Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals

Rue de l'Institut 89

1330 Rixensart, Belgium.

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine (Boostrix™) (263855).
Other Study vaccine	Placebo
eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Date of protocol	Final Version 01: 28 January 2015
Date of protocol amendment	Amendment 1 Final: 29 May 2015 Amendment 2 Final: 15 July 2015
Title	Immunogenicity and safety study of GSK Biologicals' dTpa vaccine, Boostrix™ (263855) in pregnant women.
Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Co-ordinating author	PPD, Scientific Writer

eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Date of protocol	Final Version 01: 28 January 2015
Date of protocol amendment	Amendment 1 Final: 29 May 2015 Amendment 2 Final: 15 July 2015
Title	Immunogenicity and safety study of GSK Biologicals' dTpa vaccine, Boostrix™ (263855) in pregnant women.
Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Contributing authors	• PPD, Project-Level CRDL • PPD, Clinical Research and Development Lead (CRDL) • PPD ***, Medical Director, Vaccines, Spain*** • PPD ***, Medical Affairs Manager, Vaccines, Spain*** • PPD, Project Statistician • PPD ***and*** PPD, Study Delivery Leads • PPD, GVCL Project Manager • PPD and PPD, Global Clinical Regulatory Affairs Representatives • PPD and PPD, Clinical Safety Representatives • PPD, Global Patents Representative • PPD, Study Data Manager • PPD, Senior Manager, Biometrics • PPD, Vaccines Supply Coordinator • PPD, Director, Global Medical Affairs • PPD, Study Delivery Manager • PPD, Local Delivery Lead (LDL), Australia • PPD, LDL, Canada • PPD, LDL, Spain

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Date of protocol amendment	Amendment 2 Final: 15 July 2015
Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Sponsor signatory	Htay Htay Han, Project Level CRDL, Rotavirus and Tdap Maternal vaccination, GlaxoSmithKline Biologicals.

Signature _____

Date _____

For internal use only

- ----------Checksum----------!Ver.!Created On - -
552cb61e98ad426988e436831e69cba1351ae35d 2.0 7/17/2015 12:12:04 PM - -
---------- -

Protocol Amendment 2 Rationale

Amendment number: Amendment 2
Rationale/background for changes: The protocol is being amended to include Spain in the study. The reasons for this Spain-specific amendment are listed below: • Based on the feedback from the Spanish Ethics Committee, the evaluation related to the acceptance of cocooning has been added in the protocol. • The objectives and endpoints to include cocooning are added in the protocol. • The eligibility criteria for participation of household contacts are defined in the protocol. • The study procedures for household contacts are included. • The list of contributing authors has been updated.

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Date of protocol amendment	Amendment 2 Final: 15 July 2015
Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Investigator name	_____
Signature	_____
Date	_____

For internal use only

- ----------Checksum----------!Ver.!Created On - -
552cb61e98ad426988e436831e69cba1351ae35d 2.0 7/17/2015 12:12:04 PM - -
---------- -

Sponsor Information

Sponsor

GlaxoSmithKline Biologicals

Rue de l'Institut 89

1330 Rixensart, Belgium

Sponsor Medical Expert for the Study

Refer to the local study contact information document.

Sponsor Study Monitor

Refer to the local study contact information document.

Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2

GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding.

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.7.

SYNOPSIS

Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Indication	Booster immunisation against diphtheria, tetanus and pertussis diseases. The study population for this study will include pregnant women.
Rationale for the study and study design (Amended: 15 July 2015)	• Rationale for the study On June 22, 2011, the Advisory Committee on Immunization Practices (ACIP) made recommendations for use of dTap vaccine in unvaccinated pregnant women and updated recommendations on cocooning and special situations [CDC, 2011]. In 2013, the ACIP recommended the combined reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTap) vaccine for pregnant women during every pregnancy irrespective of previous history of dTap vaccination [CDC, 2011]. Following the initial recommendation in the US by ACIP, temporary dTap immunisation programmes for pregnant women have been implemented in 18 countries including UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina and some provinces in Australia and Spain [Joint Committee on Vaccination and Immunization (JCVI), 2012; Pharmaceutical Management Agency (PHARMAC), 2012; TAG, 2013]. Since 2013, vaccination during pregnancy is also recommended in Belgium between the 24th and 32nd week of pregnancy [CSS, 2013]. The National Advisory Committee on Immunization in Canada recommends that all pregnant women following 26 weeks of pregnancy who have not received a dose of pertussis-containing vaccine in adulthood should be encouraged to receive dTap vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are 26 weeks gestation or greater may be offered dTap vaccination irrespective of their immunisation history. [Warshawsky, 2014; Public Health Agency of Canada, 2014]. The important impact of maternal immunisation in decreasing the incidence of infant pertussis has been demonstrated recently by the Public Health England (PHE) pertussis maternal immunisation program in an analysis of data from the Clinical Practice Research Datalink (a primary care database of 520 English general practices). After a maternal pertussis vaccination program was introduced in October 2012 in response to a pertussis outbreak, the number of pertussis

cases in infants younger than 3 months of age and the number of hospitalizations decreased significantly [Amirthalingam, 2014]. A study conducted to assess the safety of pertussis vaccination during pregnancy in UK using the Clinical Practice Research Datalink showed no evidence of an increased risk of stillbirth or any adverse events related to pregnancy [Donegan, 2014]. Another randomized, double-blind, placebo controlled trial conducted using *Adacel* (dTap, Sanofi Pasteur) in 33 pregnant women aged 18 to 45 years at 30 to 32 weeks gestation did not find increased risk of adverse events among women or their infants [Munoz, 2014].

In light of these recommendations and observations, further clinical evaluation of the safety and immunogenicity of reduced antigen-content acellular pertussis vaccines in pregnant women is scientifically warranted.

GSK Biologicals' reduced-antigen-content dTpa vaccine, *Boostrix*, first licensed for use in Germany in 1999, is indicated for booster vaccination for individuals from the age of four years onwards. The immunogenicity, reactogenicity and safety of this vaccine have been established in a number of clinical trials in the different populations for which it is indicated [Minh, 1999; Turnbull, 2001; Van Damme, 2004; Meyer, 2008].

Review of reports to Vaccine Adverse Event Reporting System in pregnant women who received a dose of dTap vaccine did not identify any concerning patterns in maternal, infant, or foetal outcomes [Zheteyeva, 2012]. In addition, a clinical study concluded that administering dTap during pregnancy increased antibody concentrations against diphtheria and pertussis antigens and maternal immunisation with dTap may prevent neonatal pertussis infection [Gall, 2011]. GSK has performed reproductive and developmental toxicity studies in female rats and rabbits. The developmental toxicity study to assess embryo-foetal and pre- and postnatal development in female rats at a dose approximately 40 times the human dose (on a mL/kg basis) revealed no evidence of harm to the foetus due to *Boostrix*. The study conducted on rabbits to evaluate the effects of *Boostrix* on female fertility, implantation and embryo-foetal development did not show adverse effects on embryo-foetal development or survival.

Considering the multiple countries which have recently instituted recommendations regarding the use of dTap vaccine in pregnant women along with the limited safety data of *Boostrix* in pregnant women currently available, an

investigation of safety and immunogenicity of *Boostrix* in a clinical trial is warranted.

- Rationale for the study design

In order to support the use of *Boostrix* in pregnant women, this phase IV, observer-blind, placebo-controlled and randomised study will be conducted to assess the immunogenicity and safety of the vaccine given during 27-36 weeks of gestation in healthy women aged 18-45 years. This period of pregnancy is considered to be outside the critical susceptibility window for organogenesis. Transfer of maternal antibodies to the infants is also seen to be optimal in this trimester.

The subjects in this study will be randomised to two groups:

- dTpa Group: This group will consist of pregnant women who will receive a single dose of *Boostrix* at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1).
- Control Group: This group will consist of pregnant women who will receive a single dose of placebo (saline water) at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1).

The study will adopt a cross-over study design. Subjects in the dTpa group who receive a single dose of *Boostrix* at 27-36 weeks of gestation will receive a dose of the placebo post-delivery (within 72 hours); while subjects in the Control group who receive placebo at 27-36 weeks of gestation will receive a dose of *Boostrix* post-delivery (within 72 hours).

Infants born to mothers enrolled in this study will be followed-up in two separate clinical studies: DTPA (BOOSTRIX)-048 PRI and DTPA (BOOSTRIX)-049 BST: 048. Infants will be given the primary vaccination course of *Infanrix hexa* in DTPA (BOOSTRIX)-048 PRI study and a booster dose in the second year of life in DTPA (BOOSTRIX)-049 study in order to generate safety and immunogenicity data. The impact of maternal *Boostrix* vaccination on immune response of infants to primary and booster DTPa vaccination will also be evaluated in these studies.

Since pregnant women are a vulnerable population and the experience of clinical trials in this population is limited, high quality of obstetric, perinatal and infant care will be a requirement for all trial sites, ensuring optimal data collection

as well as access to emergency facilities, if required. In addition, sites that can guarantee high compliance with long-term follow-up of the children will be selected.

- Rationale for the use of placebo

Since this study will be conducted in countries where dTap vaccination for pregnant women is not yet widely implemented and in the absence of an established active control for pertussis vaccination in this population, a placebo will be used. Based on the cross-over study design, pregnant women who receive placebo in the Control Group will receive a dose of *Boostrix* post-delivery. Vaccinating the mothers with dTpa vaccine post-delivery may provide some degree of protection against pertussis due to the cocooning effect [CDC, 2013]. This is also in line with the ACIP recommendations which state that women should be administered a dose of dTpa vaccine immediately postpartum in case dTpa vaccine was not administered during pregnancy.

In addition, all the eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

Objectives (Amended: 15 July 2015)

Primary

- To demonstrate that the maternally transferred antibodies against pertussis in the dTpa Group is superior to that in the Control Group in terms of geometric mean concentrations (GMCs) for the pertussis antibodies, in the cord blood sample.

  Criterion:

  – The lower limit (LL) of the 95% confidence interval (CI) of the GMC ratio [dTpa Group divided by Control Group] for anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibodies is ≥ 1.5.

Secondary

- To assess the safety of a single dose of *Boostrix* in pregnant women, administered during 27-36 weeks of gestation, in terms of the outcomes of pregnancy and listed pregnancy-related adverse events of interest/neonate-related events of interest up to study end (Visit 4).

- To assess the immunogenicity of a single dose of

Boostrix administered during pregnancy in terms of seropositivity status for antibodies against pertussis, in the cord blood sample.

- To assess the immunogenicity of a single dose of *Boostrix* administered during pregnancy in terms of seroprotection/seropositivity status, vaccine response and GMCs for antibodies against diphtheria, tetanus and pertussis, one month post-vaccination.
- To evaluate the reactogenicity of a single dose of *Boostrix* administered during pregnancy and post-delivery in terms of solicited symptoms during the 8-day (Day 0 – Day 7) follow-up period after vaccination.
- To assess the safety of a single dose of *Boostrix* administered during pregnancy and post-delivery in terms of unsolicited symptoms during the 31-day (Day 0 – Day 30) follow-up period after vaccination and serious adverse events (SAEs) during the period from Visit 1 up to Visit 4.
- ***To assess the acceptance rate of a single dose of Boostrix among eligible household contacts of the infants born to pregnant women enrolled in Spain, as part of an assessment of cocooning.***
- ***To assess the safety of a single dose of Boostrix in terms of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after the vaccination.***

Study design

- Experimental design: Phase IV, observer-blind, randomised, placebo-controlled, multi-centric, multi-country study with two cross-over groups.
- Duration of the study: The intended duration of the study will be approximately 5 months for each subject.
  - Epoch 001: Booster vaccination starting at Screening visit (Day -14 to 0) and ending at Visit 4 (post-delivery Month 2).
- Study groups: The study groups are defined as follows:
  - dTpa Group: This group will consist of pregnant women who will receive a single dose of *Boostrix* at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1) and will receive a dose of the placebo post-delivery (within 72 hours).
  - Control Group: This group will consist of pregnant

women who will receive a single dose of placebo at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1) and will receive a dose of *Boostrix* post-delivery (within 72 hours).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
dTpa Group	340	18 years - 45 years	x
Control Group	340	18 years - 45 years	x

Synopsis Table 2 Study groups and treatment foreseen in the study (Amended: 15 July 2015)

Treatment name	Vaccine name	Study Groups	
		dTpa Group	Control Group
*Boostrix**	dTpa	x	x
Placebo for dTpa vaccine	Placebo	x	x

All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

Synopsis Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	observer-blind

- Sampling schedule: Blood samples will be collected at the following time-points:
  - Pre-Vacc (Visit 1): Before the booster vaccination, approximately 5 mL of blood sample will be collected from all subjects.
  - Post-Vacc (Visit 2): One month after the booster vaccination, approximately 5 mL of blood sample will be collected from all subjects.
  - Cord blood (Visit 3): approximately 2.5mL of blood sample from the umbilical cord will be collected from all subjects.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An independent data monitoring committee (IDMC) (including obstetrician, paediatrician, statistician and a neonatologist) will be put in place to oversee the safety aspects of *Boostrix* in the clinical study i.e. each SAE/congenital anomaly/foetal malformation case/incidence of grade 3 local and general solicited adverse events (AEs) will be reviewed by this committee.

Number of subjects	The target will be to enrol approximately 680 eligible subjects who will be randomly assigned to two study groups in a 1: 1 ratio (approximately 340 subjects in each group).
Endpoints (Amended: 15 July 2015)	**Primary** • Immunogenicity with respect to components of the study vaccine received during pregnancy, one month post vaccination – Anti-PT, anti-FHA and anti-PRN antibody concentrations. **Secondary** • Outcome of pregnancy in terms of pregnancy outcomes up to study end (Visit 4*)*. – Pregnancy outcomes will include live birth with no congenital anomalies, live birth with congenital anomalies, still birth with no congenital anomalies, still birth with congenital anomalies, elective termination with no congenital anomalies and elective termination with congenital anomalies. • Outcome of pregnancy in terms of listed pregnancy-related adverse events of interest/ neonate-related events of interest up to study end (Visit 4). – Listed pregnancy-related adverse events of interest/ neonate-related events of interest will include gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labour, premature uterine contractions, intrauterine growth restriction/poor foetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine haemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic ischaemic encephalopathy and failure to thrive/growth deficiency. Immunogenicity with respect to components of the study vaccine received during pregnancy, one month post vaccination – Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN seroprotection/seropositivity status and antibody concentrations. – Vaccine response to PT, FHA and PRN

  - Vaccine response to anti-D and anti-T

- Immunogenicity with respect to components of the study vaccine, in the cord blood sample.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status.
- Solicited local and general symptoms (at Visit 1 and Visit 3).
  - Occurrence of each solicited local/general symptoms during the 8-day (Day 0-Day 7) follow-up period after the vaccination.
- Unsolicited adverse events (at Visit 1 and Visit 3).
  - Occurrence of unsolicited AEs within 31 days (Day 0 – Day 30) after any vaccination, according to the **Med**ical **D**ictionary for **R**egulatory **A**ctivities (MedDRA) classification.
- Serious adverse events ***(SAEs)***.
  - Occurrence of serious adverse events from Dose 1 up to study end (Visit 4).
- ***Percentage of household contacts of the infants born to pregnant women vaccinated in Spain who accepted Boostrix vaccine as part of an assessment of cocooning among the eligible household contacts.***
- ***Occurrence of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after vaccination.***

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
AE:	Adverse Event
ATP:	According-To-Protocol
CDC:	Centers for Disease Control and Prevention, USA
CI:	Confidence Interval
dT:	Reduced antigen content diphtheria and tetanus toxoids
DTP:	Diphtheria-Tetanus-Pertussis
dTpa/dTap:	Combined reduced antigen content diphtheria-tetanus-acellular pertussis vaccine
DTPa:	Diphtheria-Tetanus-acellular Pertussis
eCRF:	electronic Case Report Form
EDD:	Estimated date of delivery
EGA:	Estimated gestational age
ELISA:	Enzyme-Linked ImmunoSorbent Assay
eTDF:	Electronic Temperature excursion Decision Form
FHA:	Filamentous Haemagglutinin
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IMP:	Investigational Medicinal Product

IRB:	Institutional Review Board
IU/ml:	International Units per ml
LAR:	Legally Acceptable Representative
LL:	Lower Limit
LMP:	Last menstrual period
LSC:	Local Study Contact
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MedDRA:	Medical Dictionary for Regulatory Activities
PRN:	Pertactin
PT:	Pertussis Toxoid
RDE:	Remote Data Entry
RSI:	Reference Safety Information
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual

GLOSSARY OF TERMS (Amended: 15 July 2015)

Adequate contraception:

Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- ***abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,***
- ***oral contraceptives, either combined or progestogen alone,***
- ***injectable progestogen,***
- ***implants of etenogestrel or levonorgestrel,***
- ***estrogenic vaginal ring,***
- ***percutaneous contraceptive patches,***
- ***intrauterine device or intrauterine system,***
- ***male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,***
  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- ***male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),***
- ***male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).***

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event:

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Blinding:

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of

blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 5.3 for details on observer-blinded studies).

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

Congenital anomalies: The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC, 2007] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the foetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception.

Live-born neonates with transient (postural) defects, infectious conditions or biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognised congenital birth defect.

Eclampsia: Features of pre-eclampsia accompanied by new-onset generalized seizures.

Elective termination: Expulsion of products of conception with medical or surgical assistance. The termination of the pregnancy can be elective or therapeutic.

Eligible: Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Epoch: An epoch is a self-contained set of consecutive time-points or a single time-point from a single protocol. Self-

	contained means that data collected for all subjects at all time-points within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.7.2 and 10.4 for details on criteria for evaluability).
Failure to thrive/growth deficiency:	Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.
Gestational diabetes:	Onset or first recognition of abnormal glucose tolerance during pregnancy (the diagnosis is based on administration of glucose challenge test at 24-28 weeks gestation).
Household contact	***People living under the same roof with the infant.***
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Intrauterine growth restriction/poor foetal growth:	Estimated or actual birth weight below the 10^{th} percentile for gestational age.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Live birth:	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement.

Maternal death:	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
Menarche:	***Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).***
Menopause:	***Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.***
Neonatal death:	Death of newborn at any time from birth to 28 days of life, regardless of gestational age.
Neonatal hypoxic ischaemic encephalopathy:	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty in initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or due to another cause.
Post-partum haemorrhage:	Excessive blood loss after delivery i.e. estimated blood loss in excess of 500 ml after vaginal delivery and estimated blood loss in excess of 1000 ml after Caesarean delivery. The other symptoms are ≥10% drop in haematocrit, need for blood transfusion, symptomatic hypotension, dizziness, pallor and oligouria.
Pre-eclampsia:	Hypertension (>140 and/or >90 mmHg) and proteinuria (>300 mg in a 24 hr urine specimen) occurring after the 20^{th} week of gestation.

Pregnancy-related hypertension:	Hypertension (>140 and/or >90 mmHg) occurring after , 20 weeks of gestation and up to 6 weeks postpartum combined with abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen).
Premature labour:	Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.
Premature rupture of membranes:	Spontaneous rupture of foetal membranes that occurs before the onset of labour.
Premature uterine contraction:	Uterine contractions without cervical change.
Preterm birth:	Birth before 37 weeks of gestation.
Preterm premature rupture of membranes:	Spontaneous rupture of foetal membranes that occurs before the onset of labour before 37 weeks of gestation.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The International Conference on Harmonisation (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.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Small for gestational age:	Birth weight less than 10% for infants of same gestational age and gender in same population

Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Stillbirth:	Death of the foetus(es) at ≥22 weeks of gestation, occurring antepartum or intrapartum.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vaginal or intrauterine haemorrhage:	Vaginal or intrauterine haemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours post-delivery).

TRADEMARKS

The following trademark is used in the present protocol.

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

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

1. INTRODUCTION

1.1. Background

Pertussis, "whooping cough", caused by *Bordetella pertussis* is a highly contagious and potentially life-threatening respiratory illness that is a cause of morbidity and mortality in infants less than six months of age. It is also a cause of morbidity in adolescents and adults. Compared to older children and adults, infants aged less than 12 months have higher rates of pertussis disease and the largest burden of pertussis-related deaths. Most of these cases, including hospitalisations and deaths, occur in infants less than two months of age as they are too young to be vaccinated [CDC, 2011].

Since 2011, increased pertussis cases or outbreaks have been reported in several countries. In the United States of America, forty nine states and Washington D.C. reported increases in the pertussis cases in 2012 compared to 2011 [CDC, 2015]. The incidence of pertussis among infants exceeds that observed among children and adolescents [CDC, 2012]. The number of pertussis cases reported in Australia has also been increasing with nearly 40,000 cases reported in 2011 and 2012. While the rates are highest in the primary school-aged children, due to the waning of vaccine-induced immunity, the impact of the disease remains greatest in infants under one year of age [Communicable Disease Control Directorate, 2011].

The United Kingdom is also in the midst of a large outbreak of pertussis. A national increase in the laboratory-confirmed cases of pertussis has been observed in England and Wales, with a large number of cases being reported in very young infants [Health Protection Report, 2012].

Different vaccination strategies can be implemented to protect infants against pertussis. Universal vaccination of pre-school children, adolescents, adults, or selective immunisation of unvaccinated postpartum mothers and other family members (cocooning) not only protects the vaccinated group, but also increases herd immunity and hence reduces the risk of disease transmission to unvaccinated or incompletely vaccinated infants. However, due to difficulties of full implementation, these strategies are not very effective to control the outbreak of pertussis in infants less than 6 months of age [Mooi, 2007].

Transfer of maternal antibodies against pertussis may have some protective effect in the infants. However, low levels of the maternal antibodies and rapid decay of the antibodies in the infants often still leave the infant at high risk for pertussis. If the maternal antibody levels are increased by maternal immunisation either before or during pregnancy, this approach might provide some degree of protection to the mother and infant during a vulnerable period immediately after birth [Leuridian, 2011].

Several studies have suggested that presence of maternal pertussis antibodies can inhibit active pertussis-specific antibody production in the child, known as blunting. This blunting effect might reduce protection after the first months of life. However, data suggest that blunting is overcome after the third dose of the primary vaccination and the potential benefit of protection from maternal antibodies in newborn infants outweighs the

potential risk of blunting the infant's response to DTPa vaccine [CDC, 2011; Hardy-y-Fairbanks, 2013]. Also, studies have shown that use of acellular pertussis vaccines (DTPa) compared to whole-cell diphtheria-tetanus-pertussis (DTP) vaccines confer higher levels of antibodies in women before pregnancy. These DTPa vaccines are unlikely to adversely affect pertussis antibody responses among infants born to mothers with high antibody levels [Englund, 1995].

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

On June 22, 2011, the Advisory Committee on Immunization Practices (ACIP) made recommendations for use of dTap vaccine in unvaccinated pregnant women and updated recommendations on cocooning and special situations [CDC, 2011]. In 2013, the ACIP recommended the combined reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTap) vaccine for pregnant women during every pregnancy irrespective of previous history of dTap vaccination [CDC, 2013]. Following the initial recommendation in the US by ACIP, temporary dTap immunisation programmes for pregnant women have been implemented in 18 countries including UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina and some provinces in Australia and Spain [Joint Committee on Vaccination and Immunization (JCVI), 2012; Pharmaceutical Management Agency (PHARMAC), 2012; TAG, 2013]. Since 2013, vaccination during pregnancy is also recommended in Belgium between the 24th and 32nd week of pregnancy [CSS, 2013]. The National Advisory Committee on Immunization in Canada recommends that all pregnant women following 26 weeks of pregnancy who have not received a dose of pertussis-containing vaccine in adulthood should be encouraged to receive dTap vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are 26 weeks gestation or greater may be offered dTap vaccination irrespective of their immunisation history [Warshawsky, 2014; Public Health Agency of Canada, 2014].

The important impact of maternal immunisation in decreasing the incidence of infant pertussis has been demonstrated recently by the Public Health England (PHE) pertussis maternal immunisation program in an analysis of data from the Clinical Practice Research Datalink (a primary care database of 520 English general practices). After a maternal pertussis vaccination program was introduced in October 2012 in response to a pertussis outbreak, the number of pertussis cases in infants younger than 3 months of age and the number of hospitalizations decreased significantly [Amirthalingam, 2014]. A study conducted to assess the safety of pertussis vaccination during pregnancy in UK using the Clinical Practice Research Datalink showed no evidence of an increased risk of stillbirth or any adverse events related to pregnancy [Donegan, 2014]. Another randomized, double-blind, placebo controlled trial conducted using *Adacel* (dTap, Sanofi Pasteur) in 33 pregnant women aged 18 to 45 years at 30 to 32 weeks gestation did not find increased risk of adverse events among women or their infants [Munoz, 2014].

In light of these recommendations and observations, further clinical evaluation of the safety of reduced antigen-content acellular pertussis vaccines in pregnant women is scientifically warranted.

GSK Biologicals' reduced-antigen-content dTpa vaccine, *Boostrix*, first licensed for use in Germany in 1999, is indicated for booster vaccination for individuals from the age of four years onwards. The immunogenicity, reactogenicity and safety of this vaccine have been established in a number of clinical trials in the different populations for which it is indicated [Minh, 1999; Turnbull, 2001; Van Damme, 2004; Meyer, 2008].

Review of reports to Vaccine Adverse Event Reporting System in pregnant women who received a dose of dTap vaccine did not identify any concerning patterns in maternal, infant, or foetal outcomes [Zheteyeva, 2012]. In addition, a clinical study concluded that administering dTap during pregnancy increased antibody concentrations against diphtheria and pertussis antigens and maternal immunisation with dTap may prevent neonatal pertussis infection [Gall, 2011]. GSK has performed reproductive and developmental toxicity studies in female rats and rabbits. The developmental toxicity study to assess embryo-foetal and pre- and postnatal development in female rats at a dose approximately 40 times the human dose (on a mL/kg basis) revealed no evidence of harm to the foetus due to *Boostrix*. The study conducted on rabbits to evaluate the effects of *Boostrix* on female fertility, implantation and embryo-foetal development did not show adverse effects on embryo-foetal development or survival.

Considering the multiple countries which have recently instituted recommendations regarding the use of dTap vaccine in pregnant women along with the limited safety data of *Boostrix* in pregnant women currently available, an investigation of safety and immunogenicity of *Boostrix* in a controlled clinical trial is warranted.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of *Boostrix*.

1.2.2. Rationale for the study design (Amended: 15 July 2015)

In order to support the use of *Boostrix* in pregnant women, this phase IV, observer-blind, placebo-controlled and randomised study will be conducted to assess the immunogenicity and safety of the vaccine given during 27-36 weeks of gestation in healthy women aged 18-45 years. This period of pregnancy is considered to be outside the critical susceptibility window for organogenesis. Transfer of maternal antibodies to the infants is also seen to be optimal in this trimester.

The subjects in this study will be randomised to two groups:

- dTpa Group: This group will consist of pregnant women who will receive a single dose of *Boostrix* at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1).
- Control Group: This group will consist of pregnant women who will receive a single dose of placebo (saline water) at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1).

The study will adopt a cross-over study design. Subjects in the dTpa group who receive a single dose of *Boostrix* at 27-36 weeks of gestation will receive a dose of the placebo post-delivery (within 72 hours); while subjects in the Control group who receive placebo at 27-36 weeks of gestation will receive a dose of *Boostrix* post-delivery (within 72 hours).

Infants born to mothers enrolled in this study will be followed-up in two separate clinical studies: DTPA (BOOSTRIX)-048 PRI and DTPA (BOOSTRIX)-049 BST: 048. Infants will be given the primary vaccination course of *Infanrix hexa* in DTPA (BOOSTRIX)-048 PRI study and a booster dose in the second year of life in DTPA (BOOSTRIX)-049 BST: 048 study in order to generate safety and immunogenicity data. The impact of maternal *Boostrix* vaccination on immune response of infants to primary and booster dTpa vaccination will also be evaluated in these studies.

Since pregnant women are a vulnerable population and the experience of clinical trials in this population is limited, high quality of obstetric, perinatal and infant care will be a requirement for all trial sites, ensuring optimal data collection as well as access to emergency facilities, if required. In addition, sites that can guarantee high compliance with long-term follow-up of the children will be selected.

In addition, all the eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

1.2.3. Rationale for the use of placebo

Since this study will be conducted in countries where dTap vaccination for pregnant women is not yet widely implemented and in the absence of an established active control for pertussis vaccination in this population, a placebo will be used. Based on the cross-over study design, pregnant women who receive placebo in the Control Group will receive a dose of *Boostrix* post-delivery. Vaccinating the mothers with dTpa vaccine post-delivery may provide some degree of protection against pertussis due to the cocooning effect [CDC, 2013]. This is also in line with the ACIP recommendations which state that women should be administered a dose of dTpa vaccine immediately postpartum in case dTpa vaccine was not administered during pregnancy.

1.3. Benefit: Risk Assessment

Please refer to the Investigator's brochure for information regarding the summary of potential risks and benefits of *Boostrix*.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine *Boostrix*		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007].	Anaphylaxis following vaccine administration is an exclusion criterion for study participation and a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
Syncope	As outlined in the Reference Safety Information, syncope (fainting) can occur following or even before any vaccination especially in adolescents as a psychogenic response to the needle injection.	It is important that procedures are in place to avoid injury from fainting. All subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
Extensive swelling of vaccinated limb	Given that the active ingredients of *Boostrix* are conjugated to tetanus toxoid carrier protein, an exaggerated local (Arthus-like) reaction are occasionally reported following receipt of a diphtheria- or tetanus- containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin from 2 to 8 hours after injections and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid.	Any untoward symptoms experienced by the subject after receiving the vaccine should be reported to the investigator.
Study Procedures		
Not applicable		
Other		
Not applicable		

1.3.2. Benefit Assessment

By receiving the *Boostrix* vaccine, the subjects may have the benefit of being protected against diphtheria, tetanus and pertussis diseases.

1.3.3. Overall Benefit:Risk Conclusion

The benefit:risk profile of *Boostrix* for vaccination of subjects against diphtheria, tetanus, and pertussis continues to be favourable.

2. OBJECTIVES

2.1. Primary Objective

- To demonstrate that the maternally transferred antibodies against pertussis in the dTpa Group is superior to that in the Control Group in terms of geometric mean concentrations (GMCs) for the pertussis antibodies, in the cord blood sample.

  Criterion:

  – The lower limit (LL) of the 95% confidence interval (CI) of the GMC ratio [dTpa Group divided by Control Group] for anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibodies is ≥ 1.5.

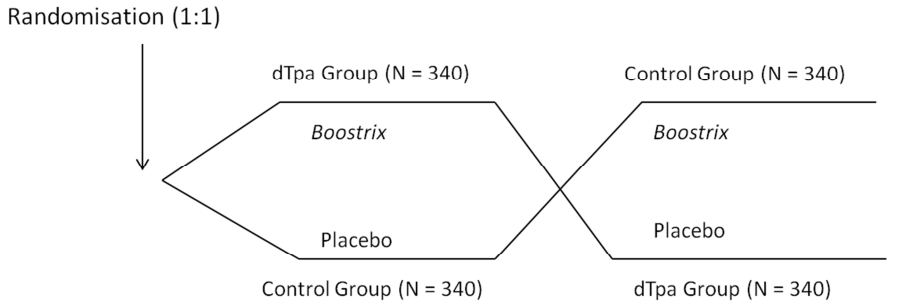
Refer to Section 10.1 for the definition of the primary endpoint.

2.2. Secondary objectives (Amended: 15 July 2015)

- To assess the safety of a single dose of *Boostrix* in pregnant women, administered during 27-36 weeks of gestation, in terms of the outcomes of pregnancy and listed pregnancy-related adverse events of interest/neonate-related events of interest up to study end (Visit 4).
- To assess the immunogenicity of a single dose of *Boostrix* administered during pregnancy in terms of seropositivity status for antibodies against pertussis, in the cord blood sample.
- To assess the immunogenicity of a single dose of *Boostrix* administered during pregnancy in terms of seroprotection/seropositivity status, vaccine response and GMCs for antibodies against diphtheria, tetanus and pertussis, one month post-vaccination.
- To evaluate the reactogenicity of a single dose of *Boostrix* administered during pregnancy and post-delivery in terms of solicited symptoms during the 8-day (Day 0 – Day 7) follow-up period after vaccination.
- To assess the safety of a single dose of *Boostrix* administered during pregnancy and post-delivery in terms of unsolicited symptoms during the 31-day (Day 0 – Day 30) follow-up period after vaccination and serious adverse events (SAEs) during the period from Visit 1 up to Visit 4.
- ***To assess the acceptance rate of a single dose of Boostrix among eligible household contacts of the infants born to pregnant women enrolled in Spain, as part of an assessment of cocooning.***
- ***To assess the safety of a single dose of Boostrix in terms of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after the vaccination.***

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW (AMENDED: 15 JULY 2015)



					Study Conclusion
Visits	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	Day -14 to 0	Day 0	Day 30	At birth	Post-delivery Month 2
Blood sample:		Pre-Vacc	Post-Vacc	Cord Blood	

Epoch 001

N: Number of subjects planned to be enrolled
Pre-vacc: Blood sample to be collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc: Blood sample to be collected one month after the booster vaccination in pregnant women (Visit 2).

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IV, observer-blind, randomised, placebo-controlled, multi-centric, multi-country study with two cross-over groups. ***All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.***
- Duration of the study: The intended duration of the study will be approximately 5 months for each subject.
  - Epoch 001: Booster vaccination starting at Screening visit (Day -14 to 0) and ending at Visit 4 (post-delivery Month 2).
- Study groups: The study groups are defined as follows:
  - dTpa Group: This group will consist of pregnant women who will receive a single dose of *Boostrix* at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1) and will receive a dose of the placebo post-delivery (within 72 hours).

– Control Group: This group will consist of pregnant women who will receive a single dose of placebo at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1) and will receive a dose of *Boostrix* post-delivery (within 72 hours).

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

Table 1 Study groups and epoch foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
dTpa Group	340	18 years - 45 years	x
Control Group	340	18 years - 45 years	x

The study groups and treatment foreseen in the study are presented in Table 2.

Table 2 Study groups and treatment foreseen in the study (Amended: 15 July 2015)

Treatment name	Vaccine name	Study Groups	
		dTpa Group	Control Group
Boostrix *	dTpa	x	x
Placebo for dTpa vaccine	Placebo	x	x

All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

- Control: placebo control
- Vaccination schedule:
  - All subjects will receive a single dose of *Boostrix* or placebo at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1). Subjects who receive *Boostrix* at Visit 1 will receive a dose of placebo post-delivery (Visit 3) while those who receive placebo at Visit 1 will receive *Boostrix* post-delivery (Visit 3).
  - ***All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning. Although the vaccine can be administered anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.***
- Treatment allocation: randomised.
- Blinding: Observer-blind. Refer to Section 5.3 for details of the of blinding procedure.

The blinding of study epoch is presented in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	observer-blind

- Sampling schedule: Blood samples will be collected at the following time-points:
  - Pre-Vacc (Visit 1): Before the booster vaccination, approximately 5 mL of blood sample will be collected from all subjects.
  - Post-Vacc (Visit 2): One month after the booster vaccination, approximately 5 mL of blood sample will be collected from all subjects.
  - Cord blood (Visit 3): approximately 2.5 mL of blood sample from the umbilical cord will be collected from all subjects.
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An independent data monitoring committee (IDMC) (including obstetrician, paediatrician, statistician and a neonatologist) will be put in place to oversee the safety aspects of *Boostrix* in the clinical study i.e. each SAE/congenital anomaly/foetal malformation case/incidence of grade 3 local and general solicited adverse events (AEs) will be reviewed by this committee (See Section 5.4.1 for details).

4. STUDY COHORT

4.1. Number of subjects/centres

Approximately 680 pregnant women between 18-45 years will be enrolled in this study. These subjects should be 27-36 weeks of gestation at the time of vaccination. Age of the pregnant women, gestational age of the foetus, centre and country will be the minimization factor for randomisation of pregnant women. Blood samples will be taken from all subjects in order to evaluate the immunogenicity endpoints.

The subjects will be enrolled into the two groups in a 1:1 ratio.

Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

Overview of the recruitment plan:

- Enrolment will be terminated when the target number of subjects will be achieved.
- The study will be monitored by a local Study Monitor.
- The treatment allocation and enrolment of subjects into the study will be tracked using a randomisation system on internet (SBIR).
- Centre, age of the pregnant women (≥ 18- <25 years, ≥ 25- <35 years and ≥ 35- ≤45 years), gestational age of foetus (27-32 weeks and 33-36 weeks) and country will be the minimization factor for randomisation.

4.2. Inclusion criteria for enrolment (Amended: 15 July 2015)

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

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

Inclusion criteria for study subjects:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject prior to performing any study specific procedure, as per local regulations.
- A healthy pregnant woman between, and including, 18 and 45 years of age at the time of screening.
- Pregnant subjects at $27^{0/7}$-$36^{6/7}$ weeks (completed 27 weeks but not 37 weeks) of gestation at the time of vaccination (Visit 1), as established by ultrasound examination.
- Not at high risk for complications, as determined by the obstetrical algorithm for identification of eligible subjects and the Obstetrical Risk Assessment Form.
- No significant foetal abnormalities, as observed by the level II ultrasound testing conducted after 18 weeks of gestation.
- Nuchal translucency scan, serum testing and any other prenatal tests, if conducted, should suggest normal pregnancy.
- Willing to have the infant born immunised with *Infanrix hexa* and *Prevenar 13*, as per national recommendations, in the follow-up clinical studies DTPA (BOOSTRIX)-048 PRI and DTPA (BOOSTRIX)-049 BST: 048.
- Subjects who do not plan to give their child for adoption or place the child in care.

Inclusion criteria for household contacts in Spain:

- ***Household contacts living in the same house as that of the infant.***
- ***Household contacts or parent(s)/LAR(s) of the household contacts who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. reporting of SAEs).***
- ***Written informed consent obtained from the household contacts or the parent(s)/LAR(s) prior to vaccination, as per local regulations.***
- ***Household contacts who are eligible to receive a booster dose of DTP-containing vaccine according to the Summary of Product Characteristics (SmPC) of Boostrix and according to the local governmental recommendations in Spain.***

- ***Female household contacts of non-childbearing potential may be enrolled in the study .***
  - ***Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.***

Please refer to the glossary of terms for the definition of menarche and menopause.

- ***Female household contacts of childbearing potential may be enrolled in the study , if the household contact***
  - ***has practiced adequate contraception for 30 days prior to vaccination,***
  - ***has a negative pregnancy test on the day of vaccination and***
  - ***has agreed to continue adequate contraception for 2 months after receiving the vaccine dose.***

Please refer to the glossary of terms for the definition of adequate contraception.

Please refer to APPENDIX B for the Obstetrical Risk Assessment Form.

4.3. Exclusion criteria for enrolment (Amended: 15 July 2015)

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

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

Exclusion criteria for study subjects:

- Subjects diagnosed with multiple pregnancies (twins, triplets etc.).
- Previous vaccination containing diphtheria, tetanus or pertussis antigens or diphtheria and tetanus toxoids at any time during the current pregnancy.
- Women with co-morbid medical or obstetric conditions that in the opinion of the investigator have the potential to complicate the pregnancy course and outcomes [for eg., such as hypertension (requiring medications), uterine anomalies and bleeding disorders etc.].
- Gestational diabetes as determined by glucose tolerance test conducted after 20 weeks of gestation, as per local recommendations of the country [Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of diabetes in Canada, 2013; International Association of Diabetes and Pregnancy Study groups Consensus Panel, 2010; GEDE, 2006].
- History of early onset (<34 weeks of gestation) of eclampsia/pre-eclampsia in previous pregnancy.
- History of major congenital anomalies in previous pregnancies.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine anytime during the current pregnancy or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period within the period starting 30 days before and 30 days after the dose of vaccine with the exception of seasonal influenza vaccine that can be administered anytime during the study period.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Serious underlying medical condition [e.g., immunosuppressive disease or therapy, human immunodeficiency virus infection, collagen vascular disease, epilepsy, diabetes mellitus, chronic hypertension, moderate to severe asthma, lung/heart disease, liver/kidney disease, infections including TORCHES (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis) infections].
- History of an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine.
- History of transient thrombocytopenia or neurological complications (for convulsions or hypotonic-hyporesponsive episodes) following an earlier immunisation against diphtheria and/or tetanus
- Significant mental illness (e.g. schizophrenia, psychosis and major depression).
- Family history (first degree relatives only) of congenital anomalies, recurrent pregnancy losses (two or more consecutive losses) and unexplained neonatal death(s) in the subject.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- History of febrile illness within the past 72 hours.
- History of physician-diagnosed or laboratory-confirmed pertussis within the past five years.

- Anything that would prevent subject from completing the study or put the subject at risk, as determined by the investigator.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.5°C /99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C /100.4°F on rectal route.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the dose of study vaccine, or planned administration during the study period, with the exception of anti-D (Rh)-immunoglobulin.
- History of chronic excessive alcohol consumption and/or drug abuse.

Exclusion criteria for household contacts in Spain:

- ***Child in care.***

Please refer to the glossary of terms for the definition of child in care.

- ***Concurrently participating in another clinical study, at any time during the study period, in which the household contact has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).***
- ***Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period.***
- ***History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.***
- ***History of an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine.***
- ***Acute disease and/or fever at the time of enrolment.***
  - ***Fever is defined as temperature ≥ 37.5°C /99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C /100.4°F on rectal route. The preferred route of recording temperature will be axillary in household contacts.***
  - ***Household contacts with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.***
- ***Anything that would put the household contact at risk, as determined by the investigator.***
- ***Pregnant or lactating household contacts.***
- ***Household contacts planning to become pregnant or planning to discontinue contraceptive precautions prior to 2 months post-vaccination.***

5. CONDUCT OF THE STUDY

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

The study will be conducted in accordance with all applicable regulatory requirements.

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

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

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

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

5.2.2. Randomisation of treatment

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

5.2.2.1. Treatment allocation to the subject

The treatment numbers will be allocated by component.

5.2.2.1.1. Study group and treatment number allocation (Amended: 15 July 2015)

The target will be to enrol approximately 680 eligible subjects who will be randomly assigned to two study groups in a (1: 1) ratio (approximately 340 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre, age (≥ 18- <25 years, ≥ 25- <35 years and ≥ 35- ≤45 years), gestational age (27-32 weeks and 33-36 weeks) and country.

Minimisation factors will have equal weight in the minimisation algorithm**.**

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for each dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

All the eligible household contacts of infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning. For specific instructions with respect to treatment allocation of the household contacts in Spain, refer to the SPM.

5.2.2.1.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.4.1. Independent Data Monitoring Committee

An IDMC will monitor the safety aspects of *Boostrix* in the clinical study. An IDMC including an obstetrician, paediatrician, statistician and a neonatologist will be in charge of monitoring the safety aspects of the study and the committee will meet at regular intervals to review data on other adverse pregnancy outcomes. The frequency of the meeting will be decided in consultation with the chairman of the committee.

To facilitate the review, the IDMC will be provided with all relevant safety data including data on congenital anomaly/foetal malformation/ incidence of grade 3 local and general solicited adverse events, withdrawals due to adverse experiences and SAE data at specified times and access to data on request by an unblinded statistician. The GSK staff and other study staff will be blinded during this study.

The IDMC will have access to the individual codes and may at its discretion, decode the cases to identify the product administered to any subject and evaluate whether enrolment in the study should be halted or if any additional safety follow-ups are required for subject safety.

The operating rules of the IDMC will be established by GSK and will be documented by a charter.

5.4.2. Responsibilities

The overall responsibility of the IDMC is to protect the ethical and safety interests of subjects recruited into this study while protecting as far as possible the scientific validity of the data.

The details of the IDMC responsibilities and conduct of meetings will be provided in the IDMC Charter. The IDMC charter will also clearly state who will conduct the statistical analysis (ICH E9). Key responsibilities of the IDMC include:

- Prior to study start, the IDMC will review the protocol with special attention to safety monitoring procedures and will make recommendations for adjustments, if required.
- The IDMC will review the safety data from the study (i.e. each SAE/congenital anomaly/foetal malformation/incidence of grade 3 local and general solicited adverse events), provide GSK Biologicals with indications on safety profiles and make recommendations for consultation of regulatory Authorities and on further study conduct.
- The IDMC will review the final analysis provided by the sponsor.

5.4.3. Composition of the IDMC

IDMC members will not participate in the study, neither as principal or co-investigators nor as study patient care physicians. They can also not provide medical care to a subject enrolled in the study. The IDMC will include medically qualified experts in the field under study (obstetrician, paediatrician, neonatologist) and a biostatistician. The person specifically selected to chair the IDMC will be required not only to have appropriate training for the study but also to have experience serving on one or more IDMCs. The IDMC also may convene an ad-hoc meeting should it deem necessary for review of specific cases/safety concerns.

Neither the IDMC Chair nor the members are allowed to communicate with the investigators involved in the trial about data from the study. If needed, additional information should be obtained from the Sponsor. The sponsor should inform the investigators in case of any safety concerns observed by the IDMC.

5.4.4. GSK Biologicals' Safety Review Team

A Safety Review Team, including the Central Safety Physician, the CRDL and Biostatistician of the project, as well as Epidemiology and Regulatory representatives as core members and the IDMC will be responsible for reviewing the blinded safety data related to the investigational product on a regular basis to identify any potential safety issues or signals in order to evaluate and agree on action plans, if necessary.

The IDMC will provide recommendation to the sponsor via the GSK Safety Review Team.

5.5. Outline of study procedures (Amended: 15 July 2015)

The list of study procedures are presented in Table 4 ***and Table 5***.

Table 4 List of study procedures for study subjects (Amended: 15 July 2015)

Epoch	Epoch 001				
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	**Day -14 to 0**	**Day 0**	**Day 30**	**At birth**	**Post-delivery Month 2**
Sampling time-points		**Pre-Vacc**	**Post-Vacc**	**Cord blood**	
Informed consent	●				
Collect demographic data	●				
Medical history, including medication history and previous diphtheria/tetanus/pertussis vaccination history*	O	●			
Pregnancy screening**	●				
Data collection on household contacts §	●				
History directed physical examination	O	●			O
Check inclusion/exclusion criteria	O	●			
Pre-vaccination body temperature		●		●	
Measure/record height and weight	●				
Check contraindications and warnings and precautions		O		O	
Study group and treatment number allocation		O			
Recording of administered treatment number		●		●	
Treatment number allocation for subsequent dose (Cross-over dose)				O	
Blood sampling for antibody determination		●	●	●	
Vaccine administration		●		●	
Distribution of diary cards		O	O	O	
Record any concomitant medication/vaccination		●	●	●	●
Physical examination of newborn, including length, weight, head circumference and Apgar Score				●	
Record breastfeeding status					●
Recording and follow up of pregnancy-related adverse events and neonate-related events		●	●	●	●
Record any intercurrent medical conditions		●	●	●	●
Recording of solicited adverse events (Days 0-7) by subjects in diary card		●		●	

Epoch	Epoch 001				
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	**Day -14 to 0**	**Day 0**	**Day 30**	**At birth**	**Post-delivery Month 2**
Sampling time-points		**Pre-Vacc**	**Post-Vacc**	**Cord blood**	
Recording of non-serious adverse events (Day 0– Day 30), by subjects		●	●	●	
Recording of large injection site reactions		●		●	
Return of diary cards			O	O	O
Diary card transcription by investigator/designee			●	●	●
Recording of serious adverse events (SAEs) # and AEs leading to withdrawal		●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●
Recording of new pregnancies				●	●
Screening conclusion	●				
Study Conclusion					●

Note: The procedures to be conducted during screening visit and Visit 1 may be combined.
In case a woman gives birth to an infant between Visit 1 (Day 0) and Visit 2 (Day 30), the procedures for Visit 2 and Visit 3 will be combined. A blood sample from the mother must be taken before the cross-over vaccination is given to her.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Pre-vacc: Blood sample to be collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc: Blood sample to be collected one month after the booster vaccination in pregnant women (Visit 2).
† Father of the child should also sign the informed consent form, if required by the local laws.
* History of all medications, excluding the vitamins and supplements taken by the mother during her pregnancy before receiving the first dose of study vaccine will be recorded in the eCRF.
** Pregnancy screening will include checking of records of ultrasound testing, nuchal translucency scan, serum testing and any other prenatal tests (if performed). Refer to Section 4.2 for details regarding pregnancy screening.
# Including adverse pregnancy outcomes and listed pregnancy-related/neonate-related AEs of interest.
§***Information will be obtained by interviewing the mother after she agrees to participate in the study. These details can be collected at any of the study visits..***

Table 5 List of study procedures for household contacts in Spain

Epoch	*Epoch 001*				
Type of contact	*Screening Visit **	*Visit 1*	*Visit 2*	*Visit 3*	*Visit 4*
Time-points	*Day -14 to 0*	*Day 0*	*Day 30*	*At birth*	*Post-delivery Month 2*
Informed consent		●#			
Check inclusion/exclusion criteria		●#			
Collect demographic data		●#			
Medical history and previous DTP-containing vaccination history		●#			
Urine pregnancy test in female household contacts of child bearing potential		●#			
Pre-vaccination body temperature		●#			
*Vaccine administration***		●#			
Recording of administered treatment number		●#			
Recording of serious adverse events (SAEs) and pregnancies ‡		●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine		●	●	●	●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
**Screening visit will not be applicable for household contacts.*
***The vaccine for household contacts should be administered only after vaccination of the mother (study subject).*
#The procedures for household contacts can be performed anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.
‡The SAEs and pregnancies in household contacts should be reported from the date of vaccination till 30 days after vaccination.

The intervals between study visits are presented in Table 6.

Table 6 Intervals between study visits (Amended: 15 July 2015)

Interval*	Optimal length of interval [1]	Allowed interval[2]
Screening Visit → Visit 1	-14 to 0 days	-28 to 0 days
Visit 1 → Visit 2	30 days	21- 48 days
Visit 3 → Visit 4	60 days	45 - 75 days

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval. In case a mother gives birth to an infant before 21 days post-vaccination, she will be excluded from the ATP cohort for analysis of immunogenicity.
Household contacts can be vaccinated anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.

5.6. Detailed description of study procedures (Amended: 15 July 2015)

5.6.1. *Study procedures for study subjects:*

5.6.1.1. Procedures prior to study participation

5.6.1.1.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. The father of the child should also sign the informed consent form, if required by the local laws.

Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.1.2. Procedures during the screening visit

5.6.1.2.1. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.1.2.2. Collect demographic data

Record demographic data such as date of birth, gender, geographic ancestry and ethnicity in the subject's eCRF.

5.6.1.2.3. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF. History of any medication taken by the subject during her current pregnancy and history of previous diphtheria, tetanus, pertussis or DTPa vaccination history in the past five years should be recorded in the eCRF.

5.6.1.2.4. Pregnancy screening

Pregnancy screening including checking of records of ultrasound testing, nuchal translucency scan, serum testing and any other prenatal tests (if performed) should be recorded in the eCRF. The procedures to be conducted during screening visit and Visit 1 may be combined.

5.6.1.2.5. History directed physical examination

Perform a history directed physical examination. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.1.2.6. Record height and weight

Record the subject's height and weight in the subject's eCRF.

5.6.1.3. Procedures during the study

Note that some of the procedures to be performed during the study (such as recording medical history, checking inclusion/exclusion criteria and history directed physical examination) will also be performed at screening and are described in Section 5.6.1.2.

5.6.1.3.1. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.1.3.2. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral/axillary. If the subject has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for oral route on the day of vaccination], the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 6).

5.6.1.3.3. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF at Visit 1. The treatment number allocation for the subsequent (cross-over) dose will be performed at Visit 3. The number of the administered treatment (cross-over dose) must be recorded in the eCRF at Visit 3.

5.6.1.3.4. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) should be drawn from all subjects for each analysis of humoral immune response at Visit 1 and Visit 2. In case a woman gives birth to an infant before Visit 2, a blood sample must be collected from the subject before the cross-over vaccination is given to the subject.
- A volume of approximately 2.5mL of whole blood (to provide approximately 0.75 mL of serum) from the umbilical cord will be collected from all subjects at Visit 3.

After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.1.3.5. Study Vaccine administration (Amended: 15 July 2015)

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 6).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.
- ***The investigators will discuss with the subjects regarding the benefits of cocooning i.e. up to date vaccination of the baby's siblings with DTP-containing vaccines and vaccinating all the household contacts (people living under the same roof) eligible to receive DTP-containing vaccines as per Summary of Product Characteristics (SmPC) of Boostrix and local governmental recommendations in Spain in order to reduce the potential risk of pertussis in neonates. The subjects will be requested to provide the number of household contacts. Additionally the subjects will also be requested for the number of household contacts who refused the visit to site and the reason for refusal for subsequent eligibility determination and vaccination will be documented.***

5.6.1.3.6. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

5.6.1.3.7. Physical examination of the newborn

At Visit 3 or after the birth of the child, physical examination of the newborn will be done. The body weight, length, head circumference and Apgar Score will be recorded in the eCRF.

5.6.1.3.8. Breastfeeding status

At Visit 4, the breastfeeding status (i.e. breast milk or formula milk) will be recorded in the eCRF.

5.6.1.3.9. Recording of AEs, SAEs, pregnancies, pregnancy-related AEs and neonate-related AEs

- Refer to Section 8.2 for procedures for the investigator to record AEs, SAEs, pregnancies and pregnancy-related AEs and neonate-related AEs. Refer to Section 8.3 for guidelines and how to report SAE reports and pregnancies to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject. The subject will record body (oral/axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 7 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- All pregnancy-related AEs and neonate-related AEs will be captured in the diary card from the first receipt of study vaccine/placebo and will end at Visit 4.
- All adverse pregnancy outcomes, listed pregnancy-related and neonate-related AEs of interest will be reported as SAEs. Refer to Section 8.2.2 for details regarding listed pregnancy-related and neonate-related AEs of interest.
- Collect and verify completed diary cards during discussion with the subject on Visits 2, 3 and 4.
- After vaccination, if the subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of arm circumference) during the 8-day follow-up (Day 0-Day 7) period, they will be asked to contact study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator will record detailed information describing the AE on a specific large injection site reaction in the eCRF.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.1.3.10. Study conclusion

The investigator will:

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

5.6.2. *Study procedures for household contacts in Spain*

5.6.2.1. *Informed Consent*

The signed/witnessed/thumb printed informed consent of the household contact/parent(s)/LAR(s) must be obtained before study participation. If the household contact is below 18 years of age, the parent(s)/LAR(s) should sign the informed consent form, if required by the local laws. The subject has to visit the site to complete the informed consent process.

Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2.2. *Check inclusion and exclusion criteria*

Check all inclusion and exclusion criteria for household contacts as described in Sections 4.2 and 4.3 before enrolment.

5.6.2.3. *Collect demographic data*

Record demographic data such as age, gender, ethnicity and relationship to the infant in the household contact's eCRF.

5.6.2.4. *Medical history*

Obtain the household contact's medical history by interview and/or review of the medical records and record any pre-existing conditions or signs and/or symptoms present in a household contact prior to the vaccination in the household contact's eCRF.

5.6.2.5. *Urine pregnancy test*

Female household contacts of childbearing potential are to have a urine pregnancy test prior to study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the household contact is menstruating at the time of the study visit.

5.6.2.6. *Assess pre-vaccination body temperature*

The axillary, rectal, oral or tympanic body temperature of all household contacts needs to be measured prior to any study vaccine administration. The preferred route for

recording temperature in household contacts will be axillary. If the household contact has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for axillary route on the day of vaccination], the vaccination visit will be rescheduled within the allowed interval for this visit.

5.6.2.7. *Vaccine administration*

After completing all prerequisite procedures prior to vaccination, one dose of Boostrix will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the household contact's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit. Although the vaccine can be administered anytime during the study, it is recommended that the household contact is vaccinated preferably 2 weeks before birth of the infant. The reason for refusal of vaccination by eligible household contacts will be recorded, if applicable.

The household contacts will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.2.8. *Recording of SAEs and pregnancies*

Refer to Section 8.2 for procedures for the investigator to record SAEs and pregnancies. Refer to Section 8.3 for guidelines and how to report SAE and pregnancy reports to GSK Biologicals.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries

and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

The biological samples are presented in Table 7.

Table 7 Biological samples

Sample type	Quantity*	Unit	Time-point
Blood	5	mL	Day 0 (Pre-Vacc) and Day 30 (Post-Vacc)
Cord Blood	2.5	mL	At Birth

* Approximate quantity

5.7.3. Laboratory assays

Please refer to APPENDIX A for the address of the clinical laboratories used for sample analysis.

At Visits 1, 2 and 3, blood will be collected for measurement of immune response. All serology will be determined in GSK Biologicals' laboratories, or in a laboratory designated by GSK, using standardized, validated procedures with adequate controls (refer to Table 8).

Table 8 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off**	Laboratory†
SER	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	NA	IU/ml	.1	GSK Biologicals*
SER	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	NA	IU/ml	.1	GSK Biologicals*
SER	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*
SER	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*
SER	Bordetella pertussis.Pertactin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*

SER = Serum
ELI = Enzyme-linked immunosorbent assay (ELISA)
NA = Not Applicable
IU/ml = International units/millilitre
EU/ml = ELISA units/millilitre
*GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Rixensart, Belgium; Wavre, Belgium.
** These cut-offs might be subject to change due to assay re-development.
†Refer to APPENDIX A for the laboratory addresses.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

The immunological read-outs are presented in Table 9.

Table 9 Immunological read-outs

Blood sampling time-point		No. subjects	Component	Components priority rank
Type of contact and time-point	Sampling time-point			
Visit 1 (Day 0)	Pre-Vacc	All	PT, PRN and FHA D, T	1 2
Visit 2 (Day 30)	Post-Vacc	All	PT, PRN and FHA D, T	1 2
Visit 3 (At birth)	At birth	All*	PT, PRN and FHA	1

Pre-vacc: Blood sample to be collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc: Blood sample to be collected one month after the booster vaccination in pregnant women (Visit 2).
* Cord blood collected from umbilical cord of subjects

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 9.

5.7.5. Immunological correlates of protection

The following cut-offs are accepted as immunological correlates of protection:

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) will be measured by Enzyme-linked immunosorbent assay (ELISA). The assay cut-off of ELISA is currently set at 0.1 International Units per ml (IU/ml), which provides a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].
- No serological correlate of protection against pertussis has been established [Plotkin, 2010]. Antibodies against the pertussis components pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) will be measured by ELISA. The seropositivity cut-off for all three pertussis antibodies in ELISA is currently 5 EL.U/ml. Subjects with antibody concentration below the cut-off will be considered seronegative.

The immunological assay results will be communicated to the investigator as soon as they become available and in any case no later than 12 months after the visit date at which sampling allows the assessment of immunogenicity.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects.

For the study subjects identified as non-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of study vaccines

The candidate vaccine has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

The study vaccines are presented in Table 10.

Table 10 Study vaccines

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
Boostrix	dTpa	DT>=2IU; TT>=20IU; PT=8µg; FHA=8µg; PRN=2.5µg; Aluminium=500µg Al3+	The vaccine will be supplied as pre-filled syringes	0.5 ml	1
Placebo for dTpa vaccine	NaCl	NaCl=150mM	The placebo will be supplied as pre-filled syringes	0.5 ml	1

6.2. Storage and handling of study vaccine

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccines

The injectable vaccines must be administered intramuscularly, at a 90-degree angle into the deltoid muscle of the non-dominant arm [CDC, 2002] on the side stated in Table 11.

In order to ensure proper intramuscular injection of the vaccines, a needle of at least 1 inch (2.54 cm) length, 25 gauge will be used [Diggle, 2006; Zuckerman, 2000].

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

The dosage and administration of the study vaccines is presented in Table 11.

Table 11 Dosage and administration (Amended: 15 July 2015)

Type of contact and time-point*	volume to be administered	Study Group	Treatment name	Route [1]	Site [2]	Side [3]
Visit 1 (Day 0)	0.5 mL	dTpa Group	*Boostrix*	IM	D	N-D
		Control Group	Placebo			
Visit 3 (At birth)	0.5 mL	dTpa Group	Placebo	IM	D	N-D
		Control Group	*Boostrix*			

[1] Intramuscular (IM)
[2]Deltoid (D)
[3]Non-dominant (N-D).
Vaccination can be performed in the opposite side in case of medical indication preventing vaccination in the side stated in the table, as judged by the investigator.
Household contacts in Spain: One dose (0.5mL) of Boostrix vaccine will be administered intramuscularly as part of an assessment of cocooning.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 5% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement vial number. The replacement numbers will be allocated by component. The system will ensure, in a blinded manner, that the replacement vial matches the formulation the subject was assigned to by randomisation.

6.5. Contraindications to vaccination

The following events constitute contraindications to administration of *Boostrix* at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the

protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be oral/axillary.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

6.6. Warnings and precautions

Refer to the approved product label/package insert.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator should question the subject about any medications/products taken and vaccinations received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered starting at Screening Visit and ending at last study visit (study conclusion).
- Any concomitant vaccination administered in the period starting at Screening Visit and ending at last study visit (study conclusion). Note: Medications/vaccinations taken during pregnancy are to be recorded as medical/vaccination history.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route].
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered at any time during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.4 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before the dose of vaccine and ending 30 days after*, with the exception of seasonal influenza vaccine.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.
- Drug and/or alcohol abuse.

6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

At each study visit subsequent to the first vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. diphtheria, tetanus or pertussis infection) or are confirmed to have an alteration of their initial immune status.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF**.**

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalisation or prolongation of existing hospitalisation,

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

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

d. Results in disability/incapacity, OR

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

e. Adverse pregnancy outcomes specified in Section 8.1.5 and the listed pregnancy-related events of interest/neonate-related events of interest in Section 8.2.2 should always be considered as SAEs (medically important events) and should be reported as described in Sections 8.3.1 and 8.3.3.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

Note: Any hospitalisation due to either normal or caesarean delivery will not be considered as an SAE.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 12 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

If any study subject reports a large injection site reaction (defined as any local swelling with diameter >100 mm and/or any noticeable diffuse injection site swelling (diameter not measurable) and/or any noticeable increased circumference of the injected limb), they will be asked to contact the study personnel and come for an evaluation by the investigator as soon as possible. The investigator will record detailed information describing the AE on a specific large swelling reaction sheet in the eCRF.

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs etc.) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at

baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.5. Pregnancy outcomes

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.

The following adverse pregnancy outcomes should always be considered as SAE and will be reported as described in Sections 8.3.1 and 8.3.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation).
  - ectopic and molar pregnancy.
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study patient (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

8.2. Detecting and recording adverse events, serious adverse events, pregnancies, pregnancy-related AEs and neonate-related AEs

8.2.1. Time period for detecting and recording adverse events, serious adverse events, pregnancies, pregnancy-related AEs and neonate-related AEs (Amended: 15 July 2015)

All AEs starting within 30 days following administration of each dose of study vaccine/placebo (Day 0 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs (including adverse pregnancy outcomes, listed pregnancy-related adverse events of interest/neonate-related adverse events of interest) will begin at the first receipt of study vaccine/placebo and will end at study end (Visit 4) for each subject. See Section 8.3 for instructions on reporting of SAEs.

The time period for collecting and recording AEs, SAEs, pregnancies, pregnancy-related AEs and neonate-related AEs will begin at the first receipt of study vaccine/placebo and will end at study end (Visit 4).

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine/placebo.

SAEs that are related to the investigational vaccine will be collected and recorded from the time of the first receipt of study vaccine/placebo until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording new pregnancies will begin after delivery of the baby and will end at Visit 4. See section 8.3 for instructions on reporting of pregnancies.

The time period of reporting SAEs for household contacts will begin at the administration of Boostrix vaccine (as part of an assessment of cocooning) and end at 30 days after the vaccination. The SAEs and pregnancies in household contacts will be collected till 30 days after vaccination, irrespective of the visit in which Boostrix vaccine is administered.

An overview of the protocol-required reporting periods for AEs and SAEs is given in the table below Table 13.

Table 13 Reporting periods for adverse events, serious adverse events, pregnancies, pregnancy-related adverse events and neonate-related adverse events (Amended: 15 July 2015)

Event	Screening Visit*		V1	8 d (0-7d) post V1	31 d (0-30d) post V1	V3	8 d (0-7d) post V3	31 d (0-30 d) post V3	V4 (Study Conclusion)
			D0		V2 (D30)	At birth			Post-delivery M2
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
Pregnancy-related adverse events and neonate-related adverse events									
SAEs related to study participation or concurrent GSK medication/ vaccine									
New pregnancies									
SAEs and pregnancies in household contacts in Spain*									

Event	Screening Visit*		V1	8 d (0-7d) post V1	31 d (0-30d) post V1	V3	8 d (0-7d) post V3	31 d (0-30 d) post V3	V4 (Study Conclusion)
			D0		V2 (D30)	At birth			Post-delivery M2
SAEs related to study participation or concurrent GSK medication/ Vaccine in household contacts in Spain									

* i.e. consent obtained; V: Visit; D: Day, M: Month

***** The SAEs and pregnancies in household contacts will be reported till 30 days after vaccination, irrespective of the visit in which Boostrix vaccine is administered.***

8.2.2. Adverse events of specific interest (adverse pregnancy outcomes, listed pregnancy-related adverse events of interest/neonate-related events of interest)

All adverse pregnancy outcomes, listed pregnancy-related adverse events of interest and neonate-related events of interest occurring at any time during the period starting with the first administration of the vaccine till end of the study will be considered as SAEs and must be recorded in the appropriate section of the patient's eCRF, irrespective of intensity or whether or not they are considered administration-related.

Adverse pregnancy outcomes include:

- Live birth with congenital anomalies,
- Still birth with no congenital anomalies,
- Still birth with congenital anomalies,
- Elective termination with no congenital anomalies
- Elective termination with congenital anomalies

Listed pregnancy-related adverse events of interest/neonate-related events of interest include:

- Gestational diabetes,
- Pregnancy-related hypertension,
- Premature rupture of membranes,
- Preterm premature rupture of membranes,
- Premature labour,
- Premature uterine contractions,

- Intrauterine growth restriction/poor foetal growth,
- Pre-eclampsia and eclampsia,
- Vaginal or intrauterine haemorrhage,
- Maternal death,
- Preterm birth,
- Neonatal death,
- Small for gestational age,
- Neonatal hypoxic ischaemic encephalopathy
- Failure to thrive/growth deficiency

The definitions of the above specified pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related events of interest are adapted from [Munoz, 2013] and can be found in the GLOSSARY OF TERMS and in APPENDIX C.

8.2.3. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.4. Evaluation of adverse events and serious adverse events

8.2.4.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.4.2. Assessment of adverse events

8.2.4.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 14 Intensity scales for solicited symptoms in adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral/axillary.

The maximum intensity of local injection site redness/swelling/fever will be scored at GSK Biologicals as follows:

0 : Absent

1 : ≤ 20 mm

2 : > 20 mm and ≤ 50 mm

3 : > 50 mm

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.4.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

YES	:	There is a reasonable possibility that the vaccine contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

8.2.4.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.2.4.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

Note: hospitalisation or an unscheduled visit due to either normal or caesarean delivery will not be considered as an SAE and will not be recorded as a medically attended visit in the eCRF.

8.3. Reporting of serious adverse events, pregnancies and other events

8.3.1. Prompt reporting of serious adverse events, pregnancies and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Adverse pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related adverse events of interest that occur in the time period defined in Section 8.2 will be considered as SAE and will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware of them.

Pregnancies that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware of the pregnancy.

Table 15 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs#	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	1 week*	electronic pregnancy report	1 week*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.
# including adverse pregnancy outcomes and listed pregnancy-related/neonate-related AEs of interest.

8.3.2. Contact information for reporting serious adverse events, pregnancies and other events

Study Contact for Reporting SAEs, pregnancies and other events
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pregnancies and other events
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Fax: +PPD or +PPD Email address: PPD

8.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant after delivery, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.3.5. Updating of SAE and pregnancy information after removal of write access to the subject's eCRF

When additional SAE and pregnancy information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

8.3.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of adverse events, serious adverse events and pregnancies

8.4.1. Follow-up of adverse events and serious adverse events

8.4.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 15).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.4.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs, until the end of the study period or they are lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.4.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.7).

8.6. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational vaccines,

prior to regulatory reporting. The GSK Biologicals' Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 8.3.1).

8.7. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding **24/24 hour and 7/7 day availability**
GSK Biologicals' Central Safety Physician: Outside US/Canada: +PPD (GSK Biologicals Central Safety Physician on-call) For US/Canada only: +PPD (GSK Biologicals Central Safety Physician on-call) **GSK Biologicals' Central Safety Physician Back-up:** Outside US/Canada: +PPD US/Canada only: + PPD **Emergency Unblinding Documentation Form transmission:** Outside US & Canada: Fax: +PPD or +PPD US/Canada only: Fax: +PPD

8.8. Subject card (Amended: 15 July 2015)

Study subjects ***and the participating household contacts*** must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).

- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.4.1.2).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

9.3. Extension study

At the end of the study (study conclusion visit), the investigator will ask each subject if they are interested to allow their child to participate in the follow-up study. If a subject is not interested in allowing their child to participate in the follow-up study, the reason for refusal will be documented in the subject's eCRF.

10. STATISTICAL METHODS

10.1. Primary endpoint

- Immunogenicity with respect to components of the study vaccine, at delivery (in cord blood sample):
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations.

10.2. Secondary endpoints (Amended: 15 July 2015)

- Outcome of pregnancy in terms of pregnancy outcomes up to study end (Visit 4).
  - Pregnancy outcomes will include live birth with no congenital anomalies, live birth with congenital anomalies, still birth with no congenital anomalies, still birth with congenital anomalies, elective termination with no congenital anomalies and elective termination with congenital anomalies.
- Outcome of pregnancy in terms of listed pregnancy-related adverse events of interest/ neonate-related events of interest up to study end (Visit 4).
  - Listed pregnancy-related adverse events of interest/ neonate-related events of interest will include gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labour, premature uterine contractions, intrauterine growth restriction/poor foetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine haemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic ischaemic encephalopathy and failure to thrive/growth deficiency.
- Immunogenicity with respect to components of the study vaccine received during pregnancy, one month post vaccination:
  - Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN seroprotection/seropositivity status and antibody concentrations.
  - Vaccine response to PT, FHA and PRN
  - Vaccine response to anti-D and anti-T
- Immunogenicity with respect to components of the study vaccine, in the cord blood sample.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status.
- Solicited local and general symptoms (at Visit 1 and Visit 3).
  - Occurrence of each solicited local/general symptoms during the 8-day (Day 0-Day 7) follow-up period after the vaccination.

- Unsolicited adverse events (at Visit 1 and Visit 3).
  - Occurrence of unsolicited AEs within 31 days (Day 0 – Day 30) after any vaccination, according to the **Med**ical **D**ictionary for **R**egulatory **A**ctivities (MedDRA) classification.
- Serious adverse events ***(SAEs).***
  - Occurrence of serious adverse events from Dose 1 up to study end (Visit 4).
- ***Percentage of household contacts of the infants born to pregnant women vaccinated in Spain who accepted Boostrix vaccine as part of an assessment of cocooning among the eligible household contacts.***
- ***Occurrence of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after vaccination.***

Refer to GLOSSARY OF TERMS for the definitions of the various pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related events of interest.

10.3. Determination of sample size

It is proposed to conduct the study with a sample size of 680 subjects. Assuming a drop-out rate of approximately 20%, to compensate for subject attrition due to early withdrawal, a total of 680 subjects (340 in each group) will be randomised in a 1:1 ratio in order to obtain the desired number of 272 evaluable subjects in each group for immunogenicity analysis. Availability of 272 evaluable subjects per group (for a total of 680 subjects) will provide above 96% overall power to reach the primary endpoint for the primary maternal phase using Bonferroni adjustment on type II error. This sample size is justified by the expected difficulty to enrol pregnant women in the study and on the minimum requirement of safety data in pregnant women, as determined by EU guidelines [EMA, 2008].

Table 16 presents the Power to rule out the null hypothesis (H_0: group GMC ratio < 1.5) that dTpa Group is not superior to the Control Group.

Table 16 Power to rule out the null hypothesis (H_0: group GMC ratio < 1.5) that dTpa Group is not superior to the Control Group (N= *272* evaluable subjects per group)

Endpoint	Standard deviation* [Log_{10} (titre)]	True group ratio*	Power**
Anti-PT	0.577	2.3	**96%**
Anti-FHA	0.564	5	**>99%**
Anti-PRN	0.564	*5*	**>99%**

*anticipated conservative value (References: [Leuridian, 2011; Munoz, 2014])
** PASS2005, one sided test for difference between 2 independent groups, HA: group difference=log10 (true group ratio), one-side alpha = 0.025, Assuming common variance between the groups Using Bonferroni adjustment on type II error (overall beta=sum of type II error of each endpoint)

Table 17 presents the precision achieved with a sample of 300 subjects in each group for the various possible expected adverse pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related events of interest in terms of exact 95% CIs.

Table 17 Precision achieved with a sample of 300 subjects in each group for the various possible expected pregnancy outcomes and listed pregnancy-related adverse events of interest/ neonate-related events of interest in terms of exact 95 percent CI

No. of subjects expected (N)	Pregnancy outcome and listed pregnancy-related adverse events of interest/neonate-related events of interest	Subjects with outcome			
		n	%	Exact 95%CI	
				LL	UL
300	Stillbirth	1	0.3	0.0	1.8
	Stillbirth^	0	0.0	0.0	1.2
	Placental Abruption	3	1.0	0.2	2.9
	Placenta previa	1	0.3	0.0	1.8
	Post-partum haemorrhage	18	6.0	3.6	9.3
	Premature rupture of membranes	24	8.0	5.2	11.7
	Premature uterine contractions and premature labour	36	12.0	8.5	16.2
	Preterm delivery	35	11.7	8.3	15.7
	Intrauterine growth restriction / poor foetal growth	30	10.0	6.8	14.0
	Pregnancy related hypertension, preeclampsia and eclampsia	36	12.0	8.5	16.2
	Gestational diabetes	15	5.0	2.8	8.1
	Congenital anomalies (major anomalies)	9	3.0	1.4	5.6

n = No. of subjects with any pregnancy outcome
% = (n/N)*100; LL = Lower limit; UL = Upper limit
^Even if we observe no events for a specific outcome, the upper limit of the 95% CI will be 1.2%.
Reference paper: Munoz FM, et al. Research on vaccines during pregnancy: Protocol design and assessment of safety. Vaccine, 2013

10.4. Cohorts for Analyses

10.4.1. Total Vaccinated cohort

- The Total Vaccinated cohort (TVC) analysis will be performed per treatment actually administered. A safety analysis based on the TVC will include all subjects with the study vaccine administration documented.
- An immunogenicity analysis based on the TVC will include all subjects vaccinated during pregnancy (Visit 1) for whom data concerning at least one immunogenicity endpoint measure is available.

10.4.2. According-To-Protocol cohort for analysis of safety

The ATP cohort for safety will consist of all subjects from the TVC who complied with vaccine administration up to the end of the Epoch 001, namely:

- Who have received the dose of study vaccine (at Visit 1) according to their random assignment,
- For whom administration site of study vaccine is known, and is according to protocol,
- Who have not received a vaccine not specified or forbidden in the protocol,
- For whom the randomisation code is not broken.

10.4.3. ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who meet all eligibility criteria.
- Who comply with the procedures and intervals defined in the protocol.
- Who are within the maximum interval allowed as defined in the protocol.
- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 6.7.2) during the study.
- Who did not receive a product leading to exclusion from an ATP analysis as listed Section 6.7.2.
- Who did not present with a medical condition leading to exclusion from an ATP analysis as listed Section 6.8.
- Who have the cord blood collection at least 21 days post-vaccination.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component one month after vaccination i.e. Visit 3 in the cord blood sample.

10.4.4. *Total cohort for household contacts in Spain*

Total cohort for household contacts will include all eligible household contacts of the infants born to pregnant women vaccinated in Spain. For the analysis of safety, all vaccinated household contacts will be considered.

10.5. Derived and transformed data

- A seronegative subject is a subject whose antibody concentration is below the assay cut-off.

- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off defined (refer to Table 8). The following seropositivity thresholds are currently applicable:
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations ≥5 EL.U/mL.
- A seroprotected subject is a subject whose antibody concentration is greater than or equal to the level defining clinical protection (refer to Table 8). The following seroprotection thresholds are applicable:
  - Anti-D antibody concentrations ≥ 0.1 IU/mL
  - Anti-T antibody concentrations ≥ 0.1 IU/mL.
- Other cut-offs to be considered:
  - Anti-D antibody concentrations ≥ 1.0 IU/mL.
  - Anti-T antibody concentrations ≥ 1.0 IU/mL.
- Vaccine response one month post vaccination in pregnant women (at Visit 3) to the diphtheria and tetanus antigens is defined as:
  - For initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the assay cut-off (post-vaccination concentration ≥ 0.4 IU/mL).
  - For initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration.
- Vaccine response one month post vaccination in pregnant women (at Visit 3) to the PT, FHA and PRN antigens, is defined as:
  - For initially seronegative subjects with pre-vaccination antibody concentration below cut-off, i.e. < 5 EL.U/mL: antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 20 EL.U/mL).
  - For initially seropositive subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL: an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
  - For initially seropositive subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL: an increase in antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- The GMC calculations will be performed by taking the anti-log of the mean of the $\log_{10}$ concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

Handling of missing data: For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Safety/ Reactogenicity

- For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only subjects with documented safety data (i.e. symptom screen completed).
- For the analysis of unsolicited symptoms, SAEs and analyses that combine solicited and unsolicited symptoms, subjects with no report of the event will be considered to have not had the event. Subjects who do not report being administered concomitant medications and vaccinations will be considered to have not received any medications and vaccinations.

10.6. Analysis of demographics (Amended: 15 July 2015)

Demographic characteristics (age at the booster dose in years, race, height [cm], weight [kg], body mass index in kg/m^2), cohort description and withdrawal status will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race;
- Mean, median and standard error will be provided for continuous data such as age.

The distribution of subjects enrolled among the study sites and countries will be tabulated as a whole and per group.

Summary statistics by height [cm], weight [kg], head circumference [cm], body mass index [BMI in kg/m^2] and Apgar score of the infant will be tabulated as a whole and per group.

10.6.1. *Analysis of eligible household contacts*

Analysis of eligible household contacts will be performed on the Total cohort for household contacts in Spain.

- ***Demographic characteristics will be summarised for the eligible household contacts as a whole and per group using descriptive statistics.***
- ***Reasons for refusal of the cocooning vaccination will be summarised for the eligible household contacts as a whole and per group.***
- ***Percentage of household contacts of the infants born to pregnant women vaccinated in Spain who accepted Boostrix vaccine as part of an assessment of cocooning among the eligible household contacts will be tabulated as a whole and per group.***

10.7. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from this ATP cohort is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

10.7.1. Within group assessment:

For each treatment group, before and one month after vaccination during pregnancy and if blood sample result is available:

- Seroprotection rates and their exact 95% CIs for antibodies against diphtheria and tetanus will be calculated.
- Seropositivity rates and their exact 95% CIs for antibodies against PT, FHA, PRN, will be tabulated.
- GMCs and their 95% CIs for antibodies against all vaccine antigens will be calculated.
- The distribution of antibody concentrations one month after booster vaccination for each antigen will be displayed using reverse cumulative distribution curves.
- Vaccine response to diphtheria, tetanus and pertussis antigens and their exact 95% CI will be calculated.

In the cord blood sample, if the blood sample result is available:

- Seropositivity rates and their exact 95% CIs for antibodies against PT, FHA, PRN, will be tabulated.
- GMCs and their 95% CIs for antibodies against PT, FHA, PRN antigens will be calculated.

10.7.2. Between group assessment:

- The primary objective is to demonstrate that, the immune response in the dTpa Group is superior to that in the Control Group for the pertussis antigens, in the cord blood sample.
  - *The LL of the 95% CI of the GMC ratio [dTpa Group divided by Control Group] for anti-PT, anti-FHA and anti-PRN antibodies are ≥ 1.5.*

The CI of the group GMC ratios will be computed using a two-sample t test assuming heterogeneity of variance.

10.8. Analysis of safety (Amended: 15 July 2015)

The primary analysis will be performed on the TVC. If in any vaccine group, 5% or more of the vaccinated subjects are eliminated from the TVC, a second analysis will be performed on the ATP cohort for analysis of safety. ***Analysis of safety in household contacts will be performed on the Total cohort for household contacts in Spain.***

- The percentage of subjects with each specific pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related events of interest will be tabulated with its exact 95% CI.
- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 8-day (Day 0–Day 7) follow-up period after the vaccination will be tabulated after each dose and overall with exact 95% CI. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms and for any symptoms requiring medical attention.
- The percentage of doses followed by at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 8-day (Day 0–Day 7) follow-up period after the vaccination will be tabulated with exact 95% CI. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms and for any symptoms requiring medical attention.
- The percentage of subjects/doses reporting each individual solicited local and general AE during the 8-day (Day 0-Day 7) follow-up period after booster vaccination will be tabulated with its exact 95% CI for each group.
- All computations mentioned above will be done for Grade ≥2 (solicited symptoms only) and Grade 3 symptoms, for symptoms considered related to vaccination (general symptoms only), for Grade 3 symptoms considered related to vaccination (general symptoms only) and for symptoms that resulted in a medically-attended visit.
- Occurrence of fever and related fever will be reported per 0.5°C cumulative temperature increments as well as the occurrence of Grade 3 fever (> 39.0°C axillary temperature) with causal relationship to vaccination.
- Any large injection site reaction (defined as any local swelling with diameter > 100 mm and/or any noticeable diffuse injection site swelling (diameter not measurable) and/or any noticeable increased circumference of the injected limb) onset within 8 days (Day 0–Day 7) after each vaccination will be described in detail.
- The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects/doses with unsolicited symptoms occurring within 31 days (Day 0–Day 30) with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for Grade 3 unsolicited symptoms and for unsolicited symptoms possibly related to vaccination.

- The percentage of subjects/doses who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day and 31-day follow-up period after vaccination will be tabulated after each dose and overall with exact 95% CI.
- SAEs and withdrawal due to AEs and SAEs following booster dose up to Visit 4 will be described in detail.
- All SAEs assessed as being possibly related to study participation occurring throughout the study period will be described.
- All SAEs assessed as being possibly related to a concurrent GSK medication occurring throughout the study period will be described.
- ***For the vaccinated household contacts in Spain, SAEs following Boostrix vaccination up to 30 days will be described in detail.***

10.9. Interpretation of analyses

For analysis on the primary objective with pre-defined success criteria and an appropriate type I error control, appropriate conclusion can be drawn.

The secondary objectives of the study are descriptive and should be interpreted as such.

10.10. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.10.1. Sequence of analyses

A final analysis including all cleaned data up to Visit 4 (post-delivery Month 2) will be conducted. This analysis will include the final analysis of immunogenicity and the final analysis of solicited symptoms/unsolicited symptoms and SAEs. A statistical report and a clinical report will be written at that time.

10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. electronic Case Report Form instructions

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

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

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

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

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

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

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.

11.6. Provision of study results to investigators

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

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

13. REFERENCES

Amirthalingam, G. Et al. Effectiveness of maternal pertussis vaccination in England:an observational study. *Lancet* 2014. Available at http://dx.doi.org/10.1016/S0140-6736(14)60686-3). Accessed: 15 July 2015.

Camargo ME, Silveira L, Furuta JA, Oliveira EPT and Germek OA. Immunoenzymatic assay of anti-diphtheric toxin antibodies in human serum. *J Clin Microbiol* 1984; 20(4): 772-4.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of diabetes in Canada. Canadian J of Diabetes. 2013. 37(suppl 1): S1-212.

Canadian Immunisation Guide (Part 4). Pertussis Vaccine. Public Health Agency of Canada. 2014. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pert-coqu-eng.php. Accessed : 15 July 2015.

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf. Accessed : 15 July 2015.

Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunisation Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002, 51(RR02); 1-36.

Centers for Disease Control (CDC). Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007. http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf. Accessed: 15 July 2015.

Center for Disease Control and Prevention (CDC), Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months- Advisory Committee on Immunization Practices (ACIP), 2011. 60(41); 1424-1426.

Centres for Disease Control (CDC). Pertussis epidemic-Washington 2012(a). *MMWR* 2012; 61 (28); 517-22.

Center for Disease Control and Prevention (CDC), Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women – Advisory Committee on Immunization Practices (ACIP), 2013. 62(7); 131-35.

Centers for Disease Control and Prevention (CDC). Pertussis Outbreak trends.http://www.cdc.gov/pertussis/outbreaks/trends.html. Accessed: 15 July 2015.

Communicable Disease Control Directorate. Ongoing pertussis epidemic in Western Australia. 2011; 16 (1).

Conseil Supérieur de la Santé (CSS). Fiches de vaccination éditées par le CSS (CSS 9110). Vaccination anticoquelucheuse ; vaccination de l'adulte (2013) http://health.belgium.be/eportal/Aboutus/relatedinstitutions/SuperiorHealthCouncil/publications/factsheetsvaccination/13038500_FR ?ie2Term=center&ie2section=9130&fodnlang=fr ; Accessed : 15 July 2015

Diggle L, Deeks JJ, Pollard AJ. Effect of needle size on immunogenicity and reactogenicity of vaccines in infants: randomized controlled trial. *BMJ* 2006;333 (7568):571.

Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ.* 2014; 349:g4219.

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006); http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed : 15 July 2015

European Medicines Agency (EMA). Guideline on Risk Assessment of medicinal products on human reproduction and lactation: from data to labeling, 2008. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003307.pdf. Accessed: 15 July 2015.

Englund JA, Anderson EL, Reed GF et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics* 1995, 96:580–84.

Frits R Mooi, Sabine C de Greeff. The case for maternal vaccination against pertussis. *Lancet Infec Dis*. 2007; 7: 614-624.

Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus– diphtheria– pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol* 2011; 204:334.e1-5.

Hardy-Fairbanks AJ, Pan SJ, Kirkland KB et al. Immune Responses in Infants Whose Mothers Received Tdap Vaccine During Pregnancy. *Pediatr Infec Dis J*. 2013; 32: 1257-60.Health Protection Report. Confirmed pertussis in England and Wales: data to end-December 2012. 2013; 7(5).

International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy; International

Association of Diabetes and Pregnancy Study groups Consensus Panel. *Diabetes care*. 2010. 33 (3).

Joint Committee on Vaccination and Immunization (JCVI). JVCI meeting on pertussis immunization: August 2012. Draft minutes of discussions on the immunization of pregnant women against pertussis. Published 28 September 2012. http://transparency.dh.gov.uk/2012/09/28/jcvi-pertussis/ ; Accessed: 15 July 2015.

Leuridian et al. Effect of a pregnancy pertussis booster dose on maternal antibody titers in young infants; *The Pediatr Infec Dis J*, 2011, 30: 608-610.

Melville-Smith ME, Seagroatt VA, Watkins JT. A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralisation test in mice as a method for the estimation of tetanus antitoxin in human sera. *J Biol Stand* 1983; 11: 137-44.

Meyer CU, Habermehl P, Knuf M et al. Immunogenicity and reactogenicity of acellular pertussis booster vaccines in children: Standard pediatric versus a reduced-antigen content formulation. *Hum Vaccin.* 2008; 4(3):203-209.

Minh NN, He Q, Ramalho A, et al. Acellular vaccines containing reduced quantities of pertussis antigens as a booster in adolescents. *Paediatrics* 1999; 104:e70.

Munoz FM, Sheffield JS, Beigi RH et al. Research on vaccines during pregnancy: Protocol design and assessment of safety. *Vaccine.* 2013; 31(40): 4274-4279. http://dx.doi.org/10.1016/j.vaccine.2013.07.042

Munoz FM, Bond NH, Maccato M, et al. Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants: A Randomized Clinical Trial. *JAMA*. 2014; 311(17):1760-69.

New Zealand Pharmaceutical Management Agency (PHARMAC). Decision to amend the diphtheria, pertussis and tetanus vaccine (Boostrix) listing, 12 December 2012. http://www.pharmac.govt.nz/2012/12/12/; Accessed: 15 July 2015.

Plotkin SA. Correlates of protection Induced by Vaccination. Clin Vaccine Immunol. 2010. 17 (7) : 1055-1065.

Rüggeberg JU, Gold MS, Bayas JM, *et al*. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007; 25: 5675-84.

Spanish Group of Diabetes and Pregnancy (GEDE): Spanish Society of Diabetes (SED) , Spanish Society of Gynecology and Obstetrics (SEGO) and Spanish Association of Pediatrics (Section of Neonatology) . Care guide diabetes mellitus and pregnancy (3rd edition) . *Diabetol Av*. 2006; 22: 73-87. [Original article: Grupo Español de Diabetes y Embarazo (GEDE): Sociedad Española de Diabetes (SED), Sociedad Española de Ginecología y Obstetricia (SEGO) y Asociación Española de Pediatría (Sección de Neonatología). Guía asistencial de diabetes mellitus y embarazo (3ª edición). Av Diabetol 2006; 22: 73-87.].

Technical Advisory Group (TAG) on Vaccine-preventable Diseases. Vaccination: a shared responsibility. Quito, Ecuador 3-5 July 2013.

Turnbull FM et al, A randomized trial of two acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (Td) in adults. *Vaccine* 2001, 19:628-36.

Van Damme P, Burgess M. Immunogenicity of a combined diphtheria tetanus-acellular pertussis vaccine in adults. *Vaccine* 2004; 22:305-8.

Warshawsky B. NACI update on pertussis vaccination in pregnancy. *Can Fam Physician*. 2014; 60(6): 521.

Zheteyeva YA, Moro PL, Tepper NK, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. *Am J Obstet Gynecol* 2012; 207:59.e1

Zuckerman JN. The importance of injecting vaccines into muscles. *BMJ* 2000;321:1.

APPENDIX A CLINICAL LABORATORIES

Table 18 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 – B-1300 Wavre – Belgium

Table 19 Outsourced laboratories

Laboratory	Address
Quest Diagnostics Clinical Trials (UK)	Unit B1, Parkway West Industrial Estate Cranford Lane – Heston, Middlesex TW5 9QA UK
Quest Diagnostics Nichols Institute	33608 Ortega Highway San Juan Capistrano, CA 92675-2042 USA
CEVAC – University of Gent	De Pintelaan, 185 Gent Belgium

APPENDIX B OBSTETRICAL RISK ASSESSMENT FORM

NAME: _____

PRIMARY OBSTETRICIAN/FAMILY DOCTOR: _____

AGE: _____

DATE OF LAST MENSTRUAL PERIOD (LMP): _____

MEDICAL HISTORY (EXCLUSIONS FOR A HISTORY OF SERIOUS UNDERLYING MEDICAL CONDITIONS WILL BE BASED ON ASSESSMENT BY THE STUDY PHYSICIAN ON THE POTENTIAL FOR INCREASED RISK TO THE CURRENT PREGNANCY)

YES	NO	DIABETES MELLITUS
YES	NO	HEART DISEASE [requiring medication, previous cardiac surgery, cardiac dysfunction including coronary disease (congenital VSD surgically corrected is not an exclusion)]
YES	NO	AUTOIMMUNE DISORDER (that could affect the immune response or put the current pregnancy at risk)
YES	NO	CHRONIC KIDNEY DISEASE (requiring medication, elevated creatinine, decreased renal function)
YES	NO	NEUROLOGIC DISEASE (that could put the current pregnancy at high risk)
YES	NO	HEPATITIS/LIVER DISEASE
YES	NO	PULMONARY DISEASE (controlled asthma treated as needed with inhalers is not excluded)
YES	NO	D (Rh) SENSITIZED OR KELL ANTIBODIES
YES	NO	PREVIOUS STILLBIRTH OR NEONATAL DEATH

The list given above is not exhaustive and contains common examples.

CURRENT PREGNANCY

YES	NO	GESTATIONAL DIABETES OR HYPERTENSION REQUIRING DRUG THERAPY
YES	NO	EXPECTED TO DELIVER MULTIPLE INFANTS
YES	NO	EXPECTED TO DELIVER AN INFANT WITH A MAJOR CONGENITAL ANOMALY
YES	NO	INCOMPETENT CERVIX
YES	NO	POLYHYDRAMNIOS OR OLIGOHYDRAMNIOS
YES	NO	INTRAUTERINE GROWTH RESTRICTION
YES	NO	PSYCHIATRIC DISORDER (requiring follow up during this pregnancy by a mental health specialist)
YES	NO	ASSISTED REPRODUCTIVE TECHNOLOGY [is current pregnancy considered high risk at the time of enrolment]
YES	NO	DEEP VEIN THROMBOSIS/PULMONARY EMBOLUS/THROMBOPHILIA
YES	NO	UNCORRECTED THYROID DYSFUNCTION AT TIME OF ENROLMENT
YES	NO	CURRENT SUBSTANCE ABUSE (including Methadone maintenance treatment)
YES	NO	HYPERTENSION (not controlled by medication)

CURRENT OBSTETRICAL PROCEDURES

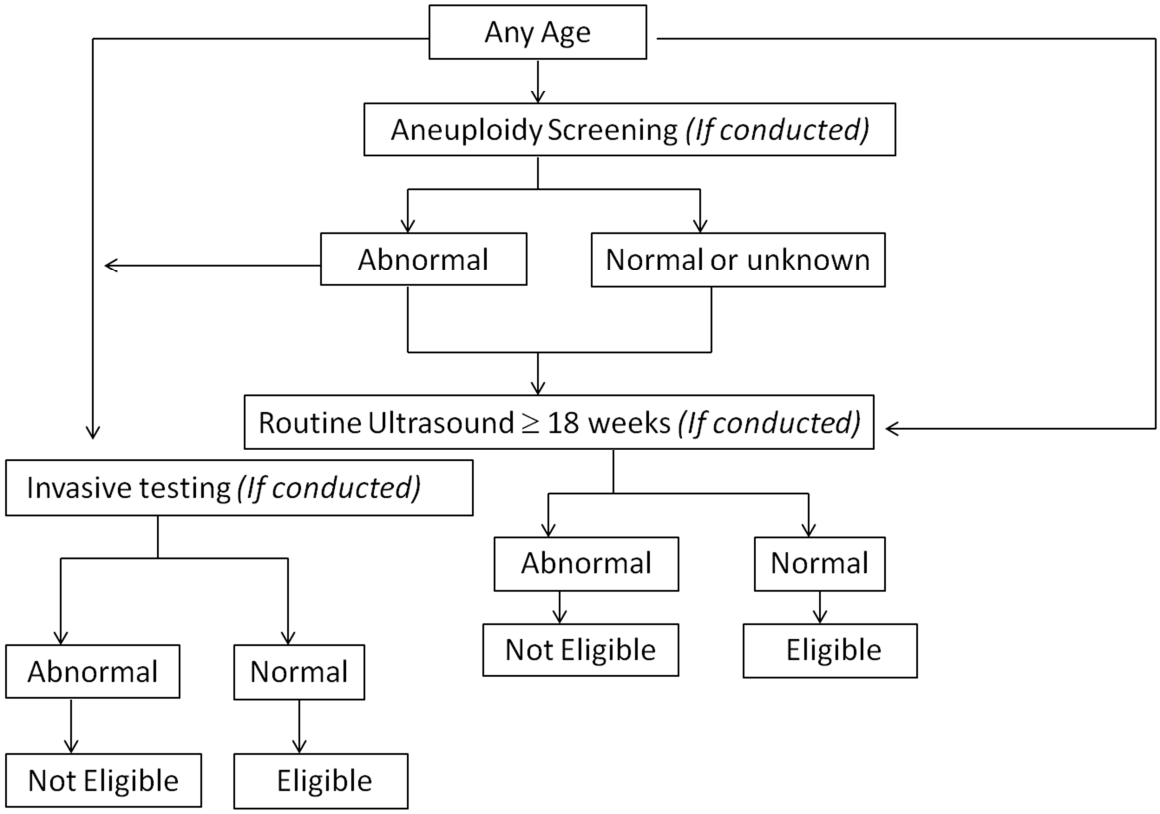
YES	NO	CONSIDERED NOT ELIGIBLE BY OSTETRICAL PROCEDURE ALGORITHM

☐ THE ABOVE NAMED PERSON IS AT "HIGH RISK" FOR SERIOUS OBSTETRICAL COMPLICATIONS AND **IS NOT ELIGIBLE** TO BE CONSIDERED FOR STUDY ENROLMENT

☐ THE ABOVE NAMED PERSON IS NOT AT "HIGH RISK" FOR SERIOUS OBSTETRICAL COMPLICATIONS AND **IS ELIGIBLE** TO BE CONSIDERED FOR STUDY ENROLMENT

SIGNATURE _____ DATE _____

Algorithm: Obstetrical Procedures to Identify Eligible subjects



APPENDIX C Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from [Munoz, 2013])

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

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

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

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
STILLBIRTH S: Stillborn, Fetal Demise/Death, Deadborn	Delivery of a death fetus after 22 0/7 weeks of gestation [EMEA, 2005]. Categories: - During pregnancy or antepartum. - Intrapartum. Subgroups: -Early Stillbirth: Delivery 22 0/7 – <28 weeks and/or ≥500 -1000 grams. -Late Stillbirth: Delivery ≥ 28 0/7 weeks and/or >1,000 grams	Overall rates [ACOG, 2009]: 6.2/1,000 births or 1 in 160 deliveries. -Early stillbirth: 3.2/1,000 births. -Late stillbirth: 3.1/1,000 births. Risk factors: Non-Hispanic black race, nulliparity, maternal age >35 years, hypertension, diabetes, obesity BMI >30, multiple gestations, smoking, drug and alcohol use, infections, growth restriction, and placental anomalies.	Includes macroscopic examination for fetal anomalies, and if available, autopsy and karyotype; cord and placental examination and pathology. Document antepartum events: maternal factors, fetal factors (e.g., IUGR), external factors (e.g., trauma), and peripartum events such as preterm premature rupture of membranes (PPROM), infection, abruption, cord events.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - American College of Obstetricians and Gynecologists. Management of stillbirth. ACOG Practice Bulletin Number 102. Obstetrics and Gynecology2009; 113: 748–61. (accessed on-line on 13/Oct/2014 at: https://stillbirthmatters.files.wordpress.com/2014/05/acog-management-of-stillbirth1.pdf)

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
CONGENITAL ANOMALIES S: Birth defects, Malformations	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC,2007] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious conditions or certain biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect.	Minor anomaly: Rates vary widely depending on study. Minor malformations and developmental variants occur in 14 – 40% of otherwise normal newborns [Leppig, 1987]. Major anomaly: Apparent at birth in approximately 3% of population [CDC, 2013].	An exact cause or mechanism for a major defect can be determined in less than 50% of the cases. Some agents cause major defects if exposure occurs during a specific critical period of gestation, but not at other times. After organogenesis has been completed (about 8 weeks after conception or 10 weeks after last menstrual period), the observable effect may be limited to fetal growth restriction or functional rather than gross structural defects [Sadler,2009]. The primary outcomes relative to stage of exposure are as follows: Pre-implantation: embryonic lethality Implantation to time of organogenesis: morphological defects. Fetal → neonatal stage: functional disorders, growth retardation, Carcinogenesis. A certain pattern of minor malformations may have important predictive value in identifying more serious associated problems, some of which may be unrecognizable at an early age. Specific patterns of multiple minor malformations may be presenting signs of a genetic condition or malformation syndrome.	Centers for Disease Control (CDC). Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007.(accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf) - Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, MooreCA. Guidelines for case classification for the National Birth Defects Preven-tion Study. Birth Defects Research Part A: Clinical and Molecular Teratology2003; 67:193–201. - Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. Association with major malformations. Journal of Pediatrics1987; 110: 530–7. -Sadler TW. Langman's medical embryology. 11th ed. Lippincott Williams and Q4Wilkins; 2009. - Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects-Atlanta, Georgia, 1978–2005. MMWR; 2013. (accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm)

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	Morphological anomalies: Abnormalities of body structure or function that are present at birth and are of prenatal origin. Categories: Minor anomaly: Anatomic variant or defect that do not have serious medical, functional or cosmetic consequences for the child. Includes those found in association with major anomalies. Major anomaly: Structural or functional defect that require surgical/medical treatment, have serious adverse effects on health or development (functional), or have significant cosmetic impact. [Rasmussen, 2003].			

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

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
MOLAR PREGNANCYS: gestational trophoblastic neoplasia, gestational trophoblastic tumor	Pregnancy marked by a neoplasm within the uterus, whereby part or all of the chorionic villi are converted into a mass of clear vesicles. Histologically distinct disease entities encompassed by this general terminology include: complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.	The incidence is estimated at 1-3 per 1000 pregnancies for partial or complete hydatidiform moles. The malignant invasive moles (choriocarcinoma and placental site trophoblastic tumour/epithelioid trophoblastic tumour) are very rare, 0.2% of the gestational trophoblastic disease cases [ESMO, 2013; ACOG, 2004]. Risk factors: extremes of maternal age and prior molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population.	The disease is most frequently diagnosed on the basis of increasing or plateauing hCG values. Patients should be monitored with serial determinations of quantitative hCG values. A baseline post-evacuation chest X-ray should be considered.	- American College of Obstetricians and Gynecologists. Diagnosis and Treatment of Gestational Trophoblastic Disease. ACOG Practice Bulletin Number 53. Obstetrics and Gynecology June 2004; 103 (6):1365-77. - M. J. Seckl, N. J. Sebire, R. A. Fisher, F. Golfier, L. Massuger & C. Sessa, on behalf of the ESMO Guidelines Working Group. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (Supplement 6): vi39–vi50.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PREGNANCY-RELATED ADVERSE EVENTS OF INTEREST				
VAGINAL OR INTRAUTERINE HEMORRHAGE S: Obstetric Hemorrhage, Major obstetric hemorrhage	Vaginal or intrauterine hemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours post-delivery). A major obstetric hemorrhage is defined as blood loss from uterus or genital tract >1500 mL or a decrease in hemoglobin of >4 gr/dl or acute loss requiring transfusion of >4 units of blood, or signs or symptoms of hypovolemia. Common causes of blood loss: - Antepartum hemorrhage: placenta previa (presence of placental tissue overlying or proximate to the internal cervical os), placental abruption (partial or total placental detachment prior to delivery of fetus), uterine rupture, bleeding from vaginal or cervical lesions, etc.	Antepartum hemorrhage: has an incidence of 2–5% of all pregnancies beyond 24 weeks [Walfish, 2009]. Infrequent (14% of cases occur before 32 weeks gestation) and up to 60% between 32-37 weeks gestation [Munoz , 2013]. Risk factors for placenta previa: prior uterine trauma, multiparity, advanced maternal age, previous C-section or other uterine surgery, and prior placenta previa. Risk factors for placental abruption: hypertension, pre-eclampsia, advanced maternal age, multiparity, maternal/paternal tobacco use, cocaine use, trauma, premature rupture of membranes, chorioamnionitis, and prior abruption. Risk factors for uterine rupture: prior uterine surgery, trauma, uterine anomalies, dystocia, use of uterotonic drugs, and abnormal placentation. Post-partum hemorrhage: Primary postpartum hemorrhage, which occurs in 4–6% of pregnancies, is caused by uterine atony in 80% or more of cases [ACOG ,2006]. Risk factors for Postpartum Hemorrhage: Prolonged labor, Augmented labor, Rapid labor,	Given the wide range of definitions applied to maternal hemorrhage, it is important to combine the clinical presentation and objective data, while keeping in mind the probability of concealed bleeding within the uterus, peritoneal cavity, and retroperitoneal space, and the relative masking of haemodynamic signs of haemorrhagic shock due to the physiological adaptations of pregnancy. Diagnosis is based on clinical presentation; ultrasound and placental pathology if available.	- American College of Obstetricians and Gynecologists. Cervical insufficiency. ACOG Practice Bulletin No. 76, Postpartum Haemorrhage International Journal of Gynecology and Obstetrics Oct 2006: 108 (4): 1034-47 (accessed on-line on 13/Oct/2014 at: https://www.acog.org/~/media/Districts/District%20II/PDFs/Final_Hemorrhage_Web.pdf - Walfish M et al. Maternal haemorrhage. Br. J. Anaesth. (2009) 103 (suppl 1): i47-i56. -Munoz et al. Research on vaccines during pregnancy: Protocol design and assessment of safety, Vaccine, (2013): 31 (40): 4274-4279, Appendixes

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	- Postpartum Hemorrhage: uterine atony, retained products of conception, abnormal placentation (abnormal attachment of the placenta to the uterine wall and includes accreta, increta, and percreta, depending on the extent of uterine invasion), genital tract trauma, uterine inversion, puerperal sepsis, uterine pathology such as fibroids, etc.	History of postpartum hemorrhage, Episiotomy, especially mediolateral, Preeclampsia, Overdistended uterus (macrosomia, twins, hydramnios), Operative delivery, Asian or Hispanic ethnicity, Chorioamnionitis. Risk factors for abnormal placentation: placenta previa with or without previous uterine surgery, prior myomectomy, prior cesarean delivery, Asherman's syndrome, submucous leiomyomata, and maternal age older than 35 years.		
PREMATURE RUPTURE OF MEMBRANES (PROM) AND PRETERM PREMATURE RUPTURE OF MEMBRANES (P-PROM)	PROM: Spontaneous rupture of fetal membranes that occurs before the onset of labor. Preterm PROM (P-PROM): Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks gestation.	Term PROM may occur in 8% of pregnancies, P-PROM in approximately one-third of all preterm births or 4% of all births [ACOG, 2007]. Risk factors: Numerous maternal and fetal factors involved, particularly infection, obstetric factors including abruption placenta, as well as previous P-PROM or premature delivery. Recurrence for P-PROM is 16-32%.	Assessment of gestational age and assessment of maternal and fetal risks, including intrauterine infection, labor, fetal compromise.	-American College of Obstetricians and Gynecologists. Premature rupture of membranes. ACOG Practice Bulletin Number 80. Obstetrics and Gynecology2007;109:1007–20.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PREMATURE UTERINE CONTRACTIONS AND PREMATURE LABOR	Premature uterine contractions: Uterine contractions without cervical change. Premature labor: Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.	Refer to incidence of preterm delivery: 12% of all live births [ACOG, 2012].	Collect any clinical and laboratory information that is available. Standard work-up may include: vaginal examination, uterine monitoring, and fetal monitoring. Work-up to determine etiology or association to study product may include: evaluation for infections (urine culture, Group B streptococcus, Chlamydia, gonococcus, *Trichomonas vaginalis*, bacterial vaginosis), drug screen, and ultrasound to rule out abruption, cord prolapse, oligo/polyhydramnios.	- American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 127. International Journal of Gynecology and Obstetrics 2012 Jun; 19(6):1308-17.
INTRAUTERINE GROWTH RESTRICTION / POOR FETAL GROWTH S: IUGR S: Fetal growth retardation	Estimated or actual birth weight below the 10th percentile for gestational age.	10% of live births [ACOG, 2013]. Risk factors: Numerous, classified as maternal, placental, fetal.	May include ultrasound (specific biometric parameters and estimated fetal weight), umbilical artery Doppler velocimetry, amniocentesis, chromosomes, and assessment of maternal risk factors (infection, hypertension, etc.). NOTE: curves used to determine %iles should account for gender and race/ethnicity	- American College of Obstetricians and Gynecologists. Fetal Growth Restriction. ACOG Committee Opinion Number 134. Obstetrics and Gynecology May 2013;121: 1122–33.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
GESTATIONAL HYPERTENTION, PREECLAMPSIA AND ECLAMPSIA S: Pregnancy Related Hypertension, Pregnancy Induced Hypertension (PIH), Toxemia	Gestational hypertension: Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least 2 separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of preeclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks postpartum Pre-eclampsia: Hypertension (>140 and/or >90 mmHg) occurring after the 20th week of gestation, and up to 6 weeks postpartum, combined with other abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen). HELLP syndrome: Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests, and low platelets (LP), with or without proteinuria. Eclampsia:	Hypertensive disease occurs in 12-22% of pregnancies [ACOG, 2001; ACOG, 2002]. As many as 25% of women with gestational hypertension will develop preeclampsia. The reported incidence of preeclampsia is 5-8% of pregnancies, usually first pregnancies. Risk factors: First pregnancy, multiple gestation, preeclampsia in previous pregnancy, chronic hypertension, pre-gestational diabetes, vascular and connective tissue disorders, nephropathy, antiphospholipid antibody syndrome, obesity, age >35 years, non-Hispanic black race.	Blood pressure elevation should be sustained and documented in two independent measurements. Additional assessments include a random or 24-hour urine protein determination of 300 mg/dL, other laboratory testing to establish severity and collection of available data on fetal well-being.	- American College of Obstetricians and Gynecologists. Chronic hypertension in pregnancy. ACOG Practice Bulletin Number 29. Obstetrics and Gynecology2001; 98:177–85. - American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin Number 33.Obstetrics and Gynecology 2002; 99:159–67.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	If the features of pre-eclampsia are accompanied by new onset generalized seizures. Chronic Hypertension with superimposed preeclampsia: Chronic hypertension definition PLUS preeclampsia definition			
GESTATIONAL DIABETES MELLITUS: Diabetes of pregnancy	Onset or first recognition of abnormal glucose tolerance during pregnancy (old definition still used by ACOG). Diagnosis based on administration of glucose challenge test at 24-28 weeks gestation	1% to 14%, with 2-5% being the most common figure [ACOG, 2001].	Includes urine glucose measurement during routine prenatal care visits; a fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or A1C ≥6.5 percent using a standardized assay, or a random plasma glucose ≥200 mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above. Glucose tolerance screening is universal at 24-28 weeks of gestation.	- American College of Obstetricians and Gynecologists. Gestational diabetes. ACOG Practice Bulletin Number 30. Obstetrics and Gynecology2001;98: 525–38.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
MATERNAL DEATH	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Direct obstetric death: death of the mother resulting from conditions or complications which are unique to pregnancy and occur during the antepartum, intrapartum, or postpartum period. Indirect obstetric death: A maternal death that is not directly due to obstetric cause (such as from previously existing disease, or disease developing during pregnancy, labor, or the puerperium but that was not unique to pregnancy.) Late Maternal Death: Death of woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.	The global maternal mortality rate is estimated to be about 210 maternal deaths per 100,000 live births [WHO,2013]. Indirect causes and obstetric hemorrhage are the largest causes of maternal death worldwide. Of the direct causes of death, hemorrhage is the leading cause of maternal death, followed by hypertensive disorders and sepsis. Regional estimates varied substantially [Say, 2014].		- Trends in Maternal Mortality: 1990 to 2013. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. (accessed on-line on 13/Oct/2014 at: http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf?ua=1) -Lale Say et al, Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2: e323–33

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

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PRETERM BIRTH	Birth before 37 weeks of gestation. Late Preterm: 34 to <37 weeks Moderate Preterm: 32 to <34 weeks Very Preterm: 28 to < 32 weeks Extreme Preterm: < 28 weeks	10-15% of all pregnancies, with most recent National Vital Statistics Report showing a decline to 11.72% in recent years. Extreme preterm birth occurs in less than 1% of live births [ACOG, 2003].	Includes physical examination and determination of gestational age, and evaluation for maternal or infant causes of premature delivery. Assessment requires gestational age assessment by best available obstetric estimate, usually prenatal ultrasound or first day of the last menstrual period if ultrasound not available. Also assessed by pediatric estimate through physical and neurological examination of newborn at birth. This is less desirable as this assessment is affected by abnormal fetal growth, placental anatomic and functional anomalies, maternal nutrition, racial and ethnic background, population and genetic factors, and birth weight for GA.	-American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 43. International Journal of Gynaecology and Obstetrics 2003;82: 127–35.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
NEONATAL DEATH	Death of newborn at any time from birth to 28 days of life, regardless of gestational age. Subgroups: Very early neonatal death: < 24hrs Early neonatal death: from birth to < 7 days Late neonatal death: 7 to < 28 days Intrapartum-related neonatal death (previously called: asphyxia deaths): neonatal death of term babies with neonatal encephalopathy or who cannot be resuscitated (or for whom resuscitation is not available). Also includes babies who die from birth injury without hypoxic brain injury)	The early neonatal death rate is estimated to be 8.4 per 1000 liveborns; 67.1% occur by day 3 of life [Vogel , 2014]. Prematurity is the main cause of early neonatal deaths (~62%).	Causes of death and rates may vary according to whether the birth setting was in a hospital or in the community	- Vogel JP et al, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 76–88.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) S: HIE, Birth Asphyxia, Perinatal Asphyxia, Neonatal encephalopathy	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or be due to another cause.	Rates may vary widely. The incidence of HIE in developed countries is estimated to be 1.5 per 1,000 live births [Kurinczuk, 2010]. Estimates in developing countries range from 2.3–26.5 per 1,000 live births [Horn,2013].	Assessed by clinical and laboratory findings: 5 minute Apgar score of 0-3, Respiratory distress and Acidosis (pH < 7.0), altered tone, depressed level of consciousness, seizures, multiorgan involvement. Diagnostic tests: - MRI is preferred imaging study. - CT can identify focal lesions, hemorrhage, diffuse cortical injury - EKG (ECG) and continuous EKG (ECG) May result in neonatal death or permanent damage to the brain and other organs. May be associated with perinatal events, rarely to prenatal events.	- Kurinczuk JJ, White-Koning M, Badawi N: Epidemiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy. Early Hum Dev 2010, 86(6):329-338. - Horn AR, Swingler GH, Myer L, Harrison MC, Linley LL, Nelson C, Tooke L, Rhoda NR, Robertson NJ: Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. J Perinat Med 2013, 41(2):211-217.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
FAILURE TO THRIVE OR GROWTH DEFICIENCY	Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.	Failure to thrive (FTT) is a common problem, however precise epidemiological data is lacking. The population prevalence of FTT has been found to range anywhere between 1.3% and 20.9% depending on the definition of FTT that is used. FTT accounts for 1–5% of paediatric hospital admissions under 2 year of age [Sullivan, 2004]	Normal newborn weight gain includes weight loss of up to 10% of birth weight in the first 1-2 weeks of life, with steady, predictable weight gain thereafter. Progress varies by gestational and post-natal age, genetic and environmental factors. Definitions vary. Fall of weight below 5th percentile for age often used. Olsen et al have described multiple different anthropometric criteria for failure to thrive. These criteria include signs of failure to gain weight (weight < 75% of median weight for chronological age, weight for chronological age < 5th percentile, weight deceleration crossing > 2 major percentile lines, etc), failure to grow (length for chronological age < 5th percentile), and failure to grow and gain weight (weight < 80% of median weight for length, body mass index < 5th percentile) [Olsen, 2007]	- Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child. February2007; 92(2):109-114. - Peter B Sullivan. Commentary: The epidemiology of failure-to-thrive in infants. Int. J. Epidemiol. (2004) 33 (4): 847-848.

If a reference is not listed, the following references were used as a source for definitions:
Cunningham F, Gary, et al., editors. Williams obstetrics. 23rd ed. New York: McGraw-Hill; 2010.
Medline Plus; 2013. Available from: http://www.nlm.nih.gov/medlineplus/
UpToDate. Available from: http://www.uptodate.com/home
American College of Obstetrics and Gynecology, Practice Bulletins, www.acog.org.
the Brighton Collaboration website at http://brightoncollaboration.org/public/resources/standards/case-definitions/pregnancy.html

APPENDIX D AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Amendment number:	Amendment 1
Amendment date:	29 May 2015
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:
The protocol is being amended for the following reasons:

- Based on the feedback from compliance/legal team, the wording related to the cocooning has been modified in the protocol.
- For the purpose of clarity and to be in line with the recent changes in the reporting timelines for pregnancies, minor modifications have been made to the safety sections.
- As per feedback from the Australian Ethics Committee,the volume of cord blood to be collected from the subjects has been updated.

The list of contributing authors has been updated.

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

Contributing authors:	• PPD ***and*** PPD, Global Clinical Regulatory Affairs Representatives

Section 2.2 Secondary objectives

- To assess the safety of a single dose of *Boostrix* in pregnant women, administered during 27-36 weeks of gestation, in terms of the outcomes of pregnancy and listed pregnancy-related adverse events of interest/neonate-related events of interest up to ~~two months post-delivery~~ ***study end(Visit 4)***.
- To assess the safety of a single dose of *Boostrix* administered during pregnancy and post-delivery in terms of unsolicited symptoms during the 31-day (Day 0 – Day 30) follow-up period after vaccination and serious adverse events (SAEs) during the period ~~between vaccination at~~***from*** Visit 1 ~~and two months post-delivery~~ ***up to Visit 4.***

Section 3 Study design overview

- Sampling schedule
  - Cord blood (Visit 3): approximately ~~5mL~~ ***2.5 mL*** of blood sample from the umbilical cord will be collected from all subjects.

Section 5.5 Outline of study procedures

Table 4 List of study procedures

Epoch	**Epoch 001**				
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	**Day -14 to 0**	**Day 0**	**Day 30**	**At birth**	**Post-delivery Month 2**
Sampling time-points		**Pre-Vacc**	**Post-Vacc**	**Cord blood**	
Informed consent†	●				
Collect demographic data	●				
Medical history, including medication history and previous diphtheria/tetanus/pertussis vaccination history*	O	●			
Pregnancy screening**	●				
History directed physical examination	O	●			O
Check inclusion/exclusion criteria	O	●			
Pre-vaccination body temperature		●		●	
Measure/record height and weight	●				
Check contraindications and warnings and precautions		O		O	
Study group and treatment number allocation		O			
Recording of administered treatment number		●		●	
Treatment number allocation for subsequent dose (Cross-over dose)				O	
Blood sampling for antibody determination		●	●	●	
Vaccine administration		●		●	
Distribution of diary cards		O	O	O	
Record any concomitant medication/vaccination		●	●	●	●
Physical examination of newborn, including ~~height~~***length***, weight, head circumference and Apgar Score				●	
Record breastfeeding status					●
~~Adverse pregnancy outcome recording and follow-up (pregnancy outcomes and pregnancy-related adverse events of interest/neonate-related)~~ ***Recording and follow up of pregnancy-related adverse events and neonate-related events***		●	●	●	●
Record any intercurrent medical conditions		●	●	●	●
Recording of solicited adverse events (Days 0-7) by subjects in diary card		●		●	
Recording of non-serious adverse events (Day 0– Day 30), by subjects		●	●	●	

Epoch	Epoch 001				
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	**Day -14 to 0**	**Day 0**	**Day 30**	**At birth**	**Post-delivery Month 2**
Sampling time-points		**Pre-Vacc**	**Post-Vacc**	**Cord blood**	
Recording of serious adverse events (SAEs)# and AEs leading to withdrawal		●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●
Recording of ***new*** pregnancies				●	●
Screening conclusion	●				
Study Conclusion					●

Note: The procedures to be conducted during screening visit and Visit 1 may be combined.
In case a woman gives birth to an infant between Visit 1 (Day 0) and Visit 2 (Day 30), the procedures for Visit 2 and Visit 3 will be combined. A blood sample from the mother must be taken before the cross-over vaccination is given to her.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Pre-vacc: Blood sample to be collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc: Blood sample to be collected one month after the booster vaccination in pregnant women (Visit 2).
† Father of the child should also sign the informed consent form, if required by the local laws.
* History of all medications, excluding the vitamins and supplements taken by the mother during her pregnancy before receiving the first dose of study vaccine will be recorded in the eCRF.
** Pregnancy screening will include checking of records of ultrasound testing, nuchal translucency scan, serum testing and any other prenatal tests (if performed). Refer to Section 4.2 for details regarding pregnancy screening.
 # *including adverse pregnancy outcomes and listed pregnancy-related/neonate-related AEs of interest.*

Section 5.6.3.4.1 Blood sampling for immune response assessments

A volume of approximately ~~5 mL~~***2.5mL*** of whole blood (to provide approximately ~~1.7~~ ***0.75*** mL of serum) from the umbilical cord will be collected from all subjects at Visit 3.

Section 5.6.3.5 Study Vaccine administration

~~Investigators will be encouraged to discuss with the subjects regarding the benefits of cocooning i.e. vaccinating anyone that cares for or comes in close contact with neonates such as family members and up-to-date vaccination of the baby's siblings with DTP vaccines in order to reduce the potential risk of pertussis in neonates. Ideally these individuals should be vaccinated two weeks prior to coming in contact with the infant. A reimbursement for cocooning vaccination will be done in countries where the recommendation for cocooning vaccination is not available. However, this will be done outside the scope of this study.~~***The investigators should discuss with the subjects about the official recommendations and/or local practice regarding the use of Tdap vaccines for individuals in close contact with neonates and up to-date vaccination of the neonate's siblings with DTP vaccines in order to reduce the potential risk of pertussis in neonates.***

Section 5.6.3.7 Physical examination of the newborn

At Visit 3 or after the birth of the child, physical examination of the newborn will be done. The body weight, ~~height~~***length***, head circumference and Apgar Score will be recorded in the eCRF.

Section 5.6.3.9 Recording of AEs, pregnancies, ~~pregnancy outcomes, and~~pregnancy-related AEs ~~of interest~~***/and*** neonate-related ~~events~~***AEs***

- Refer to Section 8.2 for procedures for the investigator to record AEs, SAEs, pregnancies~~, pregnancy outcomes~~ and pregnancy-related AEs ~~of interest~~***/and*** neonate-related ~~events~~***AEs***. Refer to Section 8.3 for guidelines and how to report SAE reports and pregnancies to GSK Biologicals.
- At each vaccination visit, diary cards will be provided to the subject. The subject will record body (oral/axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 7 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. ~~The subject will record any pregnancy outcomes and pregnancy-related AEs of interest/ neonate-related events (i.e. on the day of vaccination and during the next 30 days occurring after vaccination).~~ The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- ***All pregnancy-related AEs & neonatal AEs will captured in the diary card from the first receipt of study vaccine/placebo and will end at Visit 4.***
- ***All adverse pregnancy outcomes, listed pregnancy-related and neonate-related AEs of interest will be reported as SAEs. Refer to Section 8.2.2 for details regarding listed pregnancy-related and neonate-related AEs of interest.***

Section 5.7.2 Biological samples
Table 6 Biological samples

Sample type	Quantity*	Unit	Time-point
Blood	5	mL	Day 0 (Pre-Vacc) and Day 30 (Post-Vacc)
Cord Blood	~~5~~***2.5***	mL	At Birth

* Approximate quantity

Section 8.1.2 Definition of a serious adverse event

e. Adverse pregnancy outcomes specified in Section 8.1.5 and the listed pregnancy-related events of interest/neonate-related events of interest in Section 8.2.2 should always be considered as SAEs (medically important events) and should be reported as described in Sections 8.3.1 and 8.3.3.

Section 8.1.5 Pregnancy ***outcomes***

While pregnancy itself is not considered an AE or SAE, any ***adverse pregnancy outcome or*** pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.

The following ***adverse pregnancy outcomes*** should always be considered as SAE and will be reported as described in Sections 8.3.1 and 8.3.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation).
  - ectopic and molar pregnancy.
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study patient (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

~~When there is enough evidence to make any of the above diagnoses, the AE/SAE must be reported as per [CDC MACDP] guidelines. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.~~

~~In order to facilitate the documentation of AEs of interest in the eCRF, the guidelines [CDC MACDP] list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.~~

Section 8.2 Detecting and recording adverse events, serious adverse events, pregnancies~~, pregnancy outcomes and~~ pregnancy-related AEs ~~of interest/~~***and*** neonate-related ~~events~~***AEs***

Section 8.2.1 Time period for detecting and recording adverse events, serious adverse events, pregnancies, ~~pregnancy outcomes, and~~ pregnancy-related AEs ~~of interest~~ ***and*** neonate-related ~~events~~AEs

All AEs starting ***within*** 30 days following administration of each dose of study vaccine/placebo (Day 0 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs ***(including adverse pregnancy outcomes, listed pregnancy-related adverse events of interest/neonate-related adverse events of interest)*** will begin at the first receipt of study vaccine/placebo and will end ~~60 days (two months) following administration of the last dose of study vaccine/placebo~~***at study end (Visit 4)*** for each subject. See Section 8.3 for instructions on reporting of SAEs.

The time period for collecting and recording AEs, SAEs, pregnancies, pregnancy-related AEs and neonate-related AEs will begin at the first receipt of study vaccine/placebo and will end 60 days study end (Visit 4).

All AEs/SAEs~~/pregnancy outcomes, andpregnancy-related AEs of interest/and neonate-related events~~ leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine/placebo.

SAEs that are related to the investigational vaccine will be collected and recorded from the time of the first receipt of study vaccine/placebo until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording ***new*** pregnancies will begin after delivery of the baby and will end ***at Visit 4***~~post-delivery (study conclusion)~~. See section 8.3 for instructions on reporting of pregnancies.

~~The timriod for collecting and recording pregnancy outcomes and pregnancy-related AEs of interest/neonate-related events will begin at the first receipt of study vaccine/placebo and will end 60 days (two months) following administration of the last dose of study vaccine/placebo.~~

Table 12 Reporting periods for adverse events, serious adverse events, ***pregnancies*** **,** ~~and~~pregnancy-related adverse events ~~of interest~~***/and*** neonate-related ***adverse*** events

Event	**Screening Visit***	**V1**	**8 d (0-7d) post V1**	**31 d (0-30d) post V1**	**V3**	**8 d (0-7d) post V3**	**31 d (0-30 d) post V3**	**V4 (Study Conclusion) Post-delivery M2**
		D0		**V2 (D30)**		**At birth**		
Solicited local and general AEs								
Unsolicited AEs								
AEs/SAEs leading to withdrawal from the study								
SAEs								
Pregnancy-related adverse events ***and*** neonate-related ***adverse*** events								
SAEs related to study participation or concurrent GSK medication/ vaccine								
New pregnancies								

* i.e. consent obtained; V: Visit; D: Day, M: Month

Section 8.2.2 Adverse events of specific interest **(*adverse pregnancy outcomes*, *listed*** pregnancy-related adverse events of interest~~and~~/neonate-related events ***of interest*)**

All ***adverse pregnancy outcomes***, ***listed*** pregnancy-related adverse events of interest and neonate-related events ***of interest*** occurring at any time during the period starting with the first administration of the vaccine ***till end of the study will be considered as SAEs and*** must be recorded ~~on the Adverse Event screen~~in the ***appropriate section of the*** patient's eCRF, irrespective of intensity or whether or not they are considered administration-related.

~~Pregnancy~~***Adverse pregnancy*** outcomes include:

- ~~Live birth with no congenital anomalies,~~
- Live birth with congenital anomalies,
- Still birth with no congenital anomalies,
- Still birth with congenital anomalies,
- Elective termination with no congenital anomalies
- Elective termination with congenital anomalies

Listed ~~Pregnancy~~pregnancy-related adverse events of interest/neonate-related events ***of interest*** include:

~~Note: this list of pregnancy outcomes and pregnancy-related adverse events of interest/neonate-related events is not an exhaustive list.~~

The definitions ~~and grading~~ of ***the above specified*** ~~specific~~pregnancy outcomes and ***listed*** pregnancy-related adverse events of interest/-neonate-related events ***of interest*** are adapted from [Munoz, 2013] and can be found in the GLOSSARY OF TERMS and in APPENDIX C.

Section 8.3.1 Prompt reporting of serious adverse events, pregnancies and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 14, once the investigator determines that the event meets the protocol definition of a SAE.

Adverse pregnancy outcomes and listed pregnancy-related adverse events of interest/neonate-related adverse events of interest that occur in the time period defined in Section 8.2 will be considered as SAE and reported promptly to GSK within the timeframes described in Table 14, once the investigator becomes aware of them.

Pregnancies that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 14, once the investigator becomes aware of the pregnancy.

Section 8.3.1 Prompt reporting of serious adverse events, pregnancies and other events to GSK Biologicals.

Table 14 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs#	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
~~Pregnancy-related adverse events of interest/neonate-related events~~	~~24 hours*~~	~~electronic Expedited Adverse Event Report~~	~~24 hours*~~	~~electronic Expedited Adverse Event Report~~
Pregnancies	~~2~~ ***1***week*	electronic pregnancy report	~~2~~***1*** week*	electronic pregnancy report

Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.
 # including adverse pregnancy outcomes and listed pregnancy-related/neonate-related AEs of interest.

Section 10.2 Secondary endpoints

- Outcome of pregnancy in terms of pregnancy outcomes up to ~~two months post delivery~~ ***study end (Visit 4)***
- Outcome of pregnancy in terms of ***listed*** pregnancy-related adverse events of interest/ neonate-related events ***of interest*** up to ~~two months post-delivery~~ ***study end (Visit 4)***.

Listed pregnancy-related adverse events of interest/ neonate-related events ***of interest*** will include gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labour, premature uterine contractions, intrauterine growth restriction/poor foetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine haemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic ischaemic encephalopathy and failure to thrive/growth deficiency.

- Serious adverse events (SAEs).
  - Occurrence of serious adverse events from Dose 1 up to study end ***(Visit 4).***

    Refer to GLOSSARY OF TERMS for the definitions of the various pregnancy outcomes and ***listed*** pregnancy-related adverse events of interest/neonate-related events ***of interest***.

Section 10.3 Determination of sample size

Table 16 presents the precision achieved with a sample of 300 subjects in each group for the various possible expected ***adverse*** pregnancy outcomes and ***listed*** pregnancy-related adverse events of interest/neonate-related events ***of interest*** in terms of exact 95% Cis.

Table 16 Precision achieved with a sample of 300 subjects in each group for the various possible expected pregnancy outcomes and ***listed*** pregnancy-related adverse events of interest/ neonate-related events ***of interest*** in terms of exact 95 percent CI

No. Of subjects expected (N)	Pregnancy outcome and *listed* pregnancy-related adverse events of interest/neonate-related events *of interest*	Subjects with outcome			
		n	%	Exact 95%CI	
				LL	UL
300	Stillbirth	1	0.3	0.0	1.8
	Stillbirth^	0	0.0	0.0	1.2
	Placental Abruption	3	1.0	0.2	2.9
	Placenta previa	1	0.3	0.0	1.8
	Post-partum haemorrhage	18	6.0	3.6	9.3
	Premature rupture of membranes	24	8.0	5.2	11.7
	Premature uterine contractions and premature labour	36	12.0	8.5	16.2
	Preterm delivery	35	11.7	8.3	15.7
	Intrauterine growth restriction / poor foetal growth	30	10.0	6.8	14.0
	Pregnancy related hypertension, preeclampsia and eclampsia	36	12.0	8.5	16.2
	Gestational diabetes	15	5.0	2.8	8.1
	Congenital anomalies (major anomalies)	9	3.0	1.4	5.6

Section 10.8 Analysis of safety

- The percentage of subjects with each specific pregnancy outcomes and ***listed*** pregnancy-related adverse events of interest/neonate-related events ***of interest*** will be tabulated with its exact 95% CI.
- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 8-day (Day 0–Day 7) follow-up period after the vaccination will be tabulated ***after each dose and overall*** with exact 95% CI. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms and for any symptoms requiring medical attention.
- ***The percentage of doses followed by at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 8-day (Day 0–Day 7) follow-up period after the vaccination will be tabulated with exact 95% CI. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms and for any symptoms requiring medical attention.***
- The percentage of subjects***/doses*** reporting each individual solicited local and general AE during the 8-day (Day 0-Day 7) follow-up period after booster vaccination will be tabulated with its exact 95% CI for each group.
- Any large injection site reaction (defined as any local swelling with diameter > 100 mm and/or any noticeable diffuse injection site swelling (diameter not measurable) and/or any noticeable increased circumference of the injected limb) onset within 8 days (Day 0–Day 7) after ***each*** vaccination will be described in detail.
- The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects***/doses*** with unsolicited symptoms occurring within 31 days (Day 0–Day 30) with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for Grade 3 unsolicited symptoms and for unsolicited symptoms possibly related to vaccination.
- The percentage of subjects***/doses*** who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day and 31-day follow-up period after vaccination will be tabulated ***after each dose and overall*** with exact 95% CI.
- SAEs and withdrawal due to AEs and SAEs following booster dose up to ~~two months post delivery~~ ***Visit 4*** will be described in detail.

Appendix A Clinical Laboratories

Table 17 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium
~~GSK Biologicals Global Vaccine Clinical Laboratory, North America-Laval~~	~~Biospecimen Reception - Clinical Serology~~ ~~525 Cartier blvd West – Laval – Quebec – Canada – H7V 3S8~~
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 – B-1300 Wavre – Belgium

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Amendment number:	Amendment 2
Amendment date:	15 July 2015
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:
The protocol is being amended to include Spain in the study. The reasons for this Spain-specific amendment are listed below:

- Based on the feedback from the Spanish Ethics Committee, the evaluation related to the acceptance of cocooning has been added in the protocol.
- The objectives and endpoints to include cocooning are added in the protocol.
- The eligibility criteria for participation of household contacts are defined in the protocol.
- The study procedures for household contacts are included.
- The list of contributing authors has been updated

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

Contributing authors:	• PPD, ***Medical Director, Vaccines, Spain*** • PPD, ***Medical Affairs Manager, Vaccines, Spain*** • PPD ***and*** PPD, Study Delivery Leads

Section 1.2.2 Rationale for the study design

The following information is added.

In addition, all the eligible household contacts of the infants born to pregnant women in a subset of the study enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

Section 2.2 Secondary objectives

The following objectives are added.

- ***To assess the acceptance rate of a single dose of Boostrix among eligible household contacts of the infants born to pregnant women enrolled in Spain, as part of an assessment of cocooning.***
- ***To assess the safety of a single dose of Boostrix in terms of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after the vaccination.***

Section 3 Study design overview

The following information is added.

- Experimental design: Phase IV, observer-blind, randomised, placebo-controlled, multi-centric, multi-country study with two cross-over groups. ***All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.***

Table 2 Study groups and treatment foreseen in the study

The following footnote is added.

Treatment name	Vaccine name	Study Groups	
		dTpa Group	Control Group
Boostrix *	dTpa	x	x
Placebo for dTpa vaccine	Placebo	x	x

All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning.

- Vaccination schedule:
  - All subjects will receive a single dose of *Boostrix* or placebo at 27-36 weeks (i.e. completed 27 weeks until 36 weeks) of gestation (Visit 1). Subjects who receive *Boostrix* at Visit 1 will receive a dose of placebo post-delivery (Visit 3) while those who receive placebo at Visit 1 will receive *Boostrix* post-delivery (Visit 3).
  - ***All eligible household contacts of the infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning. Although the vaccine can be administered anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.***

Section 4.2 Inclusion criteria for enrolment

The following details are added:

Inclusion criteria for study subjects:

Inclusion criteria for household contacts in Spain:

- ***Household contacts living in the same house as that of the infant.***
- ***Household contacts or parent(s)/LAR(s) of the household contacts who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. reporting of SAEs).***
- ***Written informed consent obtained from the household contacts or the parent(s)/LAR(s) prior to vaccination, as per local regulations.***
- ***Household contacts who are eligible to receive a booster dose of DTP-containing vaccine according to the Summary of Product Characteristics (SmPC) of Boostrix and according to the local governmental recommendations in Spain.***
- ***Female household contacts of non-childbearing potential may be enrolled in the study .***
  - ***Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.***

Please refer to the glossary of terms for the definition of menarche and menopause.

- ***Female household contacts of childbearing potential may be enrolled in the study , if the household contact***
  - ***has practiced adequate contraception for 30 days prior to vaccination,***
  - ***has a negative pregnancy test on the day of vaccination and***
  - ***has agreed to continue adequate contraception for 2 months after receiving the vaccine dose.***

Section 4.3 Exclusion criteria for enrolment

The following details are added:

Exclusion criteria for study subjects:

Exclusion criteria for household contacts in Spain:

- ***Child in care.***

Please refer to the glossary of terms for the definition of child in care.

- ***Concurrently participating in another clinical study, at any time during the study period, in which the household contact has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).***
- ***Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period.***
- ***History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.***
- ***History of an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine.***
- ***Acute disease and/or fever at the time of enrolment.***
  - ***Fever is defined as temperature ≥ 37.5°C /99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C /100.4°F on rectal route. The preferred route of recording temperature will be axillary in household contacts.***
  - ***Household contacts with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.***
- ***Anything that would put the household contact at risk, as determined by the investigator.***
- ***Pregnant or lactating household contacts.***
- ***Household contacts planning to become pregnant or planning to discontinue contraceptive precautions prior to 2 months post-vaccination.***

Section 5.2.2.1.1 Study group and treatment number allocation

The following information is added.

All the eligible household contacts of infants born to pregnant women enrolled in Spain will be eligible to receive a single dose of Boostrix as part of an assessment of cocooning. For specific instructions with respect to treatment allocation of the household contacts in Spain, refer to the SPM.

Section 5.5 Outline of study procedures

The list of study procedures are presented in Table 4 ***and Table 5***.

Table 4 'List of study procedures ***for study subjects***' is updated.

Epoch	**Epoch 001**				
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Time-points	**Day -14 to 0**	**Day 0**	**Day 30**	**At birth**	**Post-delivery Month 2**
Sampling time-points		**Pre-Vacc**	**Post-Vacc**	**Cord blood**	
Informed consent	●				
Collect demographic data	●				
Medical history, including medication history and previous diphtheria/tetanus/pertussis vaccination history*	O	●			
Pregnancy screening**	●				
Data collection on household contacts§	●				
History directed physical examination	O	●			O
Check inclusion/exclusion criteria	O	●			
Pre-vaccination body temperature		●		●	
Measure/record height and weight	●				
Check contraindications and warnings and precautions		O		O	
Study group and treatment number allocation		O			
Recording of administered treatment number		●		●	
Treatment number allocation for subsequent dose (Cross-over dose)				O	
Blood sampling for antibody determination		●	●	●	
Vaccine administration		●		●	
Distribution of diary cards		O	O	O	
Record any concomitant medication/vaccination		●	●	●	●
Physical examination of newborn, including length, weight, head circumference and Apgar Score				●	
Record breastfeeding status					●
Recording and follow up of pregnancy-related adverse events and neonate-related events		●	●	●	●
Record any intercurrent medical conditions		●	●	●	●
Recording of solicited adverse events (Days 0-7) by subjects in diary card		●		●	
Recording of non-serious adverse events (Day 0– Day 30), by subjects		●	●	●	
Recording of large injection site reactions		●		●	
Return of diary cards			O	O	O
Diary card transcription by investigator/designee			●	●	●
Recording of serious adverse events (SAEs) # and AEs leading to withdrawal		●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●
Recording of new pregnancies				●	●
Screening conclusion	●				
Study Conclusion					●

Note: The procedures to be conducted during screening visit and Visit 1 may be combined.
In case a woman gives birth to an infant between Visit 1 (Day 0) and Visit 2 (Day 30), the procedures for Visit 2 and Visit 3 will be combined. A blood sample from the mother must be taken before the cross-over vaccination is given to her.

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Pre-vacc: Blood sample to be collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc: Blood sample to be collected one month after the booster vaccination in pregnant women (Visit 2).
† Father of the child should also sign the informed consent form, if required by the local laws.
* History of all medications, excluding the vitamins and supplements taken by the mother during her pregnancy before receiving the first dose of study vaccine will be recorded in the eCRF.
** Pregnancy screening will include checking of records of ultrasound testing, nuchal translucency scan, serum testing and any other prenatal tests (if performed). Refer to Section 4.2 for details regarding pregnancy screening.
# Including adverse pregnancy outcomes and listed pregnancy-related/neonate-related AEs of interest.
§Information will be obtained by interviewing the mother after she agrees to participate in the study. These details can be collected at any of the study visits.

Table 5 'List of study procedures for household contacts' is added.

Epoch	***Epoch 001***				
Type of contact	***Screening Visit#***	***Visit 1***	***Visit 2***	***Visit 3***	***Visit 4***
Time-points	***Day -14 to 0***	***Day 0***	***Day 30***	***At birth***	***Post-delivery Month 2***
Informed consent		●#			
Check inclusion/exclusion criteria		●#			
Collect demographic data		●#			
Medical history and previous DTP-containing vaccination history		●#			
Urine pregnancy test in female household contacts of child bearing potential		●#			
Pre-vaccination body temperature		●#			
Vaccine administration*		●#			
Recording of administered treatment number		●#			
Recording of serious adverse events (SAEs) and pregnancies ‡		●	●	●	●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
****Screening visit will not be applicable for household contacts.***
*****The vaccine for household contacts should be administered only after vaccination of the mother (study subject).***
#The procedures for household contacts can be performed anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.
‡The SAEs and pregnancies in household contacts should be reported from the date of vaccination till 30 days after vaccination.

Table 6 Intervals between study visits

The following footnote is added.

Interval*	**Optimal length of interval [1]**	**Allowed interval[2]**
Screening Visit → Visit 1	-14 to 0 days	-28 to 0 days
Visit 1 → Visit 2	30 days	21- 48 days
Visit 3 → Visit 4	60 days	45 - 75 days

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval. In case a mother gives birth to an infant before 21 days post-vaccination, she will be excluded from the ATP cohort for analysis of immunogenicity.
****Household contacts can be vaccinated anytime during the study, it is recommended that the vaccine is administered preferably 2 weeks before birth of the infant.***

Section 5.6 Detailed description of study procedures

The section numbers for procedures in study subjects are updated. The following changes are incorporated in Section 5.6.1.3.5-Study Vaccine administration

- ~~***The investigators should discuss with the subjects about the official recommendations and/or local practice regarding the use of Tdap vaccines for individuals in close contact with neonates and up to-date vaccination of the neonate's siblings with DTP vaccines in order to reduce the potential risk of pertussis in neonates***~~. ***The investigators will discuss with the subjects regarding the benefits of cocooning i.e. up to date vaccination of the baby's siblings with DTP-containing vaccines and vaccinating all the household contacts (people living under the same roof) eligible to receive DTP-containing vaccines as per Summary of Product Characteristics (SmPC) of Boostrix and local governmental recommendations in Spain in order to reduce the potential risk of pertussis in neonates. The subjects will be requested to provide the number of household contacts. Additionally the subjects will also be requested for the number of household contacts who refused the visit to site and the reason for refusal for subsequent eligibility determination and vaccination will be documented.***

The following subsections are included.

5.6.2 Study procedures for household contacts in Spain

5.6.2.1 Informed Consent

The signed/witnessed/thumb printed informed consent of the household contact/parent(s)/LAR(s) must be obtained before study participation. If the household contact is below 18 years of age, the parent(s)/LAR(s) should sign the informed consent form, if required by the local laws. The subject has to visit the site to complete the informed consent process.

Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2.2 Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria for household contacts as described in Sections 4.2 and 4.3 before enrolment.

5.6.2.3 Collect demographic data

Record demographic data such as age, gender, ethnicity and relationship to the infant in the household contact's eCRF.

5.6.2.4 Medical history

Obtain the household contact's medical history by interview and/or review of the medical records and record any pre-existing conditions or signs and/or symptoms present in a household contact prior to the vaccination in the household contact's eCRF.

5.6.2.5 Urine pregnancy test

Female household contacts of childbearing potential are to have a urine pregnancy test prior to study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the household contact is menstruating at the time of the study visit.

5.6.2.6 Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all household contacts needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in household contacts will be axillary. If the household contact has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for axillary route on the day of vaccination], the vaccination visit will be rescheduled within the allowed interval for this visit.

5.6.2.7 Vaccine administration

After completing all prerequisite procedures prior to vaccination, one dose of Boostrix will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the household contact's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 6). The reason for refusal of vaccination by eligible household contacts will be recorded, if applicable.

The household contacts will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.2.8 Recording of SAEs and pregnancies

Refer to Section 8.2 for procedures for the investigator to record SAEs and pregnancies. Refer to Section 8.3 for guidelines and how to report SAE and pregnancy reports to GSK Biologicals.

Section 6.3 Dosage and administration of study vaccines

Table 11 Dosage and administration

The following footnote is added.

Type of contact and time-point*	volume to be administered	Study Group	Treatment name	Route [1]	Site [2]	Side [3]
Visit 1 (Day 0)	0.5 mL	dTpa Group	*Boostrix*	IM	D	N-D
		Control Group	Placebo			
Visit 3 (At birth)	0.5 mL	dTpa Group	Placebo	IM	D	N-D
		Control Group	*Boostrix*			

[1] Intramuscular (IM)
[2]Deltoid (D)
[3]Non-dominant (N-D).
Vaccination can be performed in the opposite side in case of medical indication preventing vaccination in the side stated in the table, as judged by the investigator.
Household contacts in Spain: One dose (0.5mL) of Boostrix vaccine will be administered intramuscularly as part of an assessment of cocooning.

Section 8.2.1 Time period for detecting and recording adverse events, serious adverse events, pregnancies, pregnancy-related AEs and neonate-related AEs- The following information is added.

The time period of reporting SAEs for household contacts will begin at the administration of Boostrix vaccine (as part of an assessment of cocooning) and end at 30 days after the vaccination. The SAEs and pregnancies in household contacts will be collected till 30 days after vaccination, irrespective of the visit in which the vaccine is administered.

Table 13 Reporting periods for adverse events, serious adverse events, pregnancies, pregnancy-related adverse events and neonate-related adverse events-is updated as follows.

Event	Screening Visit*		V1	8 d (0-7d) post V1	31 d (0-30d) post V1	V3	8 d (0-7d) post V3	31 d (0-30 d) post V3	V4 (Study Conclusion)
			D0		V2 (D30)	At birth			Post-delivery M2
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
Pregnancy-related adverse events and neonate-related adverse events									
SAEs related to study participation or concurrent GSK medication/ vaccine									
New pregnancies									
SAEs and pregnan-cies in household contacts in Spain*									
SAEs related to study participation or concurrent GSK medication/ Vaccine in household contacts in Spain									

* i.e. consent obtained; V: Visit; D: Day, M: Month,

***** The SAEs and pregnancies in household contacts will be reported till 30 days after vaccination, irrespective of the visit in which the vaccine is administered.***

Section 8.8 Subject card is updated as mentioned below.

Study subjects ***and participating household contacts*** must be provided with the address and telephone number of the main contact for information about the clinical study.

Section 10.2 Secondary endpoints- The following changes are included.

- Serious adverse events ***(SAEs).***
  - Occurrence of serious adverse events from Dose 1 up to study end (Visit 4).
- ***Percentage of household contacts of the infants born to pregnant women vaccinated in Spain who accepted Boostrix vaccine as part of an assessment of cocooning among the eligible household contacts.***
- ***Occurrence of SAEs among the vaccinated household contacts of the infants born to pregnant women in Spain, as part of an assessment of cocooning, from the day of vaccination till 30 days after vaccination.***

Section 10.4.4 Total cohort for household contacts in Spain is added as given below.

Total cohort for household contacts will include all eligible household contacts of the infants born to pregnant women vaccinated in Spain. For the analysis of safety, all vaccinated household contacts will be considered.

Section 10.6 Analysis of demographics

The following section is added.

10.6.1 Analysis of eligible household contacts

Analysis of eligible household contacts will be performed on the Total cohort for household contacts in Spain.

- ***Demographic characteristics will be summarised for the eligible household contacts as a whole and per group using descriptive statistics.***
- ***Reasons for refusal of the cocooning vaccination will be summarised for the eligible household contacts as a whole and per group.***
- ***Percentage of household contacts of the infants born to pregnant women vaccinated in Spain who accepted Boostrix vaccine as part of an assessment of cocooning among the eligible household contacts will be tabulated as a whole and per group.***

Section 10.8 Analysis of safety

The following changes are included.

The primary analysis will be performed on the TVC. If in any vaccine group, 5% or more of the vaccinated subjects are eliminated from the TVC, a second analysis will be performed on the ATP cohort for analysis of safety. ***Analysis of safety in household contacts will be performed on the Total cohort for household contacts in Spain.***

- ***For the vaccinated household contacts in Spain, SAEs following Boostrix vaccination up to 30 days will be described in detail.***

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116945 [DTPA (BOOSTRIX)-047]
EudraCT number	2014-001119-38
Date of protocol amendment	Amendment 2 Final: 15 July 2015
Detailed Title	A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix™ in pregnant women.
Sponsor signatory	Htay Htay Han, Project Level CRDL, Rotavirus and Tdap Maternal vaccination, GlaxoSmithKline Biologicals.
Signature	PPD
Date	17 July 2015

For internal use only

- ----------Checksum----------!Ver.!Created On - -
552cb61e98ad426988e436831e69cba1351ae35d 2.0 7/17/2015 12:12:04 PM - -
---------- -