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

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b (DTPa-IPV/Hib) conjugate vaccine (Infanrix™-IPV/Hib). [213503 (DTPA-IPV)]
eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Date of protocol	Protocol Version 3 Final: 21 January 2016
Date of protocol amendment	Protocol Amendment 1 Final: 11 October 2016
Title	Immunogenicity and safety of GSK Biologicals' combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b (DTPa-IPV/Hib) conjugate vaccine
Detailed Title	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Co-ordinating author	PPD, Scientific Writer, contractor for GSK Biologicals
Contributing authors (Amended 11 October 2016)	• PPD, Clinical Research and Development Lead (CRDL), contractor for GSK Biologicals • PPD***, CRDL*** • PPD***, Clinical and Epidemiology Project Leader (CEPL)*** • PPD***, Project Delivery Lead*** • PPD***, Study Delivery Lead, Aixial contractor for GSK Biologicals*** • PPD, Study Delivery Manager • PPD Vaccine Supply Coordinator, contractor for GSK Biologicals • PPD***, Clinical Trial Supplies Manager***, ***Aixial contractor for GSK Biologicals*** • PPD, Safety Representative • PPD***, Study Statistician*** • PPD, Project Statistician • PPD, Lead Statistician • PPD***, Director Biostatistics*** • PPD, Project Data Manager

eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Date of protocol	Protocol Version 3 Final: 21 January 2016
Date of protocol amendment	Protocol Amendment 1 Final: 11 October 2016
Title	Immunogenicity and safety of GSK Biologicals' combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b (DTPa-IPV/Hib) conjugate vaccine
Detailed Title	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Contributing authors (continued) (Amended 11 October 2016)	• PPD ***and*** PPD ***, Clinical Laboratory Sciences (CLS)*** Project Manager • PPD ***, CLS Study Manager, Business & Decision Life Sciences contractor for GSK Biologicals*** • PPD, Global Patent Representative • PPD ***, Global Patent Representative*** • PPD, ***Senior Medical Manager CIS*** • PPD, ***Manager***, Global RA • PPD ***, Manager, Global RA*** • PPD, ***Local Head of Clinical Operations*** • PPD ***, Local Delivery Lead*** • PPD, Study Data Manager • PPD ***, Oversight Data Manager***

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Date of protocol amendment	Protocol Amendment 1 Final: 11 October 2016
Detailed Title	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology Project Leader (CEPL), DTP, Polio, Hib containing vaccines R&D Center Belgium
Signature	_____
Date	_____

Protocol Amendment 1 Rationale

Amendment number:	Amendment 1

Rationale/background for changes:

- As per Russian legislation, only parents or adoptive parents can give consent for the enrolment of their child in a clinical trial. No other persons are allowed to give consent on behalf of a minor to participate in a clinical trial. Therefore the wording "parents/Legally Acceptable Representative(s) (LAR[s])" should be replaced by the wording "parents/adoptive parents". This change was implemented by the local team in the Russian translation of the protocol and informed consent form after obtaining approval from competent authorities and ethics committees in order to meet Russian legislation requirements. The purpose of this amendment is to replace "parents/LAR(s)" by "parents/adoptive parents" in order to ensure consistency in wording between local protocol and central protocol.
- The list of study personnel and the function names have been updated.

Protocol Amendment 1 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 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 ***parents/adoptive parents***.
- 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, 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.

(Amended 11 October 2016)

eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Date of protocol amendment	Protocol Amendment 1 Final: 11 October 2016
Detailed Title	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

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

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.3.2**.**

SYNOPSIS

Detailed Title	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Indication	Active immunisation against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b (Hib) diseases from the age of 2 months.
Rationale for the study and study design	Rationale for the study GlaxoSmithKline (GSK) Biologicals' *Infanrix-IPV/Hib* is licensed for primary vaccination in 74 countries in the world, including most European countries. *Infanrix-IPV/Hib* has been extensively studied in clinical trials that established its immunogenicity and safety [Lim, 2011; Phua, 2008; Gilca, 2006]. To date, more than 70 million commercial doses have been distributed, and routine use of the vaccine has confirmed its good safety profile. In the Russian Federation, a three-dose primary vaccination of infants is currently recommended against hepatitis B with doses administered at birth, 1 month and 6 months of age and against diphtheria, tetanus, pertussis, poliomyelitis and Hib with doses administered at 3, 4.5 and 6 months of age. The Russian Federation also recommends a booster vaccination of infants against diphtheria, tetanus, pertussis, poliomyelitis and Hib at 18 months of age. GSK Biologicals' DTPa-IPV/Hib vaccine (*Infanrix-IPV/Hib*) combines antigens to diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b diseases in one single injection and complements to the current local standard of care for the hepatitis B immunization. The present study is being performed to support the registration of *Infanrix-IPV/Hib* in the Russian Federation. Rationale for the study design The aim of the present study is to evaluate the immune response, safety and reactogenicity induced by the combined DTPa-IPV/Hib vaccine when administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and as a booster dose at 18 months of age according to the Russian immunisation schedule.

The study will adopt a single group, open-label design.

Objectives

Primary

- To assess the immune response to the study vaccine in terms of seroprotection status for diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the third dose of primary vaccination.

Secondary

- To assess the immune response to the study vaccine in terms of seroprotection to diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the booster vaccination.
- To assess the immune response to the study vaccine in terms of antibody concentrations or titres against diphtheria, tetanus, Hib, poliovirus types 1, 2 and 3 antigens, and pertussis antigens, one month after the third dose of primary vaccination and one month after the booster vaccination.
- To assess the safety and reactogenicity of the study vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

Study design

- Experimental design: Phase III, open-label, multi-centric, single-country study with a single group.
- Duration of the study: Approximately 16 months per subject.
  - Epoch 001 (Primary epoch): Primary phase starting at Visit 1 (Day 0) and ending at Visit 4 (Month 4).
  - Epoch 002 (Booster epoch): Booster phase starting at Visit 5 (Month 15) and ending at Visit 6 (Month 16).
- Study group: The study group and epochs foreseen in the study are presented in Synopsis Table 1.

Synopsis Table 1 Study group and epochs foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001 (Primary epoch)	Epoch 002 (Booster epoch)
DTPa-IPV/Hib Group	~ 235	3 months - 4 months	x	
DTPa-IPV/Hib Group	~ 235	18 months- 19 months		x

Synopsis Table 2 presents the study group and treatment foreseen in the study.

Synopsis Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		DTPa-IPV/Hib Group
Infanrix-IPV/Hib	DTPa-IPV	x
	Hib	x

- Control: This is an uncontrolled study.
- Treatment group and vaccination schedule: All subjects will receive three doses of primary vaccination at 3, 4.5 and 6 months of age and a single dose of booster vaccination at 18 months of age:
  - DTPa-IPV/Hib Group: Subjects who will receive DTPa-IPV/Hib vaccine (*Infanrix-IPV/Hib*).
- Blinding: (Refer to Synopsis Table 3).

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001 (Primary epoch)	open
Epoch 002 (Booster epoch)	open

- Sampling schedule: Two blood samples (approximately3.5 ml each) will be taken from all subjects: one blood sample will be taken one month after the primary vaccination course (Visit 4) and the second blood sample will be taken one month after the booster vaccination (Visit 6).
- Type of study: self-contained.
- Data collection: electronic Case Report Form (eCRF).

Number of subjects

Approximately 235 subjects aged three to four months at the time of first primary vaccination visit will be enrolled in this study.

Endpoints

Primary

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the third dose of primary vaccination.
  - Anti- PT, anti-FHA and anti-PRN antibody seropositivity status, one month after the third dose of primary vaccination.

Secondary

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the third dose of primary vaccination.
  - Anti- PT, anti-FHA and anti-PRN antibody seropositivity status, one month after the third dose of primary vaccination.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, anti-PRP, anti-PT, anti-FHA, anti-PRN antibody concentrations or titres, one month after the third dose of primary vaccination and one month after the booster vaccination.
- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Days 0-3) follow-up period after each primary vaccination dose and following the booster vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Days 0-30) follow-up period after each primary vaccination dose and following the booster vaccination.
- Serious adverse events.
  - Occurrence of SAEs from Dose 1 up to study end.

TABLE OF CONTENTS

PAGE

SPONSOR INFORMATION 7

SYNOPSIS 8

LIST OF ABBREVIATIONS 18

GLOSSARY OF TERMS 21

TRADEMARKS 24

1. INTRODUCTION 25
   - 1.1. Background 25
   - 1.2. Rationale for the study and study design 25
     - 1.2.1. Rationale for the study 25
     - 1.2.2. Rationale for the study design 26
   - 1.3. Benefit : Risk Assessment 26
     - 1.3.1. Risk Assessment 26
     - 1.3.2. Benefit Assessment 27
     - 1.3.3. Overall Benefit: Risk Conclusion 28

2. OBJECTIVES 28
   - 2.1. Primary objective 28
   - 2.2. Secondary objectives 28

3. STUDY DESIGN OVERVIEW 29

4. STUDY COHORT 30
   - 4.1. Number of subjects/centres 30
   - 4.2. Inclusion criteria for enrolment 31
   - 4.3. Exclusion criteria for enrolment 31

5. CONDUCT OF THE STUDY 33
   - 5.1. Regulatory and ethical considerations, including the informed consent process 33
   - 5.2. Subject identification and randomisation of treatment 34
     - 5.2.1. Subject identification 34
     - 5.2.2. Randomisation of treatment 34
       - 5.2.2.1. Randomisation of supplies 34
       - 5.2.2.2. Treatment allocation to the subject 34
         - 5.2.2.2.1. Treatment number allocation 34
         - 5.2.2.2.2. Treatment number allocation for subsequent doses 34
   - 5.3. Method of blinding 35
   - 5.4. General study aspects 35
   - 5.5. Outline of study procedures 35
   - 5.6. Detailed description of study procedures 37
     - 5.6.1. Informed consent 37
     - 5.6.2. Check inclusion and exclusion criteria 37

5.6.3. Collect demographic data 37
5.6.4. Medical and vaccination history 37
5.6.5. Physical examination 38
5.6.6. Record gestational age 38
5.6.7. Measure/record height and weight 38
5.6.8. Assess pre-vaccination body temperature 38
5.6.9. Check contraindications, warnings and precautions to vaccination 38
5.6.10. Pre-vaccination measurement of limb circumference at the site of injection before booster vaccination at Visit 5 38
5.6.11. Treatment number allocation 39
5.6.12. Study Vaccine administration 39
5.6.13. Sampling 39
5.6.13.1. Blood sampling for antibody determination 39
5.6.14. Check and record concomitant vaccination and intercurrent medical conditions 39
5.6.15. Recording of AEs and SAEs 40
5.6.16. Study conclusion 41
5.7. Biological sample handling and analysis 41
5.7.1. Use of specified study materials 42
5.7.2. Biological samples 42
5.7.3. Laboratory assays 42
5.7.4. Biological samples evaluation 43
5.7.4.1. Immunological read-outs 43
5.7.5. Immunological correlates of protection 44

6. STUDY VACCINE AND ADMINISTRATION 45
6.1. Description of study vaccine 45
6.2. Storage and handling of study vaccine 45
6.3. Dosage and administration of study vaccine 46
6.4. Replacement of unusable vaccine doses 47
6.5. Contraindications to subsequent vaccination 47
6.6. Warnings and precautions 48
6.7. Concomitant medications/products and concomitant vaccinations 48
6.7.1. Recording of concomitant medications/products and concomitant vaccinations 48
6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses 49
6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses 49

7. HEALTH ECONOMICS 49

8. SAFETY 50
8.1. Safety definitions 50
8.1.1. Definition of an adverse event 50
8.1.2. Definition of a serious adverse event 51
8.1.3. Solicited adverse events 52
8.1.3.1. Solicited local (injection-site) adverse events 52
8.1.3.2. Solicited general adverse events 52

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events 52
8.2. Detecting and recording adverse events and serious adverse events 53
8.2.1. Time period for detecting and recording adverse events and serious adverse events 53
8.2.2. Post-Study adverse events and serious adverse events 55
8.2.3. Evaluation of adverse events and serious adverse events 55
8.2.3.1. Active questioning to detect adverse events and serious adverse events 55
8.2.3.2. Assessment of adverse events 56
8.2.3.2.1. Assessment of intensity 56
8.2.3.2.2. Assessment of causality 58
8.2.3.3. Assessment of outcomes 59
8.2.3.4. Medically attended visits 59
8.3. Reporting of serious adverse events 59
8.3.1. Prompt reporting of serious adverse events and other events to GSK Biologicals 59
8.3.2. Contact information for reporting serious adverse events and other events to GSK Biologicals 60
8.3.3. Completion and transmission of SAE reports to GSK Biologicals 60
8.3.3.1. Back-up system in case the electronic reporting system does not work 60
8.3.4. Updating of SAE information after removal of write access to the subject's eCRF 60
8.3.5. Regulatory reporting requirements for serious adverse events 61
8.4. Follow-up of adverse events and serious adverse events 61
8.4.1. Follow-up of adverse events and serious adverse events 61
8.4.1.1. Follow-up during the study 61
8.4.1.2. Follow-up after the subject is discharged from the study 61
8.5. Treatment of adverse events 62
8.6. Subject card 62

9. SUBJECT COMPLETION AND WITHDRAWAL 62
9.1. Subject completion 62
9.2. Subject withdrawal 62
9.2.1. Subject withdrawal from the study 62
9.2.2. Subject withdrawal from investigational vaccine 63

10. STATISTICAL METHODS 64
10.1. Primary endpoint 64
10.2. Secondary endpoints 64
10.3. Determination of sample size 65
10.4. Cohorts for Analyses 65
10.4.1. Total vaccinated cohort for the primary epoch 66
10.4.2. According-to-protocol cohort for analysis of immunogenicity of the primary epoch 66
10.4.3. Total vaccinated cohort for the booster epoch 66

10.4.4. According-to-protocol cohort for analysis of immunogenicity of the booster epoch....66
10.5. Derived and transformed data....67
10.6. Analysis of demographics....68
10.7. Analysis of immunogenicity....68
10.8. Analysis of safety....68
10.9. Interpretation of analyses....69
10.10. Conduct of analyses....70
10.10.1. Sequence of analyses....70
10.10.2. Statistical considerations for interim analyses....70

11. ADMINISTRATIVE MATTERS....70
11.1. electronic Case Report Form instructions....70
11.2. Study Monitoring by GSK Biologicals....71
11.3. Record retention....71
11.4. Quality assurance....72
11.5. Posting of information on publicly available clinical trial registers and publication policy....72
11.6. Provision of study results to investigators....72

12. COUNTRY SPECIFIC REQUIREMENTS....73

13. REFERENCES....73

LIST OF TABLES

PAGE

Table 1 Study group and epochs foreseen in the study....30
Table 2 Study group and treatment foreseen in the study....30
Table 3 Blinding of study epochs....30
Table 4 List of study procedures (Amended 11 October 2016)....36
Table 5 Intervals between study visits....37
Table 6 Biological samples....42
Table 7 Humoral Immunity (Antibody determination)....43
Table 8 Immunological read-outs....44
Table 9 Study vaccine....45
Table 10 Dosage and administration....46
Table 11 Solicited local adverse events....52
Table 12 Solicited general adverse events....52
Table 13 Reporting periods for adverse events and serious adverse events....54
Table 14 Intensity scales for solicited symptoms in infants/toddlers....56
Table 15 Timeframes for submitting serious adverse event, reports to GSK Biologicals....59
Table 16 Exact 95 percentage CI for the different values of observed seroprotection / seropositivity rates for a sample size of 200 evaluable subjects....65
Table 17 GSK Biologicals laboratories....75
Table 18 Outsourced laboratories....75

LIST OF APPENDICES

PAGE

APPENDIX A CLINICAL LABORATORIES 75

APPENDIX B AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL 76

LIST OF ABBREVIATIONS

AE:	Adverse Event
ATP:	According-To-Protocol
BMI:	Body Mass Index
CDC:	Centers for Disease Control and Prevention, USA
CEPL:	***Clinical and Epidemiology Project Leader***
CI:	Confidence Interval
CLS:	***Clinical Laboratory Sciences***
cm:	Centimetre
CRDL:	***Clinical Research and Development Lead***
CSR:	Clinical Study Report
D:	Diphtheria
DTPa:	Diphtheria-Tetanus-acellular Pertussis
eCRF:	electronic Case Report Form
ELISA:	Enzyme Linked Immunosorbant Assay
eTDF:	Electronic Temperature excursion Decision Form
FHA:	Filamentous Haemagglutinin
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline
Hib:	*Haemophilus influenzae* type b
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation

IEC:	Independent Ethics Committee
IM:	Intramuscular
IMP:	Investigational Medicinal Product
IPV:	Inactivated Poliovirus vaccine
IRB:	Institutional Review Board
IU:	International Unit
kg:	Kilogram
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
mg:	Milligram
mIU:	Milli-international units
ml:	Millilitre
NEUTRA:	Neutralising antibody assay
PI:	Prescribing Information
PRN:	Pertactin
PT:	Pertussis
R:	Right
RCC:	Reverse Cumulative distribution Curve
RDE:	Remote Data Entry
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
T:	Thigh

TVC:	Total Vaccinated Cohort
WHO:	World Health Organization

(Amended 11 October 2016)

GLOSSARY OF TERMS

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 open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
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.
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 timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints 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).
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.
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.
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 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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects 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.

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

(Amended 11 October 2016)

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Infanrix® -IPV/Hib	Combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b conjugate vaccine

1. INTRODUCTION

1.1. Background

Combination vaccines induce immunity against multiple diseases in a single injection. Therefore, they facilitate delivery of complex vaccinations in a simplified manner and promote better vaccine coverage, compliance and cost-effectiveness by decreasing the number of injections needed to immunise a child [Kalies, 2006; Zinke, 2010]. Combination vaccines, particularly the Diphtheria-Tetanus- Pertussis (DTP) based vaccines, have become a part of the routine paediatric practice as they are widely accepted as a means of conferring protection against several diseases simultaneously [Zepp, 2009].

Haemophilus influenzae type b (Hib) is a bacterium responsible for severe pneumonia, meningitis and other invasive diseases almost exclusively in children aged less than 5 years. The World Health Organization (WHO) recommendation to immunise all infants with a Hib conjugate vaccine is now implemented in more than 100 countries [WHO, 2009]. The importance of prevention of these bacterial infections through vaccination is gaining fast recognition among Health Authorities.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of *Infanrix-IPV/Hib*.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

GlaxoSmithKline (GSK) Biologicals' *Infanrix-IPV/Hib* is licensed for primary vaccination in 74 countries in the world, including most European countries. *Infanrix-IPV/Hib* has been extensively studied in clinical trials that established its immunogenicity and safety [Gilca, 2006; Lim, 2011; Phua, 2008]. To date, more than 70 million commercial doses have been distributed, and routine use of the vaccine has confirmed its good safety profile.

In the Russian Federation, a three-dose primary vaccination of infants is currently recommended against hepatitis B with doses administered at birth, 1 month and 6 months of age and against diphtheria, tetanus, pertussis, poliomyelitis and Hib with doses administered at 3, 4.5 and 6 months of age. The Russian Federation also recommends a booster vaccination of infants against diphtheria, tetanus, pertussis, poliomyelitis and Hib at 18 months of age. GSK Biologicals' DTPa-IPV/Hib vaccine (*Infanrix-IPV/Hib*) combines antigens to diphtheria, tetanus, pertussis, poliomyelitis and Hib diseases in one single injection. This complements the current local standard of care for the hepatitis B immunization in Russian infants.

The present study is being performed to support the registration of *Infanrix-IPV/Hib* in the Russian Federation.

1.2.2. Rationale for the study design

The aim of the present study is to evaluate the immune response, safety and reactogenicity induced by the combined DTPa-IPV/Hib vaccine when administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and as a booster dose at 18 months of age according to the Russian immunisation schedule.

The study will adopt a single group, open-label design as all the subjects will receive the same vaccine.

1.3. Benefit : Risk Assessment

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of *Infanrix-IPV/Hib*.

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 (Infanrix-IPV/Hib)		
Important identified risk: Hypersensitivity	People may develop allergic reactions to any type of vaccine and/or its components. Hypersensitivity reactions to vaccines highly vary in severity, ranging from mild to potentially life-threatening hypersensitivity reactions. Severe allergic reactions to vaccines are rare but tend to occur within hours after vaccination.	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. History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine is an exclusion criteria for enrolment to the study.
Important identified risk: Apnoea in infants born prematurely	Apnoea of prematurity is due to immaturity of the neurological and respiratory system in premature infants. The risk appears to be related to the degree of prematurity of the infant.	Only subjects born full-term (gestation period of 37-42 weeks completed) will be enrolled.
Important identified risk: Waning of acellular pertussis vaccine induced immunity	Waning of pertussis immunity is considered a pharmacological class effect for acellular pertussis containing vaccine. Potential cases of break-through infections cannot be excluded after vaccination with Infanrix-IPV/Hib.	GSK will continue close monitoring of waning of acellular pertussis vaccine induced immunity and post-marketing lack of efficacy cases through routine pharmacovigilance.
Important identified risk: Temperature of ≥ 40.0 C	In rare occasion, hyperpyrexia above 40,0°C may occur after vaccination, particularly associated with booster vaccination.	Acute disease and/or fever at the time of enrolment is an exclusion criteria; Temperature of ≥ 40.0°C (tympanic or axillary temperature) within 48 hours of vaccination, not due to another identifiable cause is a contraindication to further administration of Infanrix-IPV/Hib

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Important identified risk: Hypotonic hyporesponsive episode	HHE occurs more commonly in early childhood after primary vaccination and particularly after the first dose of vaccine. Most HHE events have been associated with whole cell pertussis-containing vaccines (36-250 episodes per 100,000 doses). A much lower rate of HHE has been observed following vaccination with acellular pertussis vaccine (4-140 episodes per 100,000 doses)	Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination is a contraindication to further administration of Infanrix-IPV/Hib
Important identified risk: Convulsions with or without fever	Seizures occurring soon after immunization are mostly triggered by fever induced by the vaccine or are not vaccine related. Febrile convulsions usually occur in individuals aged between 3 months and 6 years with a peak incidence at 18 months	History of any neurological disorders or seizures is an exclusion criteria for enrolment to the study
Important potential risk: Encephalopathy		Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours is a contraindication to further administration of Infanrix-IPV/Hib
Study Procedures		
Syncope	Spontaneous Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Syncope after vaccination itself is usually not a serious event, and patients generally recover within a few minutes, but can potentially produce serious harm from the trauma of falling or accidents.	Procedures should be in place to avoid injuries from falls following syncope

1.3.2. Benefit Assessment

Diphtheria, tetanus, pertussis, poliomyelitis and diseases caused by *Haemophilus influenzae* type b are a common cause of disease in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, pertussis, poliomyelitis and diseases caused by *Haemophilus influenzae* type b has been evidenced in countries in which infants are routinely immunised against these diseases. Clinical trial and post-marketing data demonstrate the substantial benefit of *Infanrix-IPV/Hib* vaccination worldwide.

1.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential or identified risks identified in association with *Infanrix-IPV/Hib* are justified by the potential benefits (prevention) that may be afforded to subject(s) receiving *Infanrix-IPV/Hib* vaccine.

2. OBJECTIVES

2.1. Primary objective

- To assess the immune response to the study vaccine in terms of seroprotection status for diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the third dose of primary vaccination.

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

2.2. Secondary objectives

- To assess the immune response to the study vaccine in terms of seroprotection to diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the booster vaccination.
- To assess the immune response to the study vaccine in terms of antibody concentrations or titres against diphtheria, tetanus, Hib, poliovirus types 1, 2 and 3 antigens, and pertussis antigens, one month after the third dose of primary vaccination and one month after the booster vaccination.
- To assess the safety and reactogenicity of the study vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

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

3. STUDY DESIGN OVERVIEW

Study Group:	DTPa-IPV/Hib Group (N=235)					
Study Vaccine:	*Infanrix-IPV/Hib*					
Visit:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time-points:	Day 0	Month 1.5	Month 3	Month 4	Month 15	Month 16
Age of subjects:	3 months	4.5 months	6 months	7 months	18 months	19 months
Vaccination and BS:	V1	V2	V3	Post-Pri BS	Booster	Post-Booster BS
Epochs:	**Primary epoch**				**Booster epoch**	

V = Primary vaccination
BS = Blood Sample
Post-Pri = One month after the third dose of primary vaccination course
Post-Booster = One month after booster vaccination

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 III, open-label, multi-centric, single-country study with a single group.
- Duration of the study: The intended duration of the study is approximately 16 months, per subject.
  - Epoch 001 (Primary epoch): Primary phase starting at Visit 1 (Day 0) and ending at Visit 4 (Month 4).
  - Epoch 002 (Booster epoch): Booster phase starting at Visit 5 (Month 15) and ending at Visit 6 (Month 16).

Study group: The study group and epochs foreseen in the study are presented in Table 1.

Table 1 Study group and epochs foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001 (Primary epoch)	Epoch 002 (Booster epoch)
DTPa-IPV/Hib Group	~ 235	3 months - 4 months	x	
DTPa-IPV/Hib Group	~ 235	18 months – 19 months		x

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

Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		DTPa-IPV/Hib Group
Infanrix-IPV/Hib	DTPa-IPV	x
	Hib	x

- Control: uncontrolled.
- Treatment group and vaccination schedule: All subjects will receive three doses of primary vaccination at 3, 4.5 and 6 months of age and a single dose of booster vaccination at 18 months of age.
  - DTPa-IPV/Hib Group: Subjects who will receive DTPa-IPV/Hib vaccine (*Infanrix-IPV/Hib*).
- Blinding: This is an open-label study (Refer Table 3).

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001 (Primary epoch)	open
Epoch 002 (Booster epoch)	open

- Sampling schedule: Two blood samples (approximately 3.5 ml each) will be taken from all subjects: one blood sample will be taken one month after the primary vaccination course (Visit 4) and the second blood sample will be taken one month after the booster vaccination (Visit 6).
- Type of study: This is a self-contained study.
- Data collection: electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

Approximately 235 subjects aged three to four months at the time of first dose of primary vaccination will be enrolled in this study. Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

Overview of the recruitment plan:

- This study will be conducted at multiple centers in Russia.
- Enrolment will be terminated when at least 235 subjects have been enrolled.
- Recruitment of subjects into the study will be tracked using GSK Biologicals' central randomisation system on Internet (SBIR).
- Recruitment will be monitored by the Study Monitor.

4.2. Inclusion criteria for enrolment

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:

- Subjects' parent(s)/***adoptive parent(s)*** 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).
- A male or female child between 3 and 4 months (between, and including, 90 and 120 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent(s)/***adoptive parent(s)*** of the subject prior to performing any study specific procedure.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born full-term (i.e. after a gestation period of at least 37 completed weeks)**.**

(Amended 11 October 2016)

4.3. Exclusion criteria for enrolment

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:

- Child in care
  Please refer to the glossary of terms for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day-29 to Day 0), 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 since birth. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day (for paediatric subjects), 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 starting 30 days before the first dose and ending 30 days after the last dose of vaccine administration, with the exception of hepatitis B and other vaccines given as part of the national immunisation schedule and as part of routine vaccination practice, that are allowed at any time during the study period. Seasonal or pandemic influenza vaccine can be given at any time during the study, and according to the Summary of Product Characteristics and national recommendations.
- 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).
- Previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis and Hib diseases.
- History of diphtheria, tetanus, pertussis, poliomyelitis and Hib diseases.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects.
- Serious chronic illness.
- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥37.5°C for oral, axillary or tympanic route, or ≥38.0°C for 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 since birth or planned administration during the study period.

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.

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

GSK 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's parent(s)/***adoptive parent(s)*** 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 informed consent must be obtained from each subject's parent(s)/***adoptive parent(s)***, 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.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

(Amended 11 October 2016)

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to subjects on whose behalf consent has been provided to participate in the study, according to the range of subject identification numbers allocated to each study centre.

5.2.2. Randomisation of treatment

This is a single group non- randomised study. All eligible subjects will receive the primary and booster doses of DTPa-IPV/Hib vaccine in the primary and booster epochs respectively. The central randomisation system (SBIR) will be used to allocate treatment numbers to the subjects and also to track enrolment in the study.

5.2.2.1. Randomisation of supplies

Randomisation of supplies will not be performed. A sequential list of treatment numbers will be generated and the supplies will be sent to the centres /warehouses.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Treatment number allocation

Allocation of a treatment number to a subject at the investigator site will be performed using a randomisation system on internet (SBIR).

After obtaining the signed and dated ICF from the subject's parent(s)/***adoptive parent(s)*** 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 provide the treatment number to be used for the first dose. The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

(Amended 11 October 2016)

5.2.2.2.2. 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 for the subsequent doses.

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

5.3. Method of blinding

The study will be conducted in an open-label manner since this is a single-group study.

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.

5.5. Outline of study procedures

The list of study procedures is presented in Table 4.

Table 4 List of study procedures (Amended 11 October 2016)

Age of subjects	**3 months**	**4.5 months**	**6 months**	**7 months**	**18 months**	**19 months**
Epochs	**Epoch 001 (Primary epoch)**				**Epoch 002 (Booster epoch)**	
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Time-points	**Day 0**	**Month 1.5**	**Month 3**	**Month 4**	**Month 15**	**Month 16**
Sampling time-points				**Post-Pri**		**Post-Boost**
Informed consent	●					
Check inclusion/exclusion criteria	●					
Collect demographic data	●					
Medical history, including vaccination history	●					
Physical examination	●					
Record gestational age	●					
Measure/record height and weight	●					
Pre-vaccination body temperature	●	●	●		●	
Check warnings and precautions	○	○	○		○	
Check contraindications to subsequent vaccination		○	○	○	○	
Pre-vaccination measurement of limb circumference at site of injection by investigator					●	
Vaccine						
Treatment number allocation	○					
Treatment number allocation with subsequent doses		○	○		○	
Recording of administered treatment number	●	●	●		●	
Vaccine administration	●	●	●		●	
Post- vaccination observation for at least 30 minutes	○	○	○		○	
Laboratory Assays						
Blood sampling for antibody determination (approximately 3.5 ml)				●		●
Safety Assessments						
Record any concomitant medication/vaccination	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●
Distribution of diary cards	●	●	●		●	
Recording of solicited adverse events (AEs) (Days 0-3) by subjects' parent(s)/***adoptive parent(s)*** in the diary cards	●	●	●		●	
Recording of non-serious adverse events (AEs) (Days 0-30) by subjects' parent(s)/***adoptive parent(s)*** in the diary cards	●	●	●		●	
Recording of Large injection site reaction					●	
Return of diary cards		○	○	○		○
Diary card transcription by investigator		●	●	●		●
Recording of serious adverse events (SAEs)	●	●	●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK vaccine	●	●	●	●	●	●
Recording of withdrawal due to AEs	●	●	●	●	●	●
Study Conclusion						●

Note: The double-line border following Month 4 and Month 16 indicate the analyses which will be performed separately on all data (i.e. data that are as clean as possible) obtained up to Month 4 (primary epoch) and Month 16 (booster epoch), respectively.

V = vaccination; Post-Pri = One month after the third dose of primary vaccination course; Post-Boost = One month after booster vaccination; ml = millilitres

● 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.

Refer to Section 8.1.3.1 and 5.6.10 for detailed explanation on the reporting of large injection site reactions

The intervals between study visits are presented in Table 5. These intervals determine each subject's evaluability in the according-to-protocol analyses.

Table 5 Intervals between study visits

Interval	Optimal length of interval[1]	Allowed interval[2]
Birth → Visit 1	90 days	90-120 days
Visit 1→ Visit 2	45 days	28-62 days
Visit 2→ Visit 3	45 days	28-62 days
Visit 3→ Visit 4	30 days	21-48 days
Birth→ Visit 5	540 days	540-570 days
Visit 5 → Visit 6	30 days	21-48 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the analyses of the according-to-protocol (ATP) cohort of immunogenicity for the respective epochs if they make the study visit outside this interval. An interval of 21-48 days between Visit 3 and Visit 4, and between Visit 5 and Visit 6 will be considered for the ATP cohort of immunogenicity for the analysis of respective epochs. Refer Section 10.4 for the definition of the cohorts for analysis.
If a subject returns for the Visit 4 or the Visit 6 blood draw prior to completion of the 31-day safety follow-up period, the subject should continue to record this information in the diary card until 31 days post-vaccination and mail the diary card to the site. The investigator will make an attempt to obtain this information as soon as possible after the 31-day follow-up period if it is not mailed in.

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed informed consent of the subject's parent(s)/***adoptive parent(s)*** must be obtained before study participation.

(Amended 11 October 2016)

5.6.2. Check inclusion and exclusion criteria

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

5.6.3. Collect demographic data

Record demographic data such as age, gender and geographic ancestry in the subject's eCRF.

5.6.4. Medical and vaccination history

Obtain the subject's vaccination/medical history by interview and/or review of the subject's medical records and record any previous vaccines administered or pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

5.6.5. Physical examination

Perform physical examination of the subject, including assessment of body temperature. Collected information needs to be recorded in the eCRF.

Physical examination at each study visit subsequent to the vaccination visit, will be performed only if the subject's parent/***adoptive parent*** indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

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

(Amended 11 October 2016)

5.6.6. Record gestational age

Record the gestational age of the subject in the eCRF.

5.6.7. Measure/record height and weight

Measure the height and weight of the subject and record in the eCRF.

5.6.8. 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 axillary. If the subject has fever [fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 5).

5.6.9. 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.

5.6.10. Pre-vaccination measurement of limb circumference at the site of injection before booster vaccination at Visit 5

During Epoch 002 (Visit 5), baseline measurement of limb circumference at the level of the injection site should be obtained to measure the intensity of swelling. Clothing should be removed so as not to interfere with the measurement of the limb circumference. For measuring leg circumference the child should be standing or lying flat, as appropriate, as long as the leg is straight.

5.6.11. Treatment number allocation

Treatment number allocation will be performed as described in Section 5.2.2.2.1. The number of each administered treatment must be recorded in the eCRF.

5.6.12. Study Vaccine administration

- The study vaccine will be administered at Visits 1, 2, 3 and 5 as specified in Section 5.5 List of Study Procedures.
- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly at a 90-degree angle into the upper side of the thigh [CDC, 2002] on the side stated in Table 10. The vaccine should not be administered in the buttock. (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 5).

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.

5.6.13. Sampling

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

5.6.13.1. Blood sampling for antibody determination

Blood samples will be taken at Visits 4 and 6 as specified in Section 5.5 List of Study Procedures.

A volume of approximately 3.5 ml of whole blood (to provide approximately 1.2 ml of serum) should be drawn from all subjects for the analysis of humoral immune response at each pre-defined time point. After centrifugation, serum samples should be kept at –20°C or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.14. Check and record concomitant 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.

5.6.15. Recording of AEs and SAEs

- Refer to Section 8.2 for procedures for the investigator to record AEs and SAEs, Refer to Section 8.3 for guidelines and how to report SAE reports to GSK Biologicals.
- The subjects' parent(s)/***adoptive parent(s)*** will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject's parent(s)/***adoptive parent(s)***. The subject's parent(s)/***adoptive parent(s)*** will record body temperature (preferably axillary) and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days) occurring after vaccination. The subject's parent(s)/***adoptive parent(s)*** will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards during discussion with the subject's parent(s)/***adoptive parent(s)*** at Visits 2, 3, 4 and 6.
- In preparation for Epoch 002, the sites should be provided with a measurement device for recording circumference of injected limb at the level of the injection site on the day of vaccination (baseline measurement - prior to vaccination) and in case of a large swelling reaction during the next three days. The site staff should be instructed on how and where to perform the measurement of the circumference of the vaccinated limb.
- If the parent(s) /***adoptive parent(s)*** of subjects observe any large injection site reaction (defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4-day follow-up (Day 0-Day 3) period, they are to contact study personnel and to visit the investigator's office for evaluation as soon as possible.
- In addition to the diameter of the swelling and the circumference of the limb, the investigator will record the following additional symptoms/characteristics that may be associated with large injection site swelling reactions:
  - Type of swelling (local swelling only around the injection site, diffuse swelling not involving the knee joint, swelling involving the knee joint)
  - Induration at injection site (largest diameter)
  - Functional impairment (intensity – scale and description provided)

The intensity scale is provided in section 8.2.3.2.1.

- The largest or most intense score for a given day will be recorded in the eCRF at the level of the solicited symptoms and at the level of the large swelling report form.
- Any unreturned diary cards will be sought from the subject's parent(s)/***adoptive parent(s)*** through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.16. Study conclusion

The investigator will:

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

5.7. Biological sample handling and analysis

- 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 parent's/***adoptive parent's*** 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's parent(s)/***adoptive parent(s)***.

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.

(Amended 11 October 2016)

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 to be collected in this study are presented in Table 6.

Table 6 Biological samples

Sample type	Quantity	Unit	Time point	Sampling timepoint
Blood	Approximately 3.5	ml	Visit 4	(Post-Pri)
Blood	Approximately 3.5	ml	Visit 6	(Post Boost)

Post-Pri = One month after the third dose of primary vaccination course; Post-Boost = One month after booster vaccination; ml = millilitres

5.7.3. Laboratory assays

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

The details of the humoral immunity (antibody determination) is listed in Table 7.

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/ Manufacturer	Unit	Cut-off**	Laboratory*
Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELISA	In-house	IU/ml	0.1	GSK Biologicals
Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELISA	In-house	IU/ml	0.1	GSK Biologicals
Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELISA	In-house	ELU/ml***	5	GSK Biologicals
Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELISA	In-house	ELU/ml***	5	GSK Biologicals
Serum	Bordetella pertussis.Pertactin Ab.IgG	ELISA	In-house	ELU/ml***	5	GSK Biologicals
Serum	Poliovirus Sabin Type 1 Ab	NEUTRA	In-house	ED_{50}	8	GSK Biologicals
Serum	Poliovirus Sabin Type 2 Ab	NEUTRA	In-house	ED_{50}	8	GSK Biologicals
Serum	Poliovirus Sabin Type 3 Ab	NEUTRA	In-house	ED_{50}	8	GSK Biologicals
Serum	Haemophilus influenzae type b.Polyribosyl Ribitol Phosphate Ab	ELISA	In-house	µg/ml	0.15	GSK Biologicals

*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart or Wavre, Belgium.
ELISA = Enzyme Linked Immuno Sorbent Assay; NEUTRA = Neutralizing antibody assay
ELU/ml = ELISA Unit/millilitre
IU/ml = International Unit/millilitre
µg/ml = microgram/millilitre
**The assay cut-off for D, T and PRP may be subject to change
***The unit for the assay cut-offs may be subject to change

The laboratory that will perform ELISA and Neutralisation is not yet identified and will be defined before study start.

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 represented in Table 8.

Table 8 Immunological read-outs

Blood sampling time-point		No. of subjects	Component	Components priority rank
Type of contact and time-point	Sampling time-point			
Visit 4 (Month 4)	Post-Pri	All	PT, FHA, PRN PRP D, T Poliovirus types 1, 2, 3	1 2 3 4
Visit 6 (Month 16)	Post-Boost	All	PT, FHA, PRN PRP D, T Poliovirus types 1, 2, 3	1 2 3 4

Post-Pri = One month after the third dose of primary vaccination course
Post-Boost: One month after booster vaccination

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 8.

5.7.5. Immunological correlates of protection

For the following antigens in the DTPa-IPV/Hib vaccine, an immunological correlate of protection has been established:

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) will be measured by ELISA. The assay cut-off of ELISA is set at 0.1 International Units per ml (IU/ml), which provides a conservative estimate of the percentage of subjects deemed to be protected [Melville-Smith, 1983; Camargo, 1984].
- Data from subjects given unconjugated Hib vaccine suggest that, in the absence of induction of immunological memory, a concentration of 0.15 μg/ml is indicative of short-term protection, with 1 μg/ml considered indicative of long-term protection [Käyhty, 1983; Anderson, 1984].
- Antibodies against poliovirus types 1, 2 and 3 will be determined by a virus micro-neutralisation test adapted from the W H O Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. Titres will be expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. Samples with a titre greater than or equal to 1:8 will be considered as sero-positive and protective.
- No serological correlate of protection against pertussis has been established [Granström, 1987; Karpinsky, 1987]. 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 5 EL.U/ml. Subjects with antibody concentration below the cut-off will be considered seronegative.

Assessment of the protection level will be done at least 4 weeks after completing the primary vaccination course and at least 4 weeks after the administration of the booster dose.

The immunological assay results will be communicated to the investigator as soon as they become available.

The investigator is encouraged to share the immunological assay results for non-responders with the study subject's parent(s)/***adoptive parent(s)***.

For the subjects identified as non-responders, it remains the responsibility of the 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.

(Amended 11 October 2016)

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The candidate vaccine to be used 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 vaccine is labelled and packed according to applicable regulatory requirements.

Commercial vaccine are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

The details of the study vaccine is presented in Table 9.

Table 9 Study vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
Infanrix-IPV/Hib	DTPa-IPV	DT>=30IU; TT>=40IU; PT=25µg; FHA=25µg; PRN=8µg; Inactivated Poliovirus type 1=40DU; Inactivated Poliovirus type 2=8DU; Inactivated Poliovirus type 3=32DU; $Al(OH)_3$=500µg Al3+	The DTPa-IPV component is presented as a turbid white suspension in a pre-filled syringe.	0.5 ml	4
	Hib	PRP=10µg; TT~=25µg	The lyophilised Hib component is presented as a white pellet in a glass vial; it must be reconstituted before use with the liquid DTPa-IPV component.		

6.2. Storage and handling of study vaccine

The study vaccine 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 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 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 vaccine

The vaccine must be administered intramuscularly, at a 90-degree angle into the upper side of the thigh [CDC, 2002] on the right side. The vaccine should not be administered in the buttock.

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

If the other allowed vaccine (i.e. hepatitis B) is administered at the same visit, the hepatitis B vaccine will be administered at a different injection site.

The dosage and administration of the study vaccine is presented in Table 10.

Table 10 Dosage and administration

Type of contact and time-point	volume to be administered	Study Group	Treatment name	Route [1]	Site [2]	Side [3]
Visit 1 (Day 0) Visit 2 (Month 1.5) Visit 3 (Month 3) Visit 5 (Month 15)	0.5 ml	DTPa-IPV/Hib Group	*Infanrix-IPV/Hib*	IM	T*	R/L

[1] Intramuscular (IM)
[2] Thigh (T)
[3] Right (R)/Left (L)
* upper side of thigh.
Note: 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.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including extra doses to allow flexibility in enrolment at the different sites), at least 5% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of *Infanrix-IPV/Hib*. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4).

- Anaphylaxis following the administration of vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.
- Temperature of ≥ 40.0°C (tympanic or axillary temperature) within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying occurring within 48 hours of vaccination and lasting ≥3 hours.
- Seizures with or without fever occurring within 3 days of vaccination.

Note: A history of febrile convulsions, a family history of convulsions, a family history of Sudden Infant Death Syndrome or a family history of an AE following DTP vaccination do not constitute contraindications.

The following events constitute contraindications to administration of *Infanrix-IPV/Hib* 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 9.2).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be axillary.

Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered the vaccine.

6.6. Warnings and precautions

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.

DTP vaccination should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular (IM) administration to these subjects.

DTP vaccination should under no circumstances be administered intravenously.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator should question the subject's parent(s)/***adoptive parent(s)*** about any medications/products taken and vaccinations received by the subject.

(Amended 11 October 2016)

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 during the period starting from the administration of the study vaccine (Day 0) up to Day 30 post booster vaccination.
- Any concomitant vaccination administered during the period starting from the administration of the study vaccine and ending at the last study visit/contact (Day 0) up to Day 30 post booster vaccination.
- 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 for oral, axillary or tympanic route, or ≥ 38.0°C 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 vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/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 each dose of vaccine and ending 30 days after*, with the exception of hepatitis B vaccine and other vaccines given as part of the national immunisation schedule, that are allowed at any time during the study period. Seasonal or pandemic influenza vaccine can be given at any time during the study, and according to the Summary of Product Characteristics and national recommendations.

  *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.

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. 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's parent(s)/***adoptive parent(s)*** will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

(Amended 11 October 2016)

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:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccines 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 vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- 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 are 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 first 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.

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.

8.1.3. Solicited adverse events

A 4-day follow-up (Day 0-3) of solicited local (at each injection site) and general AEs will be performed after each study vaccine administration. Data concerning the following AEs will be solicited using diary cards provided by the Sponsor.

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited (Table 11):

Table 11 Solicited local adverse events

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

N.B. If parent(s)/***adoptive parent(s)*** of infants observe any large injection site reaction (defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) after the booster dose at Visit 5, 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 screen in the eCRF. In addition to the diameter of the swelling and the circumference of the limb, the investigator will need to record additional symptoms/characteristics as mentioned in Section 5.6.15.

(Amended 11 October 2016)

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited: (Table 12):

Table 12 Solicited general adverse events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

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. X-ray, 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.

8.2. Detecting and recording adverse events and serious adverse events

8.2.1. Time period for detecting and recording adverse events and serious adverse events

All AEs starting following administration of each dose of study vaccine (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 will begin at the first receipt of study vaccine and will end 30 days following administration of the last dose of study vaccine for each subject. See Section 8.3 for instructions on reporting of SAEs.

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

SAEs that are related to the investigational vaccine will be collected and recorded from the time of the first receipt of study vaccine 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's parent/***adoptive parent*** consents to participate in the study until she/he is discharged from the study.

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

(Amended 11 October 2016)

Table 13 Reporting periods for adverse events and serious adverse events

Event	Pre-V1*	V1	3 d post V1	30 d post-V1	V2	3 d post V2	30 d post-V2	V3	3 d post V3	30 d post-V3	V4	B	3 d post B	30 d post-B	(Study Conclusion)
Time-point		**D0**			**M1.5**			**M3**			**M4**	**M15**			**M16**
Age of subject	**3m**	**3m**			**4.5m**			**6m**			**7m**	**18m**			**19m**
Study Visit	**Visit 1**	**Visit 1**			**Visit 2**			**Visit 3**			**Visit 4**	**Visit 5**			**Visit 6**
Solicited local and general AEs															
Large injection site reactions															
Unsolicited AEs															
AEs/SAEs leading to withdrawal from the study															
SAEs related to the investigational vaccine															
SAEs related to study participation or concurrent GSK medication/vaccine															

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; B: Booster vaccination; d: days; D: Day; m: months; M: Month

Large injection site reactions are defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference after the booster vaccination.

8.2.2. 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 Section 8.2. 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.

8.2.3. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject's parent(s)/***adoptive parent(s)*** should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last 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.

(Amended 11 October 2016)

8.2.3.2. Assessment of adverse events

8.2.3.2.1. Assessment of intensity

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

Table 14 Intensity scales for solicited symptoms in infants/toddlers

Infant (below 12 months of age) /Toddler (15–24 months)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Increase in limb circumference post-dose 4 (according to where vaccine was administered)		Record the limb circumference at the level of the injection site
Fever*		Record temperature in °C
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

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

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

0 : Absent

1 : ≤ 5 mm

2 : > 5 mm and ≤ 20 mm

3 : > 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		Axillary
0	:	< 37.5°C
1	:	≥37.5°C and ≤ 38.0°C
2	:	> 38.0°C and ≤ 39.0°C
3	:	> 39.0°C

Prior to analysis, the increase in limb circumference as compared to the baseline pre-vaccination measurement will be scored for each subject at GSK Biologicals' as follows:

Grade 0 = Increase in limb circumference ≤5 mm

1 = Increase in limb circumference >5 mm but ≤20 mm

2 = Increase in limb circumference >20 mm but ≤40 mm

3 = Increase in limb circumference >40 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.

For unsolicited symptoms and adverse events associated with large injection site reactions (e.g. induration and functional impairment), the intensity should be assigned to one of the following categories:

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 a young child, such an AE would, for example, prevent attendance at a day-care centre and would cause the parent(s)/***adoptive parent(s)*** to seek medical advice.

(Amended 11 October 2016)

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.

8.2.3.2.2. 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 SAE 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/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccines 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. 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).

8.2.3.3. 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).

8.2.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/***adoptive parent(s)*** will be asked if the subject 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.

(Amended 11 October 2016)

8.3. Reporting of serious adverse events

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

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator determines that the event meets the protocol definition of a SAE.

Table 15 Timeframes for submitting serious adverse event, 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

* Timeframe allowed after receipt or awareness of the information.
Note: 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.

8.3.2. Contact information for reporting serious adverse events and other events to GSK Biologicals

Back-up Study Contact for Reporting SAEs
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 section 8.3) 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. Updating of SAE information after removal of write access to the subject's eCRF

When additional SAE 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 section 8.3) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

8.3.5. 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 and serious adverse events

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 30 days 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 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.

8.5. 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. Subject card

Study subjects' parent(s)/***adoptive parent(s)*** 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's parent(s)/***adoptive parent(s)***. 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' parent(s)/***adoptive parent(s)*** must be instructed to keep subject cards in their possession at all times.

(Amended 11 October 2016)

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 parents/***adoptive parent(s)*** of 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's parent(s)/***adoptive parent(s)***, 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 the subject's parent(s)/***adoptive parent(s)*** has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject's parent(s)/***adoptive parent(s)***, 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).

(Amended 11 October 2016)

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's parent(s)/***adoptive parent(s)***, 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).

(Amended 11 October 2016)

10. STATISTICAL METHODS

10.1. Primary endpoint

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the third dose of primary vaccination.
  - Anti- PT, anti-FHA and anti-PRN antibody seropositivity status, one month after the third dose of primary vaccination.

10.2. Secondary endpoints

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the booster vaccination.
  - Anti- PT, anti-FHA and anti-PRN antibody seropositivity status one month after the booster vaccination.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, anti-PRP, anti-PT, anti-FHA, anti-PRN antibody concentrations or titres, one month after the third dose of primary vaccination and one month after the booster vaccination.
- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Days 0-3) follow-up period after each primary vaccination dose and following the booster vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Days 0-30) follow-up period after each primary vaccination dose and following the booster vaccination.
- Serious adverse events.
  - Occurrence of SAEs from Dose 1 up to study end.

10.3. Determination of sample size

The target sample size is 200 subjects evaluable for analysis of immunogenicity. Considering that approximately 15% of enrolled subjects may not be evaluable for analysis of immunogenicity, 235 subjects are estimated to be enrolled. The number of evaluable subjects for the analysis of immunogenicity is not derived from any power based computations. The number of evaluable subjects for the study is based on the requirement from local regulatory authorities.

The primary objective of this study is to assess the immunogenicity of the study vaccines, in terms of seroprotection rates for antibodies against diphtheria, tetanus, PRP, poliovirus types 1, 2, 3 antigens, and seropositivity rates for antibodies against PT, FHA and PRN antigens one month after the third dose of primary vaccination.

Table 16 presents the exact 95% confidence interval (CI) for a sample size of 200 evaluable subjects according to the value observed for the seroprotection / seropositivity rates:

Table 16 Exact 95 percentage CI for the different values of observed seroprotection / seropositivity rates for a sample size of 200 evaluable subjects

Observed seroprotection / seropositivity rates expressed as a percentage	Exact 2-sided 95% CI for this observed rate for a sample size of 200 evaluable subjects	
	Lower Limit (LL)	Upper Limit (UL)
92	87.3	95.4
93	88.5	96.1
94	89.8	96.9
95	91.0	97.6
96	92.3	98.3
97	93.6	98.9
98	95.0	99.5
99	96.4	99.9
100	98.2	100

CI: Confidence interval
Reference study: DTPa-HBV-IPV-109 (105910), Group HexaNEW: Subjects received the new formulation of DTPa-HBV IPV/Hib at 3, 4 and 5 months of age.

10.4. Cohorts for Analyses

Four cohorts are defined for the purpose of the analyses:

- Total vaccinated cohort for the primary epoch
- ATP cohort for analysis of immunogenicity of the primary epoch
- Total vaccinated cohort for the booster epoch
- ATP cohort for analysis of immunogenicity of the booster epoch.

10.4.1. Total vaccinated cohort for the primary epoch

The Total vaccinated cohort for the primary epoch will include all subjects who received at least one primary vaccine dose. Thus, the Total vaccinated cohort for analysis of safety of the primary epoch will include all subjects with at least one primary vaccine dose administration documented and the Total vaccinated cohort for analysis of immunogenicity will include vaccinated subjects for whom data concerning primary immunogenicity endpoint measures are available.

10.4.2. According-to-protocol cohort for analysis of immunogenicity of the primary epoch

- The ATP cohort for analysis of immunogenicity of the primary epoch will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals relative to the primary epoch defined in the protocol, with no elimination criteria during the primary epoch of the study) from the ATP cohort for safety of the primary epoch for whom data concerning primary 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 Dose 3. The interval between Dose 3 and blood sampling at Visit 4, considered for inclusion of a subject will be 21-48 days.

10.4.3. Total vaccinated cohort for the booster epoch

The Total vaccinated cohort for the booster epoch will include all subjects who received the booster dose of study vaccine.

- The TVC for the analysis of safety of booster epoch will include all subjects with booster vaccine dose administration documented.
- The Total vaccinated cohort for analysis of immunogenicity of the booster epoch will include vaccinated subjects for whom data concerning booster immunogenicity endpoint measures are available.

10.4.4. According-to-protocol cohort for analysis of immunogenicity of the booster epoch

- The ATP cohort for analysis of immunogenicity of the booster epoch will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals relative to the booster epoch defined in the protocol, with no elimination criteria during the primary epoch of the study) from the ATP cohort for safety of the booster epoch for whom data concerning immunogenicity endpoint measures of booster epoch 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 the booster dose of vaccination. The interval between study visits that will be considered for inclusion in the ATP cohort for immunogenicity of booster epoch will be 15–18 months from date of birth to booster vaccination visit and 21-48 days between the booster vaccination visit and the blood sampling at one month post-booster vaccination.

10.5. Derived and transformed data

The cut-off value is defined by the laboratory before the analysis and is described in the laboratory assays section (Section 5.7.3).

- A seronegative subject is a subject whose antibody concentration/titre is below the assay cut-off.
- A seropositive subject is a subject whose antibody concentration/titre is greater than or equal to the assay cut-off.
- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-diphtheria antibody concentrations ≥0.1 IU/ml.
  - Anti-tetanus antibody concentrations ≥0.1 IU/ml.
  - Anti-poliovirus types 1, 2 and 3 antibody titres ≥8.
  - Anti-PRP antibody concentrations ≥0.15 µg/ml.
- The geometric mean concentrations (GMCs) /geometric mean titres (GMTs) calculations will be performed by taking the anti-log of the mean of the $\log_{10}$ concentration/titre transformations. Antibody concentrations/titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation.
- Handling of missing data:

Immunogenicity

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

Safety/reactogenicity

- For a given subject and the analysis of solicited AEs 3 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited AEs based on the Total Vaccinated cohort will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

10.6. Analysis of demographics

The analysis of demographics will be performed separately for each epoch:

- The distribution of subjects enrolled among the study centers will be tabulated.
- The number of subjects who withdraw from the study will be tabulated according to the reason for drop-out.
- The deviations from specifications for age and intervals between study visits will be tabulated.

The median, mean, range and standard deviation of age (in weeks) at each vaccine dose will be computed. The median, mean and standard deviation of height in centimeter (cm) and weight in kilograms (kg) at Visit 1 will be computed. The Body Mass Index (BMI) at Visit 1 will also be computed as weight (in kg) / height² (in meters). The gender composition and geographic ancestry will be presented.

10.7. Analysis of immunogenicity

The analysis of immunogenicity will be performed separately for each epoch.

The primary analysis will be based on the ATP cohort for analysis of immunogenicity for both primary and booster epochs. If the percentage of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total vaccinated cohort will be performed on both primary and booster epochs to complement the ATP analysis. All analyses are descriptive.

Where appropriate, at each time-point that a blood-sample result is available:

- Seroprotection rates against diphtheria toxoid, tetanus toxoid, PRP antigen and poliovirus types 1, 2 and 3 antigens (with exact 95% CI [Clopper, 1934]) will be calculated.
- Seropositivity rates against PT, FHA and PRN antigens (with exact 95% CI [Clopper, 1934]) will be calculated.
- GMCs/GMTs with 95% CI will be tabulated for antibodies against each antigen.

The distribution of antibody concentrations/titres for each antigen will be displayed using reverse cumulative distribution curves (RCCs).

10.8. Analysis of safety

Analysis of safety relative to the primary epoch will include analysis of safety data collected following administration of the three primary doses of study vaccine. Analysis of safety relative to the booster epoch will include analysis of safety data collected following administration of the booster dose of study vaccine. At this second stage, in

order to avoid missing SAEs that have been reported, an SAE summary table including all the events reported during the entire study period will also be generated.

The analysis will be based on the Total vaccinated cohort for both primary and booster epochs. All analyses are descriptive.

- The overall percentage of subjects/doses with at least one local symptom (solicited or unsolicited), with at least one general symptom (solicited or unsolicited) and with any symptom (solicited or unsolicited) during the 4-day (Days 0-3) solicited follow-up period will be tabulated with exact 95% CI [Clopper, 1934] after each vaccine dose and overall primary doses. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity, for symptoms (solicited or unsolicited) leading to medical advice and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.
- The overall percentage of subjects/doses and of subjects reporting each individual solicited local and general symptom during the 4-day (Days 0-3) solicited follow-up period will be tabulated after each vaccine dose and overall primary doses, with exact 95% CI [Clopper, 1934] after each vaccine dose and overall primary doses. The same calculations will be done for each individual solicited symptom rated as grade 3 in intensity and for each individual solicited symptom assessed as causally related to vaccination.
- Occurrence of fever will be reported per 0.5°C cumulative increments.
- The verbatim reports of unsolicited AEs 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 with unsolicited AEs occurring within 31-day (Days 0-30) follow-up period after any dose (after primary or booster vaccination) with its exact 95% CI [Clopper, 1934] will be tabulated by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and AE(s)/SAE(s) leading to withdrawal from the study.
- The percentage of subjects who receive at least one concomitant medication during the 4-day (Days 0-3) solicited follow-up period and during the entire primary/booster epoch will be tabulated (with exact 95% CI [Clopper, 1934]) after each vaccine dose and overall.
- Any large injection site reaction **(**defined as a swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase in limb circumference) after booster vaccination will be described in detail.
- SAE(s) will be described in detail.

10.9. Interpretation of analyses

All analyses will be conducted in a descriptive manner.

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

The analyses will be performed stepwise:

- A final analysis of the primary epoch will be conducted on all immunogenicity and safety data obtained up to one month after administration of the third primary dose of study vaccine (Visit 4), as soon as the data will be as clean as possible. This will include the analysis of the primary immunogenicity objectives related to the primary epoch and analysis of solicited symptoms and unsolicited symptoms reported within the 4-day (Days 0-3) period and 31-day (Days 0-30) period following the primary vaccination, respectively, and the SAEs reported during the primary epoch.
- Analysis of the booster epoch will be conducted on all cleaned immunogenicity and safety data obtained up to one month after administration of the booster dose of study vaccine (Visit 6). This will include analysis of the secondary immunogenicity objectives related to the booster epoch and analysis of solicited symptoms and unsolicited symptoms reported within the 4-day (Days 0-3) period and 31-day (Days 0-30) period following administration of the booster dose of study vaccine, respectively, and the SAEs reported during the booster epoch. At this second stage, in order to avoid missing SAEs that have been reported, an SAE summary table including all the events reported during the entire study period will also be generated.

10.10.2. Statistical considerations for interim analyses

All analysed data will be reported in an integrated clinical study report that will be written at the end of the study.

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 enrolment 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.

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

Anderson P. The protective levels of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1984;149:1034-1035.

Camargo ME, Silveira L, Furuta JA, et al. Immunoenzymatic assay of anti-diphtheria toxin antibodies in human serum. *J Clin Microbiol* 1984;20(4):772-4.

Centre for Disease Control and Prevention (CDC), General recommendations on immunisation: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *Morb Mortal Wkly Rep* 2002; 51(RR02): 1-36.

Clopper C J, Pearson E S. The Use Of Confidence Or Fiducial Limits Illustrated In The Case Of The Binomial. *Biometrika* 1934;26(4):404-13.

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

Gilca V, Duval B, Deeks S, et al. Penta- And Hexavalent DTaP Based Vaccines Approved For Use In Canada: A Systematic Literature Review Of Immunogenicity And Reactogenicity. *Can J Infect Dis Med Microbiol* 2006;7(6):358.

Granström M, Thoren M, Blennow M, et al. Acellular Pertussis Vaccine in Adults: Adverse Reactions and Immune Response. *Eur J Clin Microbiol* 1987;6(1):18-21.

Kalies H, Grote V, Verstraeten T, et al. The Use of Combination Vaccines Has Improved Timeliness of Vaccination in Children. *Pediatr Infect Dis J* 2006;25(6):507-12.

Karpinsky KF, Hayward S and Tryphonas H. Statistical considerations in the quantitation of serum immunoglobulin levels using the enzyme-linked immunosorbent assay (ELISA). *J Immunol Methods* 1987;103:189-94.

Käyhty H, Peltola H, Karanko V,et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1983; 147:1100.

Lim FS, Phua KB, Lee BW, et al. Safety and reactogenicity of DTPa-HBV-IPV/Hib and DTPa-IPV/I-Hib vaccines in a post-marketing surveillance setting. *Southeast Asian J Trop Med Public Health* 2011;42(1):138-47.

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

Phua KB, Quak SH, Lim FS, et al. Immunogenicity, reactogenicity and safety of a diphtheria-tetanus-acellular pertussis-inactivated polio and *Haemophilus influenzae* type b vaccine in a placebo-controlled rotavirus vaccine study. *Ann Acad Med Singapore* 2008;37(7):546–53.

World Health Organization (WHO). Standard Procedure for Determining Immunity to Poliovirus using the Microneutralization Test (WHO/EPI/GEN 93.9) 1993.

WHO. Immunisation, Vaccines and Biologicals, *Haemophilus influenzae* type b 2009 http://www.who.int/immunization/topics/hib/en/index.html. Accessed on 20-January-2016.

Zepp F, Schmitt HJ, Cleerbout J, et al. Review of 8 years of experience with *Infanrix hexa*™ (DTPa-HBV-IPV/Hib hexavalent vaccine). Expert Rev. *Vaccines* 2009;8(6):663-78.

Zinke M, Disselhoff J, Gartner B, et al. Immunological persistence in 4–6 and 7–9 year olds previously vaccinated in infancy with hexavalent DTPa-HBV-IPV/Hib. *Hum Vaccin* 2010;6(2):189-93.

Zuckerman JN. The importance of injecting vaccines into muscles. *BMJ* 2000;321:1237-8.

APPENDIX A CLINICAL LABORATORIES

Table 17 GSK Biologicals laboratories

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

Table 18 Outsourced laboratories

Laboratory	Address
NEOMED- LABS Inc	525 Cartier blvd West- Laval- Quebec Canada- H7V 3S8
CERBA	7/11 rue de l'Equerre Parc d'activités « les Béthunes » F-95310 Saint Ouen L'Aumone France
BARC NV	Industriepark Zwijnaarde 3b B-9052 Gent Belgium
CEVAC - University of Gent	De Pintelaan, 185 Gent Belgium
ImmuneHealth asbl	Rue Adrienne Bolland 8/B.2, Gosselies Belgium
SGS Wavre	Vieux Chemin du Poète 10 1300 Bierges Belgium
Retroscreen Virology Ltd	Royal College Street London Biosciences Innovation Centre 2 London United Kingdom
Biomnis	Avenue Tony Garnier 17/19 BP7322 – Lyon Cedex 07 France

APPENDIX B AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D Protocol Amendment 1	
eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Amendment number:	Amendment 1
Amendment date:	11 October 2016
Co-ordinating author:	PPD (Project Manager Scientific Writer, Keyrus Biopharma Contractor for GSK Biologicals)

Rationale/background for changes:

- As per Russian legislation, only parents or adoptive parents can give consent for the enrolment of their child in a clinical trial. No other persons are allowed to give consent on behalf of a minor to participate in a clinical trial. Therefore the wording "parents/Legally Acceptable Representative(s) (LAR[s])" should be replaced by the wording "parents/adoptive parents". This change was implemented by the local team in the Russian translation of the protocol and informed consent form after obtaining approval from competent authorities and ethics committees in order to meet Russian legislation requirements. The purpose of this amendment is to replace "parents/LAR(s)" by "parents/adoptive parents" in order to ensure consistency in wording between local protocol and central protocol.
- The list of study personnel and the function names have been updated.

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

- On the **protocol cover page**, the following contributing authors have been added and the following function names have been updated.
  - PPD ***, CRDL***
  - PPD , ~~Project Level CRDL~~ ***Clinical and Epidemiology Project Leader (CEPL)***
  - PPD , ~~Study Delivery Lead~~ ***Project Delivery Lead***
  - PPD ***, Study Delivery Lead, Aixial contractor for GSK Biologicals***
  - PPD , ***Clinical Trial Supplies Manager***, ***Aixial contractor for GSK Biologicals***
  - PPD ***, Study Statistician***

- PPD ***, Director Biostatistics***
- PPD ***and*** PPD ***, Clinical Laboratory Sciences (CLS)*** ~~CLS~~ Project Manager
- PPD ***, CLS Study Manager, Business & Decision Life Sciences contractor for GSK Biologicals***
- PPD ***, Global Patent Representative***
- PPD , ***Senior Medical Manager CIS*** ~~Regional Clinical Operations Head~~
- PPD , ***Manager*** ~~Specialist~~, Global RA
- PPD ***, Manager, Global RA***
- PPD , ***Local Head of Clinical Operations*** ~~Senior Local Study Manager~~
- PPD ***, Local Delivery Lead***
- PPD ***, Oversight Data Manager***

- On the **Protocol Amendment 1 Investigator Agreement page**, the following change has been done:
  - 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~~ ***parents/adoptive parents***.
- In the **List of abbreviations**, the following changes have been done:

CEPL:	***Clinical and Epidemiology Project Leader***
CLS:	***Clinical Laboratory Sciences***
CRDL:	***Clinical Research and Development Lead***
~~**CLS:**~~	~~Clinical Laboratories Sciences~~
~~**LAR:**~~	~~Legally Acceptable Representative~~

- In the **Glossary of terms**, the following changes have been done:

~~**Legally acceptable representative**~~ ~~**(The terms legal representative or legally authorized representative are used in some settings.)**~~	~~An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.~~

- In **Section 4.2 Inclusion criteria for enrolment**, the following changes have been done:
  - Subjects' parent(s)/~~Legally Acceptable Representative(s) [LAR(s)]~~ ***adoptive parent(s)*** 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 parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** of the subject prior to performing any study specific procedure.
- In **Section 5.1 Regulatory and ethical considerations, including the informed consent process**, the following changes have been done:
  - Subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** informed consent.

  Freely given and written informed consent must be obtained from each subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***, as appropriate, prior to participation in the study.
- In **Section 5.2.2.2.1 Treatment number allocation**, the following changes have been done:

  After obtaining the signed and dated ICF from the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** 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 provide the treatment number to be used for the first dose. The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.
- In **Table 4 List of study procedures**, the following changes have been done:

Recording of solicited adverse events (AEs) (Days 0-3) by subjects' parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** in the diary cards	•	•	•		•	
Recording of non-serious adverse events (AEs) (Days 0-30) by subjects' parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** in the diary cards	•	•	•		•	

- In **Section 5.6.1 Informed consent**, the following changes have been done:

  The signed informed consent of the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** must be obtained before study participation.

- In **Section 5.6.5 Physical examination**, the following changes have been done:

  Physical examination at each study visit subsequent to the vaccination visit, will be performed only if the subject's parent/~~LAR~~ ***adoptive parent*** indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

- In **Section 5.6.15 Recording of AEs and SAEs**, the following changes have been done:

  – The subjects' parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.

  – At each vaccination visit, diary cards will be provided to the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***. The subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** will record body temperature (preferably axillary) and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days) occurring after vaccination. The subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** will be instructed to return the completed diary card to the investigator at the next study visit.

  – Collect and verify completed diary cards during discussion with the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** at Visits 2, 3, 4 and 6.

  – If the parent(s) /~~LAR(s)~~ ***adoptive parent(s)*** of subjects observe any large injection site reaction (defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4-day follow-up (Day 0-Day 3) period, they are to contact study personnel and to visit the investigator's office for evaluation as soon as possible.

  – Any unreturned diary cards will be sought from the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

- In **Section 5.7 Biological sample handling and analysis**, the following changes have been done

  – 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 parent's/~~LAR's~~ ***adoptive parent's*** 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.

  Any sample testing will be done in line with the consent of the individual subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***.

- In **Section 5.7.5 Immunological correlates of protection**, the following changes have been done:

  The investigator is encouraged to share the immunological assay results for non-responders with the study subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***.

- In **Section 6.7 Concomitant medications/products and concomitant vaccinations**, the following changes have been done:

  At each study visit, the investigator should question the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** about any medications/products taken and vaccinations received by the subject.

- In **Section 8 Safety**, the following changes have been done:

  Each subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

- In **Section 8.1.3 Solicited adverse events**, the following changes have been done:

  N.B. If parent(s) /~~LAR(s)~~ ***adoptive parent(s)*** of infants observe any large injection site reaction (defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) after the booster dose at Visit 5, 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 screen in the eCRF. In addition to the diameter of the swelling and the circumference of the limb, the investigator will need to record additional symptoms/characteristics as mentioned in Section 5.6.15.

- In **Section 8.2.1 Time period for detecting and recording adverse events and serious adverse events**, the following changes have been done:

  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's parent/~~LAR~~ ***adoptive parent*** consents to participate in the study until she/he is discharged from the study.

- In **Section 8.2.3.1 Active questioning to detect adverse events and serious adverse events**, the following changes have been done:

  As a consistent method of collecting AEs, the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** should be asked a non-leading question such as:

- In **Section 8.2.3.2.1 Assessment of intensity**, the following changes have been done:

  3 (severe) = An AE which prevents normal, everyday activities. In a young child, such an AE would, for example, prevent attendance at a day-care centre and would cause the parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** to seek medical advice.

- In **Section 8.2.3.4 Medically attended visits**, the following changes have been done:

  For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** will be asked if the subject 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.

- In **Section 8.6 Subject card**, the following changes have been done:

  Study subjects' parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** 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's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***. 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' parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** must be instructed to keep subject cards in their possession at all times.

- In **Section 9.2.1 Subject withdrawal from the study**, the following changes have been done:

  Investigators will make an attempt to contact parents/~~LARs~~ ***adoptive parent(s)*** of 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's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

  *In case a subject is withdrawn from the study because the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)*** has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***, in the eCRF.

- In **Section 9.2.2 Subject withdrawal from investigational vaccine**, the following changes have been done:

  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's parent(s)/~~LAR(s)~~ ***adoptive parent(s)***, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
EudraCT number	2013-005577-43
Date of protocol amendment **Detailed Title**	Protocol Amendment 1 Final: 11 October 2016 A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology Project Leader (CEPL), DTP, Polio, Hib containing vaccines R&D Center Belgium
Signature	PPD
Date	26 OCT 2016

For internal use only

- ----------Checksum----------!Ver.!Created On - -
fa422ff5f2d55c445c9166d51c333401bb50fec6 2.0 10/21/2016 12:23:54 PM - -
---------- -