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208236 (ROTA-096)
Protocol Amendment 2

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

Primary study vaccine and number	*Porcine circovirus* (PCV)-free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine (444563)
Other study vaccine	Lyophilized formulation of GSK's oral live attenuated HRV vaccine (*ROTARIX*)
eTrack study number and abbreviated title	208236 (ROTA-096)
Investigational New Drug (IND) number	BB-IND 16992
EudraCT number	2018-001986-18
Date of protocol	Final Version 2: 09 November 2018
Date of protocol amendment/administrative change	Amendment 1 Final: 23 September 2019 Administrative change 1 Final: 24 February 2020 ***Amendment 2: 30 March 2020***
Short title	Safety study of 2 formulations of GSK's human rotavirus (HRV) vaccine (444563), in healthy infants starting at age 6-12 weeks.
Title	A phase III, observer-blind, randomized, multi-country study to assess the reactogenicity and safety of the *Porcine circovirus* (PCV) free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine as compared to the lyophilized formulation of the GSK's HRV vaccine, when administered as a 2-dose vaccination in infants starting at age 6-12 weeks.
Co-ordinating authors	PPD , Scientific Writer PPD , Scientific Writer ***(Amended 30 March 2020)***

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Contributing authors	• PPD, Clinical & Epidemiology Project Lead (CEPL) • PPD, Clinical & Epidemiology Project Lead (CEPL) • PPD, Clinical Research and Development Leads (CRDL) • PPD, Clinical Research and Development Leads (CRDL) • PPD, Lead Statistician • PPD Statistician • PPD, Study Delivery Lead • PPD, Study Delivery Lead • PPD, Clinical Safety Representative • PPD, Oversight Data Manager • PPD, Study Data Manager • PPD, Study Data Manager • PPD, Global Regulatory Affairs Representative • PPD, Global Patents Representative • PPD, Clinical Trial Supply Manager • PPD, Clinical Trial Supply Manager

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Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and abbreviated title	208236 (ROTA-096)
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Sponsor signatory	Paul Gillard, MD Clinical & Epidemiology Project Lead, Live Viral Vaccines, RDC Belgium, GlaxoSmithKline Biologicals, SA.
Signature	_____
Date	_____

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals SA (GSK).
- 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's study vaccine and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- 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 co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- 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 will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK 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 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
B-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 Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.3.7.3

Study Contact for Reporting SAEs: refer to the local study contact information document.

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

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.3.4.1.

PROTOCOL AMENDMENT/ADMINISTRATIVE CHANGE SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 2	**30-MAR-2020**
Administrative Change 1	24-FEB-2020
Amendment 1	23-SEP-2019
Original Protocol	09-NOV-2018

Amendment 2 30-MAR-2020

Overall Rationale for the Amendment 2

This protocol amendment 2 outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity.

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Added footnote to study design figure, Figure 1 and Table 1 on study procedures specifically around Visit 3, with cross-reference to new section (Section 8.4) on study procedures during special circumstances, such as COVID-19 pandemic. Added footnote to Table 2 about study interval around Visit 2 during special circumstances, such as COVID-19 pandemic	To provide flexibility to certain study procedures in response to disease outbreak situation, as exemplified by the COVID-19 pandemic, to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity
Section 2. Schedule of activities		
Section 5.2. Overall design		
Section 8. Study assessments and procedures	Added cross-reference to new section (Section 8.4) on study procedures during special circumstances, such as COVID-19 pandemic	
Section 8.4	Added new section to provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic	

All changes are tracked in Section 12.4 (Appendix 4). Deleted text is in strikethrough and newly added text is in bold italics.

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1. SYNOPSIS

Indication:

Active immunization of infants against gastroenteritis (GE) due to rotavirus (RV).

Rationale:

Study rationale

Using advanced technology in 2010, researchers from the University of California, San Francisco identified deoxyribonucleic acid (DNA) fragments of *Porcine circovirus* type 1 (PCV-1) in GlaxoSmithKline Biologicals SA's (GSK's) human rotavirus (HRV) vaccine (*ROTARIX*). Further investigations conducted by GSK and the United States (US) Food and Drug Administration (FDA) confirmed the presence of PCV-1 DNA fragments in *ROTARIX* and in its starting materials as well as low levels of PCV-1 viral particles during production process and in the final container. PCV-1 is not known to cause disease in either animals or humans [Hattermann, 2004b; Hattermann, 2004a] and there is no evidence that the presence of PCV-1 in *ROTARIX* poses a safety risk to vaccinated subjects. Laboratory investigations showed that the anti-PCV-1 antibody seropositivity rate in vaccinated subjects was below that observed during assay qualification in samples from unvaccinated subjects [Han, 2017]. The presence of PCV-1 in *ROTARIX* is, therefore, a manufacturing quality issue [Dubin, 2013; Han, 2017].

GSK has replaced the cell bank and virus seeds used as the base production material for its HRV vaccine and in accordance with regulators, the company continues to manufacture *ROTARIX* to the existing approved standards of production and quality, to meet public health needs worldwide.

The viral potency of the PCV-free HRV vaccine (no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used) lot selected for this study (target potency of 6.8 $\log_{10}$ cell culture infective dose ($CCID_{50}$) per dose up to 7.0 $\log_{10}$ $CCID_{50}$ per dose) is in the upper range of the usual potencies of the commercial production batches, routinely released for worldwide distribution. In order to keep the titer stable until administration during the study, the PCV-free study vaccine will be stored frozen.

Only in 2 countries, i.e. Canada and the US, an upper limit for the potency titer at release was required by the Regulatory Authorities and implemented for *ROTARIX* (lyophilized formulation in the US and liquid formulation in Canada). The upper limit was set at 6.5 $\log_{10}$ $CCID_{50}$ per dose. Following discussions with the FDA, it is being considered to increase the upper limit of the potency for the liquid formulation allowing acceptable range of potencies at release of the vaccine.

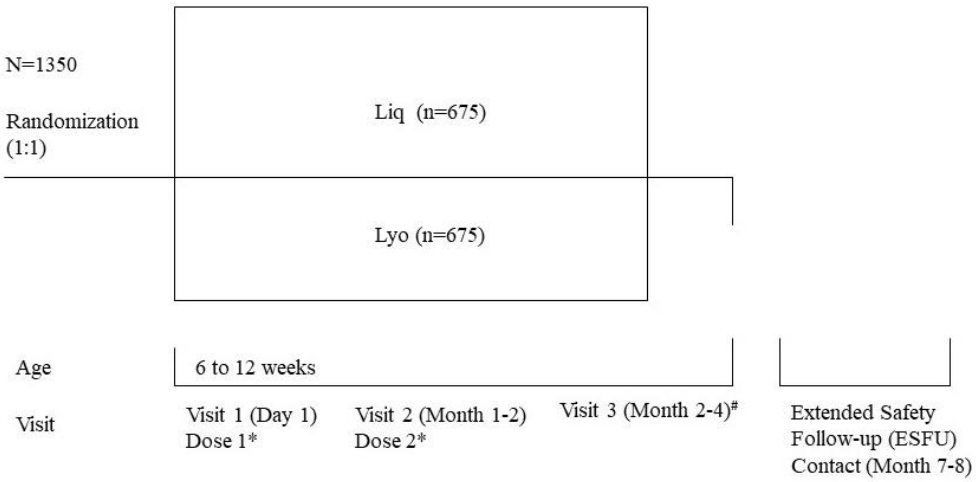
As part of the phase III studies, GSK plans to conduct study Rota-096, to evaluate the reactogenicity and safety of a PCV-free HRV liquid vaccine lot with a potency titer at release above 6.5 $\log_{10}$ $CCID_{50}$ per dose. The sample size of the study ensures completion of the total safety database size across the PCV-free development, as agreed with FDA.

A recent in-house pharmacovigilance analysis of the risk of intussusception (IS) after administration of the *ROTARIX* liquid vaccine (data lock point 15 January 2018) suggests no evidence of any association between the *ROTARIX* potency at release and the risk of IS. As no clear trend was observed in these data, FDA agreed that Rota-096 may proceed.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the reactogenicity of the liquid HRV vaccine and lyophilized HRV vaccine in terms of solicited adverse events (AEs) during the 8-day (Day 1-Day 8) follow-up period after each vaccination.	• Occurrence of each solicited general AE within 8 days (Day 1–Day 8) after each vaccination.
To assess the safety of the liquid HRV vaccine and lyophilized HRV vaccine in terms of unsolicited AEs during the 31-day (Day 1-Day 31) follow-up period after each vaccination and serious adverse events (SAEs) during the entire study period.	• Occurrence of unsolicited AEs within 31 days (Day 1–Day 31) after any vaccination, according to the medical dictionary for regulatory activities (MedDRA) classification. • Occurrence of SAEs throughout the study period (i.e. from Dose 1 of the HRV vaccine to study conclusion at the end of the follow-up period).

Overall Design:



The Extended safety follow-up (ESFU) contact (by telephone call or any other convenient procedure) will take place 6 months after the last dose of the study vaccines.

N=Target number of subjects, n=Target number of subjects in each study group.

*Two doses of the study vaccines will be administered to subjects at 1-month or 2-months interval.

#For authorized sites in Canada only, with approved site level standard operating procedures (SOP): Safety assessments scheduled at Visit 3 (Month 2-4) may take place at the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

Refer to Section 8.4 for study procedures to be considered during special circumstances (Amended 30 March 2020).

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician will review the safety data on a regular basis to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

Age	6-12 weeks	~3-5 months	~4-7 months	~9-11 months	Notes
Epoch	**Epoch 001**				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3*/****	**ESFU**	***Refer to Section 8.4 for study procedures to be considered during special circumstances (Amended 30 March 2020)***
Timepoints	**Day 1**	**Month 1-2**	**Month 2-4**	**Month 7-8**	
Informed consent	●				(See Section 12.2.3 for details)
Check inclusion/exclusion criteria	●				Recheck clinical status before randomization and/or first dose of study treatment (See Section 6.1 and 6.2 for inclusion and exclusion criteria)
Collect demographic data	●				(See Section 8.2.1 for more information)
Record gestational age at birth	●				
Medical history	●				(See Section 8.2.2 for more information)
Physical examination	●				Physical examination at each study visit subsequent to the first vaccination visit, will be performed only if the subjects' parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Physical examination information will not be captured in the eCRF for study visits subsequent to the first vaccination visit. (See Section 8.2.3 for more information)
History of previous vaccination history from birth	●				(See Section 8.2.2 for more information)
Pre-vaccination body temperature	●	●			(See Section 8.2.4 for more information)
Measure/record length and weight	●				
Vaccines					
Check criteria for temporary delay for enrollment and vaccination	O	O			(See Section 6.3 for more information)
Randomization	●				(See Section 7.2.2.2.1 for more information)
Treatment number allocation for subsequent doses		●			(See Section 7.2.2.2.2 for more information)
Check contraindications and warnings and precautions	●	●			(See Section 7.6 and 7.7 for more information)
Recording of administered treatment number	●	●			
Vaccine administration	●	●			Two oral doses of the study vaccines will be administered at 1-month to 2-months interval to subjects. (See Section 7.1 for more information)
Record regurgitation/vomiting	●	●			Any regurgitation or vomiting by the subjects after study vaccine administration should be recorded in the eCRF.

Age	6-12 weeks	~3-5 months	~4-7 months	~9-11 months	Notes
Epoch	**Epoch 001**				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3*/****	**ESFU**	***Refer to Section 8.4 for study procedures to be considered during special circumstances (Amended 30 March 2020)***
Timepoints	**Day 1**	**Month 1-2**	**Month 2-4**	**Month 7-8**	
Vaccine replacement dose administration in case of regurgitation/vomiting	●	●			If regurgitation or vomiting, which may have impaired vaccine take, occurs within 30 minutes after vaccination, a single replacement dose may be given at the same vaccination visit at the discretion of the investigator. This information should be recorded in the eCRF. The subject should continue to participate in the study.
Safety assessments					
Record any concomitant medications/vaccinations	●	●	●		Concomitant administration of routine pediatric vaccines will be allowed according to the local immunization practices in each participating country. All concomitant vaccinations given during the study period will be recorded in the eCRF (See Section 7.5 for more information)
Distribution of diary cards	O	O			
Recording of solicited AEs within 8 days after each vaccination (Day 1-Day 8) by subjects' parent(s)/LAR(s) in diary card	●	●			(See Section 12.3.6 for more information)
Recording of non-serious unsolicited AEs within 31 days after each vaccination (Day 1-Day 31) by subjects' parent(s)/LAR(s) in diary card.	●	●			(See Section 12.3.6 for more information)
Return of diary cards		O	O		
Diary card transcription by the investigator or designee		●	●		
Recording of AEs/SAEs leading to withdrawal from study	●	●	●	●	
Recording of SAEs	●	●	●	●	(See Section 12.3.6 for more information)
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	(See Section 12.3.6 for more information)
Safety contact				●	A safety follow-up contact will be done by a telephone call or any other convenient procedure to collect information on SAEs and medication taken for treatment of SAEs.
Study conclusion				●	(See Section 5.4 for more information)

ESFU=Extended safety follow-up; AE=Adverse event; SAE=Serious adverse event; LAR=Legally acceptable representative; eCRF=electronic case report form

● 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

*For authorized sites in Canada only, with approved site level standard operating procedures (SOP): Safety assessments scheduled at Visit 3 (Month 2-4) may take place at the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

Refer to Section 8.4 for study procedures to be considered during special circumstances (Amended 30 March 2020).

Whenever possible, the investigator should arrange study visits within the interval described in Table 2.

Table 2 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval
Visit 1 → Visit 2*	1–2 months	28 days-83 days after Dose 1 of HRV vaccines
Visit 2 → Visit 3	1–2 months	31 days-83 days after Dose 2 of HRV vaccines
Visit 2 → ESFU contact [2]	6 months	180 days- 210 days after Dose 2 of HRV vaccines

[1] Whenever possible the investigator should arrange study visits within this interval.

[2] A safety follow-up contact (by telephone call or any other convenient procedure) to collect information on SAEs and medication taken for treatment of SAEs.

If despite best efforts it is not possible to administer the 2nd dose of study vaccine within the allowed interval, a maximum age of 24 weeks may be used (Amended 30 March 2020).

3. INTRODUCTION

3.1. Study rationale

Using advanced technology in 2010, researchers from the University of California, San Francisco identified deoxyribonucleic acid (DNA) fragments of *Porcine circovirus* type 1 (PCV-1) in GlaxoSmithKline Biologicals SA's (GSK's) human rotavirus (HRV) vaccine (*ROTARIX*). Further investigations conducted by GSK and the United States (US) Food and Drug Administration (FDA) confirmed the presence of PCV-1 DNA fragments in *ROTARIX* and in its starting materials as well as low levels of PCV-1 viral particles during production process and in the final container. An initial retrospective laboratory investigation conducted by GSK on 40 *ROTARIX* recipients found no immunologic response against PCV-1 [Dubin, 2013]. A subsequent investigation showed an anti-PCV-1 antibody seropositivity rate of 1% (90% confidence interval [CI]: 0.3, 2.6) in recipients of *ROTARIX* (3/299 samples) and 0.3% (90% CI: 0.0, 1.6) in the placebo group (1/296 samples). The difference in post-vaccination seropositivity rates between the 2 study groups was -0.66% (90% CI: -2.16, 0.60). One subject in the vaccinated group was also seropositive before vaccination. The seropositivity rate observed in vaccinated subjects was below that observed during assay qualification in samples from unvaccinated subjects [Han, 2017]. PCV-1 is not known to cause disease in either animals or humans [Hattermann, 2004a; Hattermann, 2004b] and there is no evidence that the presence of PCV-1 in *ROTARIX* poses a safety risk to vaccinated subjects. The presence of PCV-1 in *ROTARIX* is, therefore, a manufacturing quality issue [Dubin, 2013; Han, 2017].

GSK has replaced the cell bank and virus seeds used as the base production material for its HRV vaccine and, in accordance with regulators, the company continues to manufacture *ROTARIX* to the existing approved standards of production and quality, to meet public health needs worldwide.

The viral potency of the PCV-free HRV (No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used) vaccine lot selected for this study (target potency of 6.8 $\log_{10}$ cell culture infective dose ($CCID_{50}$) per dose up to 7.0 $\log_{10}$ $CCID_{50}$ per dose) is in the upper range of the usual potencies of the commercial production batches,

routinely released for worldwide distribution. In order to keep the titer stable until administration during the study, the PCV-free study vaccine will be stored frozen.

Only in 2 countries, i.e. Canada and the US, an upper limit for the potency titer at release was required by the Regulatory Authorities and implemented for *ROTARIX* (lyophilized formulation in the US and liquid formulation in Canada). The upper limit was set at 6.5 $\log_{10}$ $CCID_{50}$ per dose. Following discussions with the FDA, it is being considered to increase the upper limit of the potency for the liquid formulation allowing acceptable range of potencies at release of the vaccine.

As part of the phase III studies, GSK plans to conduct study Rota-096, to evaluate the reactogenicity and safety of a PCV-free HRV liquid vaccine lot with a potency titer at release above 6.5 $\log_{10}$ $CCID_{50}$ per dose. The sample size of the study ensures completion of the total safety database size across the PCV-free development, as agreed with FDA.

A recent in-house pharmacovigilance analysis of the risk of intussusception (IS) after administration of the *ROTARIX* liquid vaccine (data lock point 15 January 2018) suggests no evidence of any association between the *ROTARIX* potency at release and the risk of IS. As no clear trend was observed in these data, FDA agreed that Rota-096 may proceed.

3.2. Background

Rotavirus (RV) infection is the leading cause of acute gastroenteritis (GE) and severe diarrhea in infants and young children <5 years of age [Atherly, 2009]. It has been estimated that in 2013, approximately 215 000 deaths (95% CI: 197 000, 233 000) were caused due to RV. India, Nigeria, Pakistan, and Democratic Republic of Congo accounted for approximately half (49%) of all the estimated RV deaths in 2013 [Tate, 2016].

Although RV infection rarely causes death in Europe, North America and Australia, it remains the most common cause of hospitalization for GE in children [Desselberger, 2012]. In developed countries, in addition to hospitalization for GE, RV infection also leads to major medical and societal costs. Over the last many years, the development of vaccines has been beneficial in the prevention of considerable morbidity and mortality due to RV. Two live oral RV vaccines have been licensed in many countries: one is derived from an attenuated human strain of RV and the other combines 5 bovine-human reassortant strains [Glass, 2006]. Each of these vaccines has been proven highly effective in preventing severe RV diarrhea. These vaccines could reduce deaths from diarrhea and improve child survival through programs such as childhood immunizations and diarrheal disease control in developing countries. The World Health Organization (WHO) recognizes RV vaccination as an effective measure to prevent RV infection and to reduce disease burden, and recommends its inclusion into all national infant immunization programs, particularly in countries where RV GE associated fatality rates are high among children aged <5 years (e.g. south and south-eastern Asia and sub-Saharan Africa) [WHO position paper, 2013].

GSK's HRV vaccine (*ROTARIX*) is a vaccine for oral use, containing the live attenuated HRV RIX4414 strain (referred as HRV in the document). Infants aged younger than 3 months who received the vaccine did not develop diarrhea, vomiting or fever during the

trial [Vesikari, 2004a]. The initial studies conducted by GSK in Finland showed safety, immunogenicity and efficacy of the *ROTARIX* vaccine [Vesikari, 2004b]. In Latin American and European studies, vaccine efficacy of *ROTARIX* vaccine was high, ranging from 80.5% to 90.4% against severe RV GE, and 83.0% to 96.0% against hospitalization due to RV GE during the first 2 years of life [Vesikari, 2007; Linhares, 2008]. Furthermore, results from a phase III clinical study undertaken in Singapore, Hong Kong, and Taiwan showed that during the first 2 years of life, 2 doses of *ROTARIX* vaccine provided a high level of protection against severe RV GE (vaccine efficacy: 96.1%), and had a safety profile similar to the placebo [Phua, 2012]. Such safety and efficacy studies in Europe, Latin America and Asia have confirmed that the vaccine is well-tolerated and efficacious (range: 80-96%) in preventing severe RV GE in the first 2 years of life [Cunliffe, 2014].

ROTARIX is registered in at least 130 countries and more than 400 million doses of the vaccine (lyophilized and liquid formulations) are estimated to have been distributed worldwide from its launch until July 2017.

Please refer to the current investigator's brochure (IB) for information regarding the pre-clinical and clinical studies and the epidemiological information of *ROTARIX* vaccine.

3.3. Benefit/Risk assessment

Please refer to the current IB and the prescribing information for the summary of potential risks and benefits of the *ROTARIX* vaccine**.**

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

3.3.1. Risk assessment

Important potential/identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
GSK's HRV vaccine		
IS	Spontaneous data	• Subjects will be followed up to 6 months after receipt of the vaccine to check for any safety signal. • Parent(s)/legally acceptable representative (LAR)(s) should report any untoward symptoms their child experiences after receiving the vaccine immediately to the investigator. • Parent(s)/LAR(s) will be instructed to call the doctor right away or go to the emergency department if the baby has any sign or symptom of IS after getting the vaccine, even if it has been several weeks since the last vaccine dose.
Hematochezia	Spontaneous data	
Gastroenteritis with vaccine viral shedding in infants with severe combined immunodeficiency (SCID)	Spontaneous data	
Kawasaki disease	Based on signal observed for *RotaTeq* vaccine	

Important potential/identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		• All serious adverse events (SAEs) should be reported by the investigator immediately to GSK. • Subjects with SCID will be excluded from participating in this study (Refer to Section 6.2 for more details).
Study procedures		
Allergic reaction to the vaccines	Spontaneous data	Subjects will be observed for at least 30 minutes after vaccine administration, with medical attention available in case of anaphylaxis.

3.3.2. Benefit assessment

By receiving the HRV vaccines the subject may have the benefit of being protected against RV disease.

In addition, the subjects will undergo a physical examination at the first study visit. In case the study doctor discovers any medical condition, the subject will be referred to the local healthcare system.

3.3.3. Overall Benefit: Risk conclusion

Considering the measures taken to minimize the risk to subjects participating in this study, the potential or identified risks in association with the HRV vaccines and study procedures are justified by the potential benefits (prevention/treatment) that may be afforded to subjects receiving the vaccines for immunization against RV.

4. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the reactogenicity of the liquid HRV vaccine and lyophilized HRV vaccine in terms of solicited adverse events (AEs) during the 8-day (Day 1-Day 8) follow-up period after each vaccination.	• Occurrence of each solicited general AE within 8 days (Day 1–Day 8) after each vaccination.
To assess the safety of the liquid HRV vaccine and lyophilized HRV vaccine in terms of unsolicited AEs during the 31-day (Day 1-Day 31) follow-up period after each vaccination and serious adverse events (SAEs) during the entire study period.	• Occurrence of unsolicited AEs within 31 days (Day 1–Day 31) after any vaccination, according to the medical dictionary for regulatory activities (MedDRA) classification. • Occurrence of SAEs throughout the study period (i.e. from Dose 1 of the HRV vaccine to study conclusion at the end of the follow-up period).

5. STUDY DESIGN

5.1. Scientific rationale for study design

Two oral doses of the study vaccines will be administered at 1-month or 2-months interval to subjects, according to the immunization schedule for RV vaccine administration in participating countries.

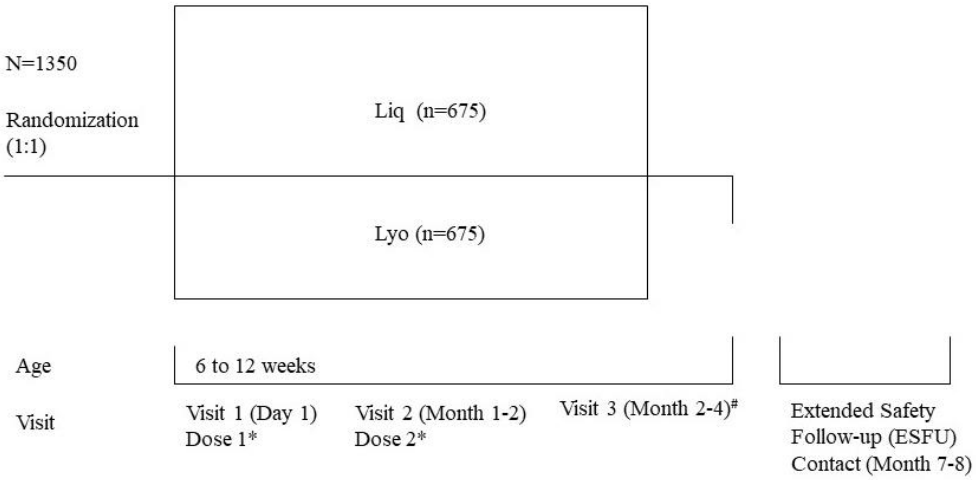
As the liquid formulation of *ROTARIX* is not licensed in the US, the lyophilized formulation of the vaccine will be used as control in all phase III studies as part of the PCV-free development plan.

Due to the difference in the appearance and volume between lyophilized HRV vaccine and PCV-free liquid HRV vaccine, the study will be observer-blinded.

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician will review the safety data on a regular basis to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine.

5.2. Overall design

Figure 1 Study design overview



The Extended safety follow-up (ESFU) contact (by telephone call or any other convenient procedure) will take place 6 months after the last dose of the study vaccines.

N=Target number of subjects, n=Target number of subjects in each study group.

*Two doses of the study vaccines will be administered to subjects at 1-month or 2-months interval.

#For authorized sites in Canada only, with approved site level standard operating procedures (SOP): Safety assessments scheduled at Visit 3 (Month 2-4) may take place at the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

Refer to Section 8.4 for study procedures to be considered during special circumstances (Amended 30 March 2020).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (SoA) (Section 2), are essential and required for study conduct.

- Type of study: self-contained
- Experimental design: Phase III, observer-blind, randomized (1:1), controlled, multi-country study with 2 parallel groups
- Duration of the study: The total duration of the study, per subject, will be approximately 7-8 months including the 6 months of extended safety follow-up (ESFU) period after the last dose of HRV vaccine
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at the ESFU contact (Month 7-8)
- Primary completion date (PCD): ESFU contact (Month 7-8)

Refer to Section 12.1.2 for the definition of PCD.

- End of study (EoS): Last subject last contact (Month 7-8)

Refer to Section 12.1.2 for the definition of EoS.

- Study groups:

Table 4 Study groups, treatments and epoch foreseen in the study

Study groups	Number of subjects	Age at Dose 1 (Min-Max)	Treatment name	Vaccine/Product names	Epoch
					Epoch 001 (observer-blind)
Liq	675	6-12 weeks	HRV Liquid (oral administration)	HRV PCV-free*	x
Lyo	675	6-12 weeks	HRV Lyophilized (oral administration)	HRV Lyo	x
				HRV Diluent	

*HRV PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

- Control: active control, GSK's lyophilized HRV vaccine.
- Vaccination schedule:
  - Two doses of HRV vaccines to be administered according to 0, 1-2-month schedule.
  - Concomitant administration of routine childhood vaccines will be allowed according to the local immunization practices in each participating country.
- Treatment allocation: Randomized with balanced allocation (1:1) using GSK's central internet randomization system (SBIR). Refer to Section 7.2.2 for detailed description of the randomization method.
- Blinding: observer-blind.

Refer to Section 7.3 for details on blinding procedures.

- Data collection: Standardized electronic case report form (eCRF). Solicited AEs will be collected using a diary card.
- Safety monitoring: An IDMC consisting of clinical experts and a biostatistician will review the safety data on a regular basis to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine.

5.3. Number of subjects

The target sample size is 1350 subjects, 675 subjects per group.

Withdrawals will not be replaced.

Overview of the recruitment plan:

- All subjects will be enrolled at multiple sites in different countries.
- Enrollment will be terminated when approximately 1350 eligible subjects will be enrolled.
- The recruitment and randomization will be monitored by SBIR.

5.4. Subject and study completion

A subject is considered to have completed the study if he/she is available for the concluding contact (ESFU contact) as described in the protocol.

Global completion of the study is required in order to provide sufficient subjects as defined in Section 10.1 Sample Size Determination**.**

6. STUDY POPULATION

6.1. Inclusion criteria for enrollment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study 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)/LAR(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 or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the subject prior to performance of any study specific procedure.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

- A male or female between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.

6.2. Exclusion criteria for enrollment

6.2.1. Medical conditions

- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.
- Very prematurely born infants (born ≤28 weeks of gestation).
- History of IS.
- Family history of congenital or hereditary immunodeficiency.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- Major congenital defects or serious chronic illness, as assessed by the investigator.
- Previous confirmed occurrence of RV GE.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- History of SCID.

6.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period.
- 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 study vaccine administration, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study, and other licensed routine childhood vaccinations.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Administration of immunoglobulins and/or any blood products from birth or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Previous vaccination against RV.

6.2.3. Prior/Concurrent clinical study experience

- 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 (drug or medical device).

6.2.4. Other exclusions

- Child in care

  Please refer to Section 12.1.2 for the definition of child in care.

6.3. Criteria for temporary delay for enrollment and vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of enrollment/or subsequent vaccination. Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral, the axillary or the rectal. Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- GE within 7 days preceding the HRV vaccine administration.

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

The treatments administered in this study are presented in Table 5.

7.1. Treatments administered

Table 5 Treatments administered

Study treatment name	HRV Liquid	HRV Lyophilized	
Vaccine/Product name	HRV PCV-free*	HRV Lyo	HRV Diluent
Presentation	Liquid vaccine in a pre-filled oral applicator	Lyophilized vaccine in a monodose glass vial	Diluent for lyophilized vaccine (calcium carbonate liquid antacid) supplied separately in a pre-filled oral applicator.
Vaccine/Product formulation	PCV-free HRV RIX4414 live attenuated $=10^{6.8\text{-}7.0}CCID_{50}$	HRV RIX4414 live attenuated $>=10^{6.0}CCID_{50}$	$CaCO_3$=60mg
Storage condition	-20°C or -4°F	+2 to +8°C or +36 to +46°F	+2 to +8°C or +36 to +46°F
Route of Administration	oral	oral	
– **Location**	Not applicable	Not applicable	
– **Directionality**	Not applicable	Not applicable	
– **Laterality**	Not applicable	Not applicable	
Number of doses to be administered	2	2	
Volume to be administered#	1.5 ml	1 ml	
Packaging and labeling	Refer to SPM for more details	Refer to SPM for more details	
Manufacturer	GSK	GSK	

*HRV PCV-free: No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.
#Refer to the study procedure manual (SPM) for storage, handling and preparation methods.
Refer to Section 2 for schedule of treatment administration.

After completing all prerequisite procedures prior to vaccination (refer to Section 7.6 regarding the contraindications to subsequent vaccination), 1 dose of study vaccine will be given orally (refer to Table 5 for details regarding the treatment administered).

In order to allow the swallowing of the entire volume of the single oral dose (of liquid or lyophilized formulation), the administration should occur in a quiet environment. The subject should be seated in a reclining position. Administer orally (i.e. into the subject's mouth toward the inner cheek) the entire content of oral applicator. Sufficient time should be allowed for the baby to swallow the vaccine solution, to avoid regurgitation or vomiting. If regurgitation or vomiting, which may have impaired vaccine take, occurs within 30 minutes after study vaccine administration, a single replacement dose may be given at the same vaccination visit at the discretion of the investigator. This information should be recorded in the eCRF. The subject should continue to participate in the study.

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 2).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis and syncope.

7.2. Method of treatment assignment

7.2.1. Subject identification

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

7.2.2. Randomization of treatment

7.2.2.1. Randomization of supplies

The numbering of HRV vaccine supplies will be performed at GSK, using a block scheme randomization in MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

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

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

7.2.2.2.1. Study group and treatment number allocation

Allocation of the subject to a study group/a treatment number at the investigator site will be performed using SBIR. The randomization algorithm will use a minimization procedure accounting for center and the country as minimization factors. Minimization factors will have equal weight in the minimization algorithm.

After obtaining the signed and dated informed consent form (ICF) from the subject's parent(s)/LAR(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 randomization system will determine the study group and 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.

When SBIR is not available, please refer to the SBIR user guide or the SPM for specific instructions.

7.2.2.2.2. 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 consistent with the allocated study group.

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

7.3. Blinding

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

7.3.1. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

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

As back-up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 6) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject's parent or LAR/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back-up process). Contact details of investigator and GSK Helpdesk are reported in the subject card.

Table 6 Contact information for emergency unblinding

GSK Helpdesk 24/24 hour and 7/7-day availability
The Helpdesk is available by phone, fax and email Phone: PPD For Canada, US and Puerto Rico Toll-free number: PPD Fax: PPD email: PPD

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life-threatening cases. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Handling, storage and replacement of study vaccines

7.4.1. Storage and handling of study vaccines

Liquid formulation of PCV-free HRV vaccine

As the PCV-free liquid HRV vaccine must be stored at -20°C, the vaccine must be thawed before being administered. Refer to the Module on Clinical Trial Supplies in the SPM for detailed instructions on the storage, handling, thawing, preparation and administration of the frozen PCV-free HRV vaccine.

The pre-filled oral applicator is shaken well before use. The vaccine (approximately 1.5 ml) should then be administered orally as a single dose.

Lyophilized formulation of HRV vaccine

To prepare lyophilized HRV vaccine for administration, the entire content of the supplied diluent (calcium carbonate buffer) should be transferred from the oral applicator into the vial of the lyophilized product via the intermediate device. The vial should be shaken well to re-suspend the vaccine. The entire volume of the re-suspended product (approximately 1 ml) should be withdrawn into the same oral applicator and the re-suspended product should then be administered promptly as a single oral dose.

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

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccines must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirement has to be considered as a temperature excursion.

Study vaccines that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site monitor).

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 vaccines**.**

7.4.2. Replacement of unusable vaccines doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 30% additional vaccine doses will be supplied to replace those that are unusable.

7.5. Concomitant medications/products and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

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

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 30 days before and ending 30 days after each dose of study vaccines.
- Any concomitant vaccination administered in the period from first study vaccination (Visit 1) and ending at the last study visit (Visit 3).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

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 ≥38.0°C/100.4°F regardless the location of measurement). The preferred location for measuring temperature in this study will be the oral, the axillary or the rectal.

- Any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered at any time during the study period for the treatment of an SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period between Visit 1 to Visit 3.

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period between Visit 1 to Visit 3. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Immunoglobulins and/or any blood products administered during the study period between Visit 1 to Visit 3.
- Long-acting immune-modifying drugs administered at any time during the study period between Visit 1 to Visit 3 (e.g. infliximab).
- The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.6. Contraindications to subsequent vaccine administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, these subjects should be encouraged to continue study participation.

- Subjects who experience any SAE judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study
- Anaphylaxis following the administration of vaccines
- Hypersensitivity reaction following the administration of the vaccines
- Any uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose for IS
- Any history of IS
- SCID

7.7. Warnings and precautions

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit.

The HRV vaccine (both lyophilized and liquid formulations) should under no circumstances be injected.

There are no data on the safety and efficacy of *ROTARIX* in infants with gastrointestinal illnesses. Administration of *ROTARIX* vaccine may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Post-marketing safety data indicate a transient increased risk of IS after vaccination, mostly within 7 days following the administration of the first dose of *ROTARIX* vaccine and, to a lesser extent, the second dose. The overall incidence of IS remains rare. Whether *ROTARIX* vaccine affects the overall risk of IS has not been established.

Therefore, parent(s)/LAR(s) should be advised to promptly report any symptoms indicative of IS (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever).

Excretion of the vaccine virus in the stools is known to occur after vaccination and lasts for 10 days on average with peak excretion around the seventh day. In clinical studies, cases of transmission of excreted vaccine virus to seronegative contacts of vaccines have been observed without causing any clinical symptoms. *ROTARIX* vaccine should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccines should be advised to observe careful hygiene (including washing their hands) when changing children's diapers.

The tip caps of the pre-filled oral applicators of diluent may contain natural rubber latex which may cause allergic reactions in individuals who are sensitive to latex.

Refer to the most recent version of the IB or label/package insert for more details on warnings and precautions.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the measures detailed in Section 8.4 may be implemented for enrolled participants. (Amended 30 March 2020)

8.1. 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.

8.2. Pre-vaccination procedures

8.2.1. Collection of demographic data

Record demographic data such as gestational age at birth, sex and race in the subject's eCRF.

8.2.2. Medical and vaccination history

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

8.2.3. Physical examination

- Perform a physical examination of the subject, including assessment of oral or axillary or rectal body temperature, length and weight.
- Collected information needs to be recorded in the eCRF.
- Physical examination at each study visit subsequent to the first vaccination visit, will be performed only if the subjects' parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.
- If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.
- Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.4. Pre-vaccination body temperature

The oral or axillary or rectal body temperature of each subject needs to be measured prior to any study vaccine administration. If the subject has fever (fever is defined as temperature ≥38.0°C/100.4°F regardless of the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Section 6.3).

8.3. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study.

8.3.1. Safety definitions

Please refer to Section 12.3 for safety definitions.

8.3.2. Time period and frequency for collecting adverse event and serious adverse event information

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 7. Refer to the Section 12.3.6.1 for details on the time period for recording safety information.

Table 7 Reporting periods for collecting safety information

Study activity	Pre-V*		V1 Dose 1	7 days Post-V1	30 days Post-V1		V2 Dose 2	7 days Post-V2	30 days Post-V2		V3 (30 days after the last dose)		ESFU (Study conclusion)
			Day 1				Month 1-2				Month 2-4		Month 7-8
Solicited general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal													
SAEs													
SAEs related to study participation or GSK concurrent medication/vaccine													

* Consent obtained. Pre-V: pre-vaccination; V = Visit.

All SAEs will be recorded and reported via Expedited Adverse Event Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in section 12.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 7. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccines, the investigator will promptly notify the study contact for reporting SAEs.

8.3.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.3.6.

Refer to Section 8.4 for measures for safety follow-up that may be implemented during special circumstances (Amended 30 March 2020).

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject's parent(s)/LAR(s) is the preferred method to inquire about AE occurrence.

8.3.4. Reporting of serious adverse events

Table 8 Timeframes for submitting serious adverse event reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Time-frame	Documents	Time-frame	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Time-frame allowed after receipt or awareness of the information.

‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.4.1. Contact information for reporting of serious adverse events

Table 9 Contact information for reporting of serious adverse events

Study contact for questions regarding SAEs
Refer to the local study contact information document
Back-up study contact for reporting SAEs
24/24 hour and 7/7-day availability: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD Canada sites only: Fax: PPD

8.3.4.2. Regulatory reporting requirements for serious adverse events

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contact. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.3.9.

8.3.6. 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 SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.3.7. Subject card

Study subjects' parent(s)/LAR(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). 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) must be instructed to keep subject cards in their possession at all times during the study duration.

8.4. Study procedures during special circumstances (Amended 30 March 2020)

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.***
- ***If despite best efforts it is not possible to send diary cards to the site within the visit window as defined in the protocol (see Table 2), the diary cards should be returned to site before study end (the last ESFU contact).***
- ***If despite best efforts it is not possible to administer the 2nd dose of study vaccine as defined in the protocol (see Table 2), a maximum age of 24 weeks may be used.***

9. DISCONTINUATION CRITERIA

9.1. Discontinuation from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who was not available for the concluding contact foreseen in the protocol.

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

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

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

Primary reason for study 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 by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AEs requiring expedited reporting
- Unsolicited non-serious AE
- Solicited AE
- Protocol deviation
- Withdrawal by subject, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*In case a subject is withdrawn from the study because the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject's parent(s)/LAR(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 an SAE/AE until resolution of the event (see Section 12.3.9).

9.2. Discontinuation of study vaccines

A 'withdrawal' from the study vaccines 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 study vaccines may continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

Primary reason relative to premature discontinuation of the study vaccines will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AEs requiring expedited reporting
- Unsolicited non-serious AE
- Solicited AE
- Not willing to be vaccinated
- Other (specify).

9.3. Lost to follow-up

A subject will be considered lost to follow-up if subject's parent(s)/LAR(s) repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject's parent(s)/LAR(s) fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject's parent(s)/LAR(s) and reschedule the missed visit as soon as possible and counsel them on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject's parent(s)/LAR(s) wishes the subject to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject's parent(s)/LAR(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the parent's/LAR's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject's parent(s)/LAR(s) continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

The target sample size is 1350 subjects (675 subjects per group).

Table 10 provides the 95% exact CI for different possible observed number of subjects with AEs for the study (675 subjects per group).

Table 10 Two-sided 95% exact confidence intervals for the true adverse event rate at different possible observed adverse event rates (675 subjects per group)

Subjects vaccinated	Observed number subjects reporting the adverse events	Observed percentage of subjects with the adverse events	95% exact confidence interval	
			Lower limit	Upper limit
675	0	0.0	0.0%	0.5%
	1	0.1	0.0%	0.7%
	10	1.5	0.7%	2.7%
	30	4.4	3.0%	6.2%
	50	7.4	5.5%	9.6%
	100	14.8	12.2%	17.7%

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis set	Description
Enrolled	All subjects who were randomized or vaccinated
Exposed	All subjects who received at least 1 dose of the study treatment. For the sake of analysis, the study group is defined by the treatment administered at Dose 1.

10.3. Statistical analyses

10.3.1. Subjects disposition

Number of enrolled, vaccinated (at least 1 vaccination, full vaccination course) subjects and reason for withdrawal, included in each study group or in total will be described.

10.3.2. Demography and baseline characteristics analyses

The median, mean, range and standard deviation of age (in weeks) at each study vaccine dose and of the gestational age at birth will be computed by study group. The median, mean and standard deviation of length (in centimeters) and weight (in kilograms) at Visit 1 will be computed by study group. The distribution of racial and sex composition of the study population will be presented.

The distribution of subjects enrolled in each country/site will be tabulated across and per study group.

Important protocol deviations including ineligibility, unblinding, mis-administration of treatment, use of prohibited medication/vaccination and deviations from intervals between vaccination Visit 1 and Visit 2 (see Table 2) will be tabulated by study group.

10.3.3. Safety analyses

The primary safety analysis will be performed on the Exposed set.

Endpoint	Statistical analysis methods
Primary	**Within groups assessment** The percentage of doses and of subjects reporting at least 1 AE (solicited or unsolicited) during the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination will be computed, along with exact 95% CI. The same calculations will be done for AEs (solicited or unsolicited) rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. The percentage of doses and of subjects reporting each individual solicited general AE will be computed, over the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited AE rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. For fever, additional analyses will be performed by 0.5°C increments. These calculations will also be performed by country, sex and frequent race. 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 (Day 1-Day 31) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination, for unsolicited AEs rated as grade 3 with causal relationship to vaccination and those that resulted in a medically attended visit. These calculations will also be performed by country. For each study group, the percentage of subjects who started taking at least 1 concomitant medication, antipyretic medication and prophylactic antipyretic medication during the 8-day (Day 1-Day 8) and 31-day (Day 1-Day 31) follow-up periods post-vaccination will be tabulated by dose, by subject for each dose and across the 2 doses. Subjects who experienced at least 1 SAE during the entire study period (from Dose 1 till ESFU contact at Month 7-8) will be summarized by study group and all SAEs will be tabulated.

10.3.4. Interim analyses

No interim analysis has been planned for this study.

10.4. Sequence of analyses

The final study report will contain the final analyses of all primary endpoints.

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

AE:	Adverse event
$CCID_{50}$:	Median cell culture infective dose (quantity of virus causing infection in 50% of exposed cells)
CI:	Confidence interval
COVID-19	Corona Virus Disease-2019
DNA:	Deoxyribonucleic acid
eCRF:	electronic case report form
EoS:	End of study
ESFU:	Extended safety follow-up
EU:	European Union
FDA:	Food and Drug Administration
GCP:	Good Clinical Practice
GE:	Gastroenteritis
GSK:	GlaxoSmithKline Biologicals SA
HRV:	Human rotavirus
IB:	Investigator's brochure
ICF:	Informed consent form
ICH:	International Conference on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IND:	Investigational new drug
IRB:	Institutional Review Board

IS:	Intussusception
LAR:	Legally acceptable representative
LSLV:	Last subject last visit
MedDRA:	Medical dictionary for regulatory activities
PCD:	Primary completion date
PCV-1:	*Porcine circovirus* type 1
RV:	Rotavirus
SAE:	Serious adverse event
SBIR:	Central internet randomization system
SCID:	Severe combined immunodeficiency
SoA:	Schedule of activities
SOP:	Standard Operating Procedure
SPM:	Study procedures manual
SUSAR:	Suspected unexpected serious adverse reaction
US:	United States
WHO:	World Health Organization

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

Blinding: A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 7.3 for details on observer-blinded studies).

Child in care: A child who has been placed under the control or protection of an agency, organization, 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.

Diarrhea: Passage of 3 or more looser than normal stools within a day.

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

End of Study (EoS): **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as follows: Last subject last visit (LSLV) (Visit X) or Last testing results released of samples collected at Visit X* For studies that involve imaging techniques for data collection: Last reading results released for all subjects from Visit X* if it occurs after LSLV. * In this case EoS must be achieved no later than 8 months after LSLV. For studies without collection of human biological samples or imaging data: Last subject last visit (Visit X). For studies with re-use human biological samples or imaging data: Last testing results released or Last reading results. In this case EoS must be achieved no later than 8 months after the start of the testing.
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardized term to replace: period, cycle, phase, stage.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization 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.
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions

Legally acceptable representative (LAR): **(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.
Primary completion date (PCD):	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
HRV PCV-free	No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.
Randomization:	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 1 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.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Study vaccine:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
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 vaccines 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.
Treatment number:	A number identifying a treatment to a subject, according to 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.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

12.1.3. Trademarks

Trademark Information

Trademarks of the GSK group of companies	Generic description
ROTARIX	Human rotavirus vaccine

Trademarks not owned by the GSK group of companies	Generic description
RotaTeq (Merck & CO., Inc.)	Rotavirus vaccine, live, oral, pentavalent

12.2. Appendix 2: Study governance considerations

12.2.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF or informed assent form, IB, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.2.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the center and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.2.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject's legally authorized representative and answer all questions regarding the study.

Subject's parent(s)/LAR(s) must be informed that the participation is voluntary.

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

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subject's parent(s)/LAR(s) must re-consent to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the subject's parent(s)/LAR(s).

12.2.4. Data protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The parent(s)/LAR(s) must be informed that subject's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject's parent(s)/LAR(s).

The parent(s)/LAR(s) must be informed that subject's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.2.5. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from last subject last visit (LSLV) for interventional studies and the completion of the analysis for non-interventional studies and will follow the guidance from the International Committee of Medical Journal Editors.

12.2.6. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

For studies that are in scope of the European Union (EU) Clinical Trial Regulation, summaries of the results of GSK interventional studies (phase I-IV) in pediatric population will also be posted within defined timelines on the publicly available EU Clinical Trial Register. If it is not possible to submit a summary of the results within the required timelines, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

Under the framework of the SHARE initiative, anonymized patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK 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.

12.2.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfill the requirements for certified copies.

All subject data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects that support the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.2.8. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the Section 12.1.2.

12.2.9. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

At the end of last study contact, the investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

12.3. Appendix 3: Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.3.1. Definition of adverse event

12.3.1.1. Adverse event definition

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

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.3.1.2. Events meeting the adverse event definition

Significant or unexpected worsening or exacerbation of the condition/indication under study.

- New conditions detected or diagnosed after study 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 study vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccines administration.
- Significant failure of expected pharmacological or biological action.

- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to AEs (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.3.3. All other AEs will be recorded as UNSOLICITED AEs.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

12.3.1.3. Events NOT meeting the adverse event definition

- 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.

12.3.2. Definition of SAE

An 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 hospitalization or prolongation of existing hospitalization,

   Note: In general, hospitalization 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 hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.

   Hospitalization 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

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, diarrhea, 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 judgment 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 hospitalization but may jeopardize 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 hospitalization.

12.3.3. Solicited adverse events

Solicited general adverse events

The following general AEs will be solicited (Table 11):

Table 11 Solicited general adverse events

Infants
Fever
Irritability/Fussiness
Diarrhea
Vomiting
Loss of appetite
Cough/runny nose

Note: Parent(s)/LAR(s) will be instructed to measure and record the oral, axillary or rectal body temperature in the evening. Should additional temperature measurements be performed at other times of day, parent(s)/LAR(s) will be instructed to record the highest temperature in the diary card.

12.3.4. Unsolicited adverse events

An unsolicited AE is an AE that was not solicited using a subject diary* and that was spontaneously communicated by a parent(s)/LAR(s) who has signed the informed consent.

*In this section and in Section 12.3.6, subject diary refers to diary card.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the parent(s)/LAR(s). In case of such events, parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by parent(s)/LAR(s) will be collected during interview with the parent(s)/LAR(s) and by review of available medical records at the next visit.

12.3.5. 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, hematology, urinalysis) or other abnormal assessments (e.g. vital signs etc.) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 12.3.1 and 12.3.2). 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 judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.3.6. Detecting and recording adverse events and serious adverse events

A paper diary, hereafter referred to as subject diary will be used in this study to capture solicited and unsolicited AEs. The subject's parent(s)/LAR(s) should be trained on how and when to complete each field of the subject diary.

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

Subject diary training should be directed at the individual(s) who will perform the measurements of AEs and who will enter the information into the subject diary. This individual may not be the subject's parent(s)/LAR(s), but if a person other than the subject's parent(s)/LAR(s) enters information into the subject diary, this person's identity must be documented in the subject diary/subject's source record. Any individual that makes entries into the subject diary must receive training on completion of the subject diary at the time of the visit when subject diary is dispensed. This training must be documented in the subject's source record.

At each vaccination visit, subject diaries will be provided to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will be instructed to measure and record the oral or axillary or rectal body temperature, and any solicited general AEs (i.e. on the day of vaccination and during the next 7 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days) occurring after vaccination. The subject's parent(s)/LAR(s) will be instructed to return the completed subject diaries to the investigator at the next study visit.

- Collect and verify completed subject diaries during discussion with the subject's parent(s)/LAR(s) on Visit 2 and Visit 3.
- Any unreturned subject diaries will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

The investigator will transcribe the collected information into the eCRF in English.

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

All AEs within 31 days following administration of each dose of study vaccines (Day 1 to Day 31) must be recorded onto 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 vaccines and will end 6 months following administration of the last dose of study vaccines for each subject. See Section 12.3.7 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.

In addition to the above-mentioned reporting requirements and in order to fulfill 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(s)/LAR(s) consents to participate in the study until she/he is discharged from the study.

12.3.6.2. Evaluation of adverse events and serious adverse events

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

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

'*Has your child acted differently or felt different in any way since receiving the vaccines or r 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 instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

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.

12.3.6.2.2. Assessment of adverse events

1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described in Table 12 and Table 13:

Table 12 Intensity scales to be used by the parent(s)/LAR(s) for solicited adverse events during the solicited follow-up period

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C/°F using any age-appropriate route.
Irritability/Fussiness	0	Behavior as usual
	1	Crying more than usual/no effect on normal activity
	2	Crying more than usual/interferes with normal activity
	3	Crying that cannot be comforted/prevents normal activity
Diarrhea $		Record the number of looser than normal stools /day
Vomiting §		Record the number of vomiting episodes/day
Loss of appetite	0	Appetite as usual
	1	Eating less than usual/no effect on normal activity
	2	Eating less than usual/interferes with normal activity
	3	Not eating at all
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

* Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral, the axillary and the rectal.

$ Diarrhea is defined as passage of 3 or more looser than normal stools within a day.

§ Vomiting is defined as 1 or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

Table 13 Intensity scales for diarrhea, vomiting and fever occurring during the solicited period

Adverse Event	Intensity grade	Parameter
Diarrhea $	0	Normal (0-2 looser than normal stools/day)
	1	3 looser than normal stools/day
	2	4-5 looser than normal stools/day
	3	≥ 6 looser than normal stools/day
Vomiting §	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥3 episodes of vomiting/day
Fever	0	temperature <38.0°C/100.4° F
	1	temperature ≥38.0°C/100.4° F – ≤38.5°C/101.3 F
	2	temperature >38.5°C/101.3 F – ≤39.5°C/103.1 F
	3	temperature >39.5°C/103.1 F

$ Diarrhea is defined as passage of 3 or more looser than normal stools within a day.

§ Vomiting is defined as 1 or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

The intensity grade for diarrhea, vomiting and fever as shown in this table will be scored at GSK.

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 judgment.

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 center and would cause the parent(s)/LAR(s) to seek medical advice).

An AE that is assessed as Grade 3 (severe) should not be confused with an 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 12.3.2.

2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each AE/SAE using clinical judgment. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine cannot be determined, the investigator should indicate the AE to be related to all products.

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 study vaccines will be considered and investigated. The investigator will also consult the IB and/or Prescribing Information for marketed products to determine his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK. 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.

Causality of all 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 study vaccine?

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

If an event meets the criteria to be determined as 'serious' (see Section 12.3.2), 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 vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

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).

12.3.6.2.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalization, 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.

12.3.7. Reporting of serious adverse events

12.3.7.1. Prompt reporting of serious adverse events to GSK

SAEs that occur in the time period defined in Section 12.3.6 will be reported promptly to GSK within the timeframes described in Table 8, once the investigator determines that the event meets the protocol definition of an SAE.

12.3.7.2. SAEs requiring expedited reporting to GSK

Once an investigator becomes aware that an 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 an 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.

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

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the study contact for reporting SAEs (refer to the Sponsor Information) or to GSK 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.

12.3.8. 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 Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 8.

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

12.3.9.1. 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 (within 24 hours for SAEs; refer to Table 8).

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 last visit of the subject.

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.

12.3.9.2. 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, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

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

GSK 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 recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

12.4. Appendix 4: Protocol Amendment/Administrative change History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	**30-MAR-2020**
Administrative Change 1	24-FEB-2020
Amendment 1	23-SEP-2019
Original Protocol	09-NOV-2018

Overall Rationale for the Amendment 2

This protocol amendment 2 outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Added footnote to study design figure, Figure 1 and Table 1 on study procedures specifically around Visit 3, with cross-reference to new section (Section 8.4) on study procedures during special circumstances, such as COVID-19 pandemic. Added footnote to Table 2 about study interval around Visit 2 during special circumstances, such as COVID-19 pandemic	To provide flexibility to certain study procedures in response to disease outbreak situation, as exemplified by the COVID-19 pandemic, to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity
Section 2. Schedule of activities		
Section 5.2. Overall design		
Section 8. Study assessments and procedures	Added cross-reference to new section (Section 8.4) on study procedures during special circumstances, such as COVID-19 pandemic	
Section 8.4	Added new section to provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic	

Detailed description of Amendment 2:

A footnote to study design figure in Section 1 (Synopsis) and Table 1 in Section 2 (Schedule of activities) and Figure 1 in Section 5.2 (Overall study design) was added, with cross-reference to the new section, Section 8.4, on guidance for study procedures during special circumstances such as COVID-19 pandemic: ***Refer to Section 8.4 for study procedures to be considered during special circumstances***.

A footnote to Table 2 was added, about study interval around Visit 2 during special circumstances, such as COVID-19 pandemic: ***If despite best efforts it is not possible to administer the 2nd dose of study vaccine within the allowed interval, a maximum age of 24 weeks may be used.***

In the following sections, amended text is indicated in ***bold italics***:

Cover page

Co-ordinating author PPD, Scientific Writer

Section 8 Study assessments and procedures

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the measures detailed in Section 8.4 may be implemented for enrolled participants.

Section 8.4 Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.***
- ***If despite best efforts it is not possible to send diary cards to the site within the visit window as defined in the protocol (see Table 2), the diary cards should be returned to site before study end (the last ESFU contact).***
- ***If despite best efforts it is not possible to administer the 2nd dose of study vaccine as defined in the protocol (see*** Table 2***), a maximum age of 24 weeks may be used.***

Detailed description of Protocol Administrative Change 1:

Title page: Changes in the name of co-ordinating author and list of contributing authors.

- Co-ordinating author: PPD ***Scientific Writer (SW),***
- PPD , ***Study Data Manager (SDM),***
- PPD , ***Clinical Trial Supply Manager (CTSM).***

Title pages, Sponsor signatory page, Investigator agreement page: The administrative change was made to correct the category of the study title (short title versus title). No changes were made to the study title itself.

~~**Title**~~ ***Short title***	Safety study of 2 formulations of GSK's human rotavirus (HRV) vaccine (444563), in healthy infants starting at age 6-12 weeks.
~~**Short title**~~ ***Title***	A phase III, observer-blind, randomized, multi-country study to assess the reactogenicity and safety of the *Porcine circovirus* (PCV) free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine as compared to the lyophilized formulation of the GSK's HRV vaccine, when administered as a 2-dose vaccination in infants starting at age 6-12 weeks.

Overall rationale for Protocol Amendment 1 (23-Sep-2019)

The protocol was amended primarily to include the possibility of home visit at Visit 3 (Month 2-4) safety assessments for authorized Canadian sites only. In addition, other administrative and editorial changes required in the protocol were also updated. The main changes are captured in the table below. The rationale for all the changes is presented thereafter.

List of main changes in Protocol Amendment 1 (23-Sep-2019) and their rationale

Section # and Name	Description of Change	Brief Rationale
Footnote for Section 1 Overall design, Table 1: Schedule of Activities and Figure 1 Study design overview	Possibility of home visit at Visit 3 (Month 2-4) safety assessment, for authorized Canadian sites only.	Home visits will be allowed only in Canada as permitted by local regulations. This provision is allowed only for sites with an approved site level Standard Operating Procedure (SOP). Sites without an appropriate approved SOP will not be permitted to perform home visits. This possibility should reduce the subject withdrawal rate from the study and reduce logistical burden of subjects' parent(s)/legally acceptable representatives (LARs). Sites from other participating countries are not permitted for home visits.
Table 6: Contact information for emergency unblinding	Deletion of a decommissioned fax number (for North America and Puerto Rico) from contact information for emergency unblinding.	To ensure the appropriate contact information is presented in the protocol and non-functional emergency contact number is deleted.

Detailed description of Protocol Amendment 1:

Title page: Changes in the name of co-ordinating author and list of contributing authors.

- Co-ordinating author: PPD ***, Scientific Writer (SW),***
- PPD ***, Clinical & Epidemiology Project Lead (CEPL),***
- PPD ***, Clinical Research and Development Lead (CRDL),***
- PPD ***, Study Delivery Lead (SDL).***

Section 1 Overall design, Table 1 Schedule of activities and Figure 1 Study design overview: a footnote was added, as home visits will be allowed only in Canada as permitted per local regulations. The provision is allowed specifically for sites in Canada with an approved site level Standard Operating Procedure (SOP). Sites without an appropriate approved SOP will not be permitted to perform home visits. This possibility should reduce the subject withdrawal rate from the study and reduce logistical burden of subjects' parent/LAR.

- ***For authorized sites in Canada only, with approved site level standard operating procedures (SOP): Safety assessments scheduled at Visit 3 (Month 2-4) may take place at the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.***

Section 1 Synopsis (Study rationale), Section 3 Introduction, Table 4 Study groups, treatments and epoch foreseen in the study, Table 5 Treatments administered and Section 12.1.2 Glossary of terms: the definition of HRV PCV-free was added**.**

- ***HRV PCV-free: No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.***

Section 6.3 Criteria for temporary delay for enrollment and vaccination: the word ***subsequent vaccination*** has been added.

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

Acute disease and/or fever at the time of enrollment/***subsequent vaccination***. Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral, the axillary or the rectal. Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

Table 6 Contact information for emergency unblinding: Deletion of decommissioned fax number (for North America and Puerto Rico) from contact information for emergency unblinding:

GSK Helpdesk 24/24 hour and 7/7-day availability
The Helpdesk is available by phone, fax and email Phone: PPD For Canada, US and Puerto Rico Toll-free number: PPD Fax: PPD ~~Fax (North America and Puerto Rico):~~ PPD email: PPD

Section 7.4.1: Storage and handling of study vaccines and Table 5: Treatments administered: text was updated to clarify that details about storage and handling of vaccines can also be found in the SPM.

Rationale:

- In Table 5: Treatments administered, the words ***"storage, handling and"*** were added in the footnote referring to the study procedure manual. The sentence will be read as "[#]Refer to the study procedure manual (SPM) for ***storage, handling and*** preparation methods".
- In Section 7.4.1 Storage and handling of study vaccines, in the description section for Liquid formulation of PCV-free HRV vaccine, the words ***storage, handling,*** were missing. To provide better clarity the same have been added. The sentence will be read as "Refer to the Module on Clinical Trial Supplies in the SPM for detailed instructions on the ***storage, handling***, thawing, preparation and administration of the frozen PCV-free HRV vaccine".

Table 9 Contact information for reporting of serious adverse events: for uniformity, the word *Canadian* has been replaced by *Canada.*

Study contact for questions regarding SAEs
Refer to the local study contact information document
Back-up study contact for reporting SAEs
24/24 hour and 7/7-day availability: **GSK Clinical Safety & Pharmacovigilance**
Outside US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD Canad~~*ian*~~ sites only: Fax: PPD

Section 12.1.1: List of abbreviations: The term SOP and the expansion Standard Operating Procedure was added.