page on their Pregnancy Registry Website. ***The forms for enrolling and reporting outcomes are also accessible to healthcare providers through the GSK Registry web page.*** In response to a 2008 request from the FDA to facilitate enrollment, GSK initiated a dedicated toll-free telephone number (PPD), at which US-based callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the US Prescribing Information in early 2009. The Prescribing Information and GSK Registry website each give a brief summary of the purpose and intent of the Registry, along with telephone ~~and fax~~ contact information. ***Fax contact information is available on the GSK Registry web page***.

Section 9.2.4 Study period

The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and ~~will now be~~ converted into a PASS ***in Q1 2014***. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Section 9.2.6 Exclusion criteria

Data from registered subjects will not be included in the analyses if the following criterion is met:

- Outcome of pregnancy is known at the time of initial report. Types of known outcomes include prenatal testing reports in which the results are abnormal or outside the reference range, indicating possible abnormality in the fetus. ~~Pregnancies in which prenatal testing indicates a normal pregnancy would also be excluded because inclusion of such pregnancies could potentially bias results toward a lower overall estimate of risk for defects~~ [Honein~~, 1999]~~. Typically pregnancies > 16 weeks gestation will have undergone prenatal testing that can identify whether a child has congenital abnormalities.

Section 9.3.2 Data to be collected

Initial and follow-up data will be collected using questionnaires. ***Data for enrollment will be collected using the Initial Notification Form. Follow-up of cases is performed within 2 months of the estimated date of delivery (EDD) to ascertain pregnancy outcome (through the Pregnancy Outcome Form) and approximately 6 months and 12 months after the EDD (for all live births for whom the contact details of their HCP will be available) to ascertain the presence of birth defects not diagnosed before (through the 6- and 12-month post-delivery Follow-Up Form).*** The following data will be collected:

- Patient identifier.
- Maternal data, including date of birth, date of last menstrual period (LMP), EDD.
- Maternal relevant medical/family history.
- Paternal relevant medical/family history.
- Type of conception.
- Prenatal testing.
- Maternal prenatal drug/vaccine exposure, including drug/vaccine name, date of administration, route of administration, dose, lot number, indication.
- Pregnancy outcome.
- Method of delivery.
- Infant/fetal information, including gestational weeks at birth/miscarriage/ termination, gender, length, weight, Apgar score.
- Description of birth defects, if applicable.
- AEs experienced by the fetus/infant or the mother.
- Reporter information.
- Any additional data that seems relevant for this study.

Section 9.4 Data sources

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP. ***Follow-up from the***

HCP of the infant post birth 6 and 12 months will be performed when the contact details are available and with consumer's permission. A toll-free telephone number for reporting AEs and vaccine-exposed pregnancies to the Registry is listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary information.

Section 9.6.1 Data collection

Initial and follow-up data will be collected using questionnaires. Initial data will be collected before the outcome is known. Follow-up of cases will be performed at the following timepoints:

- ***For consumer reports:***
  - ***At initial notification of pregnancy exposure: 2 attempts at 4-6 week intervals will be made to obtain more information about the pregnancy (e.g. estimated time of delivery (EDD) and/or last menstrual period (LMP) and to obtain permission to contact the patient's HCP***
  - ***Within 2 months after EDD, 1 additional attempt is made if permission to contact the patient's HCP has not already been granted to obtain more information about the pregnancy and obtain the permission to contact the patient's HCP.***
  - ***Within 2 months after EDD (and if the patient has not previously provided the contact information for the infant's HCP): 2 attempts at 4-6 week intervals will be made for the prospective cases reporting a live birth to obtain the contact information of the HCP supervising the health of the infant.***
- ***For the HCP reports:***
  - ***At initial notification of pregnancy exposure or once permission has been granted for reports initially received from a consumer, two attempts at 4-6 week intervals will be made to obtain more information via pregnancy follow-up form.***
  - Within ***2*** ~~3~~ months of the EDD, to ascertain outcome. ~~At least three~~ ***Two follow-up*** attempts to obtain outcome information will be made before any case is considered lost to follow-up.
- An additional follow-up ***attempt*** will be done for ~~all~~ ***the*** live births approximately 6 months and 12 months after the EDD to ascertain the presence of birth defects not diagnosed at the time of the initial follow-up. ***This follow-up will be done for the prospective reports if the consumer has granted the permission and when the contact details of the HCP attending the infant are available.***

Section 9.6.2 Processing of reports

~~Initial~~ ***R***eports are entered into the GSK safety database by ***GSK Call Center Case Management Group (CMG)*** using existing mechanisms and practices. Medical Dictionary for Regulatory Activities (MedDRA) is used in the database to code AEs.

Follow-up is conducted by the ***CMG***. The HCP is contacted if she/he requests or if initial information is insufficient or needs clarification. ~~The HCP is encouraged to keep a copy of the initial completed form in the patient's chart.~~ ***The follow-up of cases is performed as described in section 9.6.1.***

Section 9.6.2.1 Solicitation of outcome

As explained in section 9.6.1, within ~~three~~ ***two*** months after the EDD and if the HCP has not already provided the ***pregnancy*** outcome, she/he is sent an outcome form (questionnaire), ~~along with a copy of the initial completed pregnancy form~~. The mode of communication is ~~the one through which the initial information was received (telephone, fax, or postal mail)~~ ***generally via standard letter.***

Two ~~At least 3~~, attempts are made to secure the outcome information from the HCP ***via standard letter***. ~~The second and third attempts utilize all modes of contact available (mail, fax, telephone). If outcome is not received from the HCP and contact information is available for the patient, she is then contacted by mail or fax.~~

~~In the event of an abnormal outcome~~ ***For the live births*** and with the mother's permission, attempts are made to solicit information from the pediatrician and/or other specialists who have provided healthcare/consultation to the child ***until 12 months of age***.

Section 9.6.2.2 Classification of outcome

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. For purposes of analysis, pregnancy outcomes are dichotomized according to the presence or absence of birth defects. ~~The latter group is~~ ***Pregnancy outcomes are*** further categorized as: 1) live births, 2) spontaneous abortions (i.e., pregnancy losses), 3) ***Elective***/induced abortions 4) ***and Fetal deaths/Stillbirths.***

This Registry adopts a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects.

To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor, 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC inclusion list may be classified as birth defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable

to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

Section 9.7 Data analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before ***22*** ~~20~~ weeks gestation), fetal deaths/stillbirths (loss at or after ***22*** ~~20~~ weeks gestation), elective/~~therapeutic~~ ***induced*** abortions and live births. Gestational weeks are counted from the date of the LMP. The second trimester is considered to begin at week 14 and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy (i.e., multiple administrations of *Boostrix*) are classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. ~~An exact 95% confidence interval is calculated using standard statistical software~~. ***Given the descriptive nature of this study, confidence intervals will not be calculated***. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation.

Section 12 Plans for disseminating and communicating study results

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

GSK plans to continue the Registry for 5 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report ***and the DSUR*** for *Boostrix*. A final report will be written and submitted ~~after 5 years~~ ***within one year of completion of the five-year period as described in Section 6***. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within ~~8~~ ***12*** months of completion of the analysis. GSK also aims to publish the results of these studies in the ~~searchable~~ ***indexed***, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

Section 13 References

~~Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. *Teratology*. 1999; 60(6): 356-364.~~

EMA 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed on 05 October 2017.

Annex 5 Trademarks

The following trademarks are used in the present study outline. Note: In the remainder of the document, the names of the vaccines will be written without the superscript symbol ™ or ®.

Trademarks of the GSK group of companies	Generic description
Boostrix	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
Boostrix IPV	combined diphtheria, tetanus, acellular pertussis (adsorbed) and inactivated poliomyelitis vaccine
Twinrix	hepatitis A inactivated & hepatitis B (recombinant) vaccine

Trademarks not owned by the GSK group of companies	Generic description
Adacel (Sanofi Pasteur)	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed

Annex 6 Protocol Amendment 1 sponsor signatory approval

eTrack study number and Abbreviated Title	201327 (EPI-PERTUSSIS-028 VS US PR)
Date of protocol amendment	Amendment 1 Final: 05 October 2017
Detailed Title	Boostrix Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix during pregnancy or within 28 days preceding conception.
Sponsor signatory	***Narcisa Mesaros, MD*** ***Clinical and Epidemiology Project Lead,*** ***DTP Polio Hib – containing vaccines,*** ***GlaxoSmithKline Biologicals, SA***
Signature	_____
Date	_____

- ----------Checksum----------!Ver.!Created On - -
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Sponsor signatory	***Narcisa Mesaros, MD*** ***Clinical and Epidemiology Project Lead,*** ***DTP Polio Hib – containing vaccines,***
Signature	PPD
Date	23-10-2017

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