Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention	*Porcine circovirus* (PCV)-free liquid formulation of GSK oral live attenuated human rotavirus (HRV) vaccine (444563)
Other study intervention	Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells)
eTrack study number and abbreviated title	218485 (ROTA-098)
EudraCT number	2022-000708-36
Date of protocol	20 January 2023
Date of protocol amendment	Amendment 1 Final: 25 Oct 2023
Title	A phase III, open-label, randomized, controlled study to evaluate the immunogenicity and safety of inactivated poliovirus vaccine (IPV) when co-administered with *Porcine circovirus* (PCV)-free liquid formulation of an oral live attenuated human rotavirus (HRV) vaccine in healthy Chinese infants.
Brief title	A study on the immunogenicity and safety of inactivated poliovirus vaccine (IPV) when co-administered with *Porcine circovirus* (PCV)-free liquid formulation of an oral live attenuated human rotavirus (HRV) vaccine in healthy Chinese infants.
Sponsor signatory	Md Ahsan Habib, Clinical Project Lead, Live viral vaccines

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.3

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by 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.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-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 ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative (LAR).
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) 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 study.
- 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 intervention(s), and more generally about their 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 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 all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	218485 (ROTA-098)
EudraCT number	2022-000708-36
Date of protocol	20 January 2023
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Title	A phase III, open-label, randomized, controlled study to evaluate the immunogenicity and safety of inactivated poliovirus vaccine (IPV) when co-administered with *Porcine circovirus* (PCV)-free liquid formulation of an oral live attenuated human rotavirus (HRV) vaccine in healthy Chinese infants.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)
Rue de l'Institut, 89
1330 Rixensart
Belgium

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: refer to Section 8.3.3.1.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	25 Oct 2023
Original Protocol	20 January 2023

Amendment 1 (25 Oct 2023)

Overall rationale for the current Amendment: The distribution of the paper diary only at the first visit, followed by its return at the last visit, carries the risk of loss of the dairy card/incorrect data entry. Hence, distributing the paper diaries at each visit for intervention, and their return at the subsequent visit, would remediate the risk of loss of the dairy card and the corresponding solicited data between two visits. For this reason, the protocol is currently being amended.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.3: Schedule of activities	Paper dairy card to be distributed at each visit for intervention and be collected at the next visit	To remediate the risk of loss of the dairy card and solicited data between two visits
Throughout the document	The term “SPM” or “Study Procedures Manual” has been replaced with “Pharmacy Manual”	To align with the current protocol template

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale: GlaxoSmithKline Biologicals SA's (GSK) *Rotarix* liquid vaccine is currently approved in all European Economic Area (EEA) countries, United Kingdom (UK), United States (US), Japan, as well as over 90 other countries. GSK intends to register *Rotarix Porcine circovirus* (PCV)-free liquid vaccine (hereafter referred as *Rotarix* PCV-free) in China. "PCV-free" is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

In China, under the National Immunization Programme (NIP), a 3-dose primary vaccination against poliovirus is currently recommended during the first year of life in a 2, 3 and 4 months of age schedule and a booster vaccine is recommended at 4 years of age. Inactivated poliovirus vaccine (IPV) is used for the first 2 doses, and oral poliovirus vaccine (OPV) is used for the third and the fourth dose.

This study is designed to evaluate the immunogenicity and safety of IPV when co-administered with *Rotarix* PCV-free, in healthy Chinese infants.

Objectives, endpoints and estimands: See Table 5-Study objectives and endpoints from Section 3.

1.2. Schema

See Figure 1 from Section 4.1.

1.3. Schedule of Activities (SoA)

Table 1 SoA for Co-administration group

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3 [a]	Visit 4	Visit 5 [a]	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Informed consent by parent(s)/LAR(s)	●							See Section 10.1.3 for details
Check inclusion/exclusion criteria	●							See Section 5.1 for Inclusion criteria and Section 5.2 for Exclusion criteria
Collect demographic data and gestational age	●							See Section 8.2.1.1 for more information
Medical and vaccination history	●							See Section 8.2.1.2 for more information
Physical examination	●							See Section 8.2.1.3 for more information
Measure/record height and weight	●							See Section 8.2.1.3 for more information
Study intervention								
Check contraindications, warnings and precautions to study intervention administration		●		●		●		See Sections 7.1.1 and 8.2.1.4 for more information
Randomization	●							See Section 6.3 for more information
Check criteria for temporary delay for enrolment and/or study intervention administration	O	O		O		O		See Section 5.5 for more information
Study group and intervention number allocation	O							See Sections 6.3.2 and 6.3.3 for more information
Allocation of treatment number for subsequent dose				●		●		See Section 6.3.3 for more information
Body temperature before study intervention administration		●		●		●		See Section 8.2.1.3 for more information. The preferred route for measuring temperature will be axillary. Fever is defined as temperature ≥37.5°C

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3 [a]	Visit 4	Visit 5 [a]	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Administration of study intervention: *Rotarix* PCV-free		●		●				See Section 6.1 for more information
Administration of study intervention: IPV		●		●		●		See Section 6.1 for more information
Recording of administered intervention number		●		●		●		
Recording of regurgitation/vomiting		●		●				If regurgitation or vomiting occurs within 30 minutes after study intervention administration, administration of a replacement dose is not recommended. This information on regurgitation or vomiting should be recorded in the electronic Case Report Form (eCRF). The participant should continue to participate in the study
Distribution of 'Participant card'		O						See Section 8.3.5 for more information
Distribution of diary cards		●		●				
Laboratory Assessment								
Blood sampling for antibody determination (at least 2 mL)		●^				●^	●	^Blood sampling to be done before study intervention administration. Volume of the blood sample should be between 2 and 2.5 mL. See Section 8.1.1 for more information
Safety assessments								
Record any concomitant medications/vaccinations		●	●*	●	●*	●	●	See Section 6.8 for more information
Recording of solicited events post Dose 1 and Dose 2 of study intervention administration (Days 1-14*)		●		●				See Section 10.3.3 and Section 10.3.6.1 for more information
Recording of unsolicited AEs after each dose of *Rotarix* administration (Days 1-31)		●	●*	●	●*	●		See Section 10.3.4 and Section 10.3.6.1 for more information

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3 [a]	Visit 4	Visit 5 [a]	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Record any intercurrent medical conditions [b]		●	●*	●	●*	●	●	See Section 9 for more information
Recording of AEs that led to withdrawal from study	●	●	●*	●	●*	●	●	See Section 10.3.6.1 for more information.
Recording of SAEs	●	●	●*	●	●*	●	●	See Section 10.3.6.1 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●*	●	●*	●	●	See Section 10.3.6.1 for more information. The collection and reporting periods start once the participants' parents/LARs informed consent is obtained
Return of diary cards				●		●		
Diary card transcription by investigator or designee				●		●	●	
Study Conclusion							●	See Section 4.4 for more information

AE: Adverse Event; IPV: Inactivated poliovirus vaccine; LAR: Legally Acceptable Representative; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used; SAE: Serious Adverse Event; mL: milliliter

● is used to indicate a study procedure that requires documentation in the individual eCRF.

●* is used to indicate documentation activity that does not involve any site visit. These activities can be recorded by the participant and will be collected at the next site visit.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

[a] Visit 3 and Visit 5 are not applicable for the Co-administration group.

[b] immunosuppressive or immunodeficient conditions.

Note: Details of COVID-19 infection-related signs and symptoms should also be recorded in a separate eCRF page.

*Number of days for recording of solicited events after each dose of study intervention is defined by Chinese authorities [NMPA, 2019a].

Table 2 SoA for Staggered group

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Informed consent by parent(s)/LAR(s)	●							See Section 10.1.3 for details
Check inclusion/exclusion criteria	●							See Section 5.1 for Inclusion criteria and Section 5.2 for Exclusion criteria
Collect demographic data and gestational age	●							See Section 8.2.1.1 for more information
Medical and vaccination history	●							See Section 8.2.1.2 for more information
Physical examination	●							See Section 8.2.1.3 for more information
Measure/record height and weight	●							See Section 8.2.1.3 for more information
Study intervention								
Check contraindications, warnings and precautions to study intervention administration	●	●	●	●		●		See Sections 7.1.1 and 8.2.1.4 for more information
Randomization	●							See Section 6.3 for more information
Check criteria for temporary delay for enrolment and study intervention administration	O	O	O	O		O		See Section 5.5 for more information
Study group and intervention number allocation	O							See Sections 6.3.2 and 6.3.3 for more information
Allocation of treatment number for subsequent dose		●	●	●		●		See Section 6.3.3 for more information
Body temperature before study intervention administration	●	●	●	●		●		See Section 8.2.1.3 for more information. The preferred route for measuring temperature will be axillary. Fever is defined as temperature ≥ 37.5°C
Administration of study intervention: *Rotarix* PCV-free	●		●					See Section 6.1 for more information

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Administration of study intervention: IPV		●		●		●		See Section 6.1 for more information
Recording of administered intervention number	●	●	●	●		●		
Recording of regurgitation/vomiting	●		●					If regurgitation or vomiting occurs within 30 minutes after study intervention administration, administration of a replacement dose is not recommended. This information on regurgitation or vomiting should be recorded in the eCRF. The participant should continue to participate in the study
Distribution of 'Participant card'	O							See Section 8.3.5 for more information
Distribution of diary cards	●	●	●	●				
Laboratory Assessment								
Blood sampling for antibody determination (at least 2 mL)	●^				●		●	^Blood sampling before study intervention administration. Volume of the blood sample should be between 2 and 2.5 mL See Section 8.1.1 for more information
Safety assessments								
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	See Section 6.8 for more information
Recording of solicited events post Dose 1 and Dose 2 of study intervention (Days 1-14*)	●	●	●	●	●			See Section 10.3.3 and Section 10.3.6.1 for more information
Recording of unsolicited AEs after each dose of *Rotarix* administration (Days 1-31)	●	●	●	●	●			See Section 10.3.4 and Section 10.3.6.1 for more information
Record any intercurrent medical conditions [a]	●	●	●	●	●	●	●	See Section 9 for more information

Age at time of study enrolment	6-10 weeks							Notes
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	
Timepoints	Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3.5	
Recording of AEs that led to withdrawal from study	●	●	●	●	●	●	●	See Section 10.3.6.1 for more information.
Recording of SAEs	●	●	●	●	●	●	●	See Section 10.3.6.1 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	See Section 10.3.6.1 for more information. The collection and reporting periods start once the participants' parents/LARs informed consent is obtained.
Return of diary cards		●	●	●		●		
Diary cards transcription by investigator or designee		●	●	●	●	●		
Study Conclusion							●	See Section 4.4 for more information

AE: Adverse Event; IPV: Inactivated poliovirus vaccine; LAR: Legally Acceptable Representative; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used; SAE: Serious Adverse Event; mL: milliliter

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

[a] immunosuppressive or immunodeficient conditions.

Note: Details of COVID-19 infection-related signs and symptoms should also be recorded in a separate eCRF page.

*Number of days for recording of solicited events after each dose of study intervention is defined by Chinese authorities [NMPA, 2019a].

Table 3 Intervals between study visits for Co-administration group

Interval	Optimal interval	Allowed interval range	Allowed interval during special circumstances[#]
Visit 1→Visit 2	15 days	14-18 days between study enrolment and Dose 1 of IPV and *Rotarix* PCV-free	14-45 days
Visit 2→Visit 4	30 days	28-36[†] days between Dose 1 of IPV and *Rotarix* PCV-free and Dose 2 of IPV and *Rotarix* PCV-free	28-60 days
Visit 4→Visit 6	30 days	28-36[†] days between Dose 2 of IPV and *Rotarix* PCV-free and Dose 3 of IPV and BS for assessment of Rotavirus Ab, IgA	28-60 days
Visit 6→Visit 7	30 days	30-36[†] days between Dose 3 of IPV and BS for assessment of anti-poliovirus types 1, 2 and 3 Ab	30-60 days

Ab: Antibody; BS: Blood sampling; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; PCV: Porcine circovirus; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used

[†] Participants will not be eligible for inclusion in the Per Protocol Set for immunogenicity if they make the study visit outside this interval. Interval is computed as the difference between the 2 dates of the study procedure.

[#] Refer to Section 8 for more details on special circumstances (e.g., COVID-19 pandemic).

Table 4 Intervals between study visits for Staggered group

Interval	Optimal interval	Allowed interval range	Allowed interval during special circumstances[#]
Visit 1→Visit 2	15 days	14-18[†] days between Dose 1 of *Rotarix* PCV-free and Dose 1 of IPV	14-45 days
Visit 1→Visit 3	30 days	28-36[†] days between Dose 1 and Dose 2 of *Rotarix* PCV-free	28-60 days
Visit 2→Visit 4	30 days	28-36[†] days between Dose 1 and Dose 2 of IPV	28-60 days
Visit 3→Visit 5	30 days	28-36[†] days between Dose 2 of *Rotarix* PCV-free and BS for assessment of Rotavirus Ab, IgA	28-60 days
Visit 4→Visit 6	30 days	28-36[†] days between Dose 2 and Dose 3 of IPV	28-60 days
Visit 6→Visit 7	30 days	30-36[†] days between Dose 3 of IPV and BS for assessment of anti-poliovirus types 1, 2 and 3 Ab	30-60 days

Ab: Antibody; BS: Blood sampling; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used

[†] Participants may not be eligible for inclusion in the Per Protocol Set for immunogenicity if they make the study visit outside this interval. Interval is computed as the difference between the 2 dates of the study procedure.

[#] Refer to Section 8 for more details on special circumstances (e.g., COVID-19 pandemic).

2. INTRODUCTION

2.1. Study rationale

GSK's *Rotarix* liquid vaccine is currently approved in all EEA countries, UK, US, Japan, as well as over 90 other countries. GSK intends to register *Rotarix* PCV-free liquid vaccine (hereafter referred as *Rotarix* PCV-free) in China. "PCV-free" is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

In China, under the NIP, a 3-dose primary vaccination against poliovirus is currently recommended during the first year of life in a 2, 3 and 4 months of age schedule and a booster vaccine is recommended at 4 years of age. IPV is used for the first 2 doses, and OPV is used for the third and the fourth dose.

This study is designed to evaluate the immunogenicity and safety of IPV when co-administered with *Rotarix* PCV-free, in healthy Chinese infants.

2.2. Background

RV infects almost every child before they reach the age of 3 to 5 years and is the leading cause of acute gastroenteritis (GE) and diarrhea, which can lead to severe dehydration [Atherly, 2009]. Prior to the introduction of RV vaccines in 2006, RV was accountable for an estimated 528 000 deaths worldwide annually, with the largest number of deaths occurring in the Sub-Saharan Africa region [WHO position paper, 2021; Tate, 2016; Bányai, 2018]. In 2013, several years after the launch of RV vaccines, it has been estimated that approximately 215 000 deaths (95% confidence interval [CI]: 197 000, 233 000) were caused by RV infection. India, Nigeria, Pakistan, and Democratic Republic of Congo accounted for approximately half (49%) of all the estimated RV deaths in 2013 [Dennehy, 2008; Tate, 2016]. In China, 42.6% of all the hospitalizations for severe GE, 32.5% of outpatient visits for diarrhea and 9.3% of all diarrhea episodes in community settings are caused by RV [Fu, 2018].

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 RVGE-associated fatality rates are high among children aged <5 years (e.g., South and South-Eastern Asia and Sub-Saharan Africa) [WHO position paper, 2021].

GSK HRV vaccine (*Rotarix*) is registered in around 130 countries and more than 790 million doses of the vaccine (lyophilized and liquid formulations) are estimated to have been distributed worldwide from its launch until July 2022.

Please refer to the current investigator's brochure (IB) for information regarding the preclinical studies, clinical studies and epidemiology studies of *Rotarix* vaccine.

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of *Rotarix* can be found in the IB and of IPV can be found in the Prescribing Information (PI).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 5 Study objectives, endpoints and estimands

Objectives	Endpoints and estimands
Primary (Confirmatory)	
• To demonstrate the immunological non-inferiority of IPV when co-administered with *Rotarix* PCV-free compared with IPV administered alone.	• Anti-poliovirus types 1, 2 and 3 neutralizing Ab seroconversion rate* 1 month post Dose 3 of IPV in the Co-administration and Staggered groups.
Secondary (Descriptive)	
• To evaluate the immunogenicity of IPV when co-administered with *Rotarix* PCV-free and when administered alone.	• Anti-poliovirus types 1, 2 and 3 neutralizing Ab GMTs at 1 month post Dose 3 of IPV in the Co-administration and Staggered groups. • Percentage of participants with anti-poliovirus types 1, 2 and 3 neutralizing Ab titers ≥1:8 and ≥1:64 at 1 month post Dose 3 of IPV in the Co-administration and Staggered groups.
• To evaluate the immunogenicity of *Rotarix* PCV-free when co-administered with IPV and when administered alone.	• Anti-RV IgA Ab seroconversion rate** 1 month post Dose 2 in the Co-administration and Staggered groups. • Anti-RV IgA Ab GMCs at 1 month post Dose 2 of *Rotarix* PCV-free in the Co-administration and Staggered groups. • Percentage of participants with anti-RV IgA Ab concentrations ≥90 U/mL at 1 month post Dose 2 of *Rotarix* PCV-free in the Co-administration and Staggered groups.
• To evaluate the reactogenicity of *Rotarix* PCV-free and IPV in terms of solicited systemic events. • To assess the safety of *Rotarix* PCV-free in terms of unsolicited AEs and serious adverse events (SAEs) and safety of IPV in terms of SAEs.	• Solicited AEs – For each solicited systemic event, percentage of participants reporting the occurrence of the event within 14 days (Day 1- Day 14) after Dose 1 and Dose 2 of *Rotarix* and IPV • Unsolicited AEs – Percentage of participants reporting the occurrence of unsolicited AEs within 31 days (Day 1- Day 31) after each dose of *Rotarix*, according to the MedDRA classification. • SAEs: – Percentage of participants reporting SAEs from the first dose of the study intervention up to study end in the Co-administration and Staggered groups.

Ab: Antibody; GMC: Geometric mean Ab concentration; GMT: Geometric mean Ab titer; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; MedDRA: Medical Dictionary for Regulatory Activities; mL: milliliter; PCV: *Porcine circovirus*; SAE: Serious Adverse Event; U: Unit

*Seroconversion rate for IPV neutralizing Ab is defined as percentage of participants with

- Titer ≥1:8 at 1 month after 3 dose primary schedule of IPV in participants with titer <1:8 pre-vaccination
- Titer ≥4-fold increase in titer 1 month after 3 dose primary vaccination schedule in participants with titer ≥1:8 pre-vaccination.
  Note: the 4-fold increase will take into consideration the expected decline in maternal antibodies with estimated half-life of 28 days.

**Seroconversion rate for anti-RV IgA Ab is defined as the percentage of participants who were initially seronegative (i.e., with anti-RV IgA Ab concentration <20 U/mL prior the first dose of *Rotarix*) and developed anti-RV IgA Ab concentration ≥20 U/mL at 1 month post Dose 2.

Refer to Section 8 for details on SAEs.

Refer to Section 9.3 and Section 9.4 for additional details on statistical analyses.

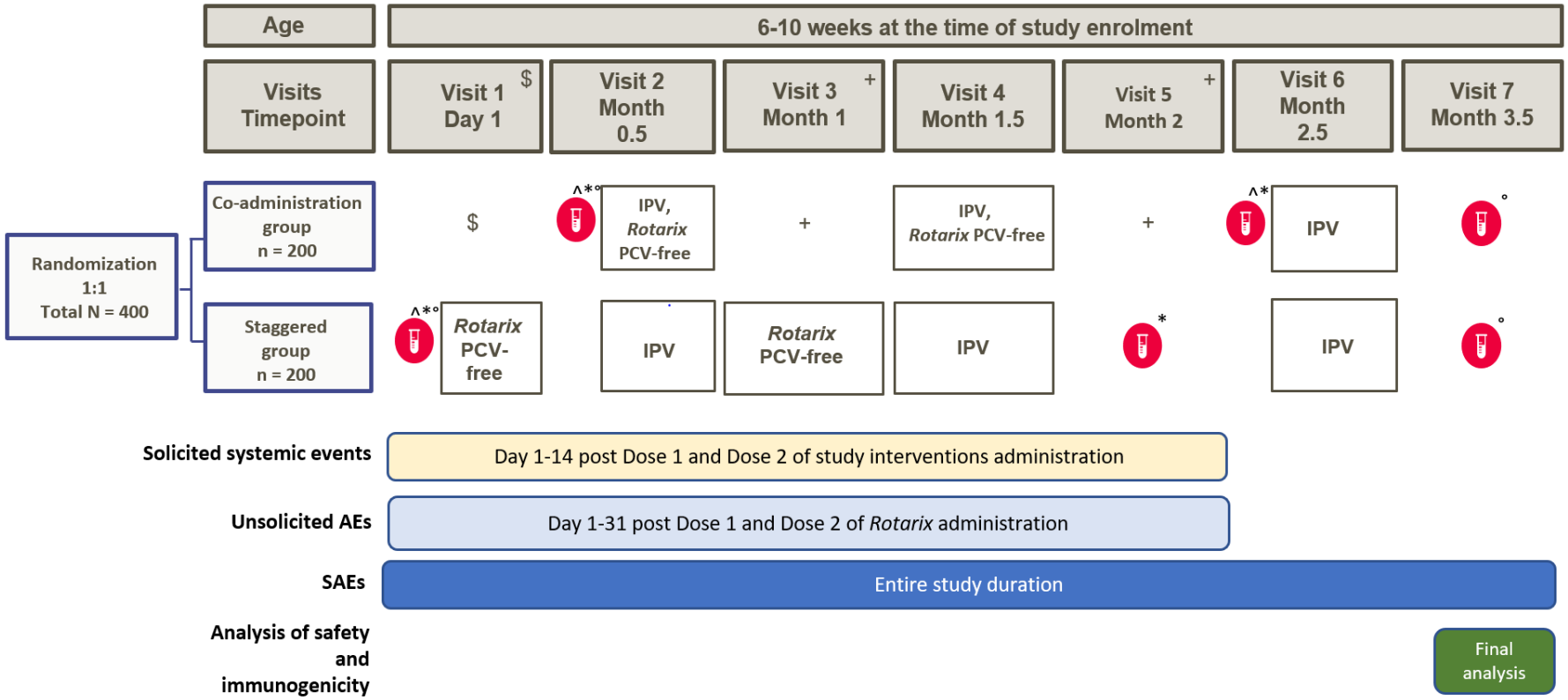
Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

4. STUDY DESIGN

4.1. Overall design

The study design is presented in Figure 1.

Figure 1 Study design overview



AE: Adverse Event; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used; SAE: Serious Adverse Event; N: Total number of participants planned to be enrolled; n: Planned number of participants in each group.
Study interventions: IPV (Co-administered vaccine) and *Rotarix* PCV-free (Study vaccine).
$ Refer to the Schedule of activities (SoA; Section 1.3) for Co-administration group. Note: For the Co-administration group, unsolicited AEs will be collected from visit 2 till visit 6.
+ Visit not applicable for participants in the Co-administration group.
^ Blood sampling to be done before study intervention administration.
° Blood sample for anti-poliovirus types 1, 2 and 3 antibodies measurement.
* Blood sample for anti-RV IgA antibody measurement.

- **Experimental design**: Phase III, open-label, randomized, controlled study with 2 groups (see Figure 1).
- **Duration of the study**: The total duration of the study, per participant, will be approximately 3.5 months.
- **Control**: active comparator, i.e., staggered administration of licensed IPV and *Rotarix* PCV-free.
- **Blinding**: Open-label. Refer to Section 6.3.4 for details.
- **Data collection**: Standardized electronic Case Report Form (eCRF). Solicited systemic events will be collected using a diary card. Refer to Section 10.3.6.1 for details on recording and follow-up of SAEs.
- **Primary Completion Date (PCD):** Visit 7 (Month 3.5).
- **End of Study (EoS):** EoS is defined as last subject last visit (LSLV) (Visit 7) or date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV. Refer to Section 4.4 for details.

Table 6 Study groups, intervention and blinding

Study groups	Number of participants	Age (Min-Max)	Study interventions	Blinding
Co-administration	200	6-10 weeks*	IPV, *Rotarix* PCV-free	Open-label
Staggered	200	6-10 weeks*	IPV, *Rotarix* PCV-free	Open-label

IPV: Inactivated poliovirus vaccine; Max: maximum; Min: minimum; PCV: *Porcine circovirus*
* 6-10 weeks at the time of study enrolment

4.2. Scientific rationale for study design

In China, under the NIP, a 3-dose primary vaccination against poliovirus is currently recommended during the first year of life in a 2, 3 and 4 months of age schedule. *Rotarix* should be given in a 2-dose schedule between 6-24 weeks of age with an interval of at least 4 weeks between doses. Till date, there is no data available on the immunogenicity and safety of IPV when co-administered with *Rotarix* PCV-free, in healthy Chinese infants.

The current study is therefore designed to assess the immunogenicity and safety of IPV when it is co-administered with *Rotarix* PCV-free, compared to administration of the vaccines separately. There are 2 parallel arms:

- **Co-administration group:** participants will receive *Rotarix* PCV-free co-administered with IPV at Month 0.5 and Month 1.5, and IPV at Month 2.5.
- **Staggered group:** participants will receive *Rotarix* PCV-free at Day 1 and Month 1, and IPV at Month 0.5, Month 1.5, and Month 2.5.

The study will enroll infants 6-10 weeks of age. This will ensure compliance with the recommendations mentioned below, including for participants of the Co-administration group who will receive the first dose of *Rotarix* and IPV at 2 weeks after enrolment:

- As per CDC recommendation, the first dose of *Rotarix* should be given before an infant is 15 weeks of age and the second dose before they turn 8 months old.
- As per EU SmPC recommendation, the first dose of *Rotarix* may be administered from 6 weeks of age. There should be an interval of at least 4 weeks between doses. The second dose should preferably be given before 16 weeks of age but must be completed by the age of 24 weeks.
- In China, IPV is recommended as 2 doses at the age of 2 and 3 months and no later than 13 weeks of age for the first dose.

Please refer to the IB for further information on *Rotarix*.

Please refer to the PI for further information on Beijing Biological Products Institute Co.,Ltd. IPV.

4.3. Justification for dose

Two oral doses of *Rotarix* PCV-free will be administered at approximately 1 month interval to participants, according to the immunization schedule of *Rotarix* licensed outside of China.

Three doses of IPV will be administered in a 2, 3 and 4 months of age schedule, according to the recommended schedule for vaccination against poliovirus in China.

4.4. EoS definition

A participant is considered to have completed the study if the participant returns for the last visit or is available for the last scheduled procedure as described in the protocol.

EoS is defined as LSLV (Visit 7) or date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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

- Participants' parent(s)/Legally Acceptable Representative(s) (LAR), who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
- Healthy participants as established by medical history and clinical examination before entering into the study.
- A male or female of Chinese origin, between and including, 6 and 10 weeks (42-76 days) of age at the time of study enrolment.
- Born after a gestation period of 36 to 42 weeks inclusive.

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- History of severe combined immunodeficiency.
- History of seizures or progressive neurological disease.
- Family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception (IS).
- History of IS.
- Major congenital defects, or serious chronic illness as assessed by the investigator.
- Any contraindications to IPV.
- Previous confirmed occurrence of rotavirus gastroenteritis (RVGE).
- History of poliomyelitis.
- Participants with confirmed or suspected Coronavirus Disease 2019 (COVID-19).

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions (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 interventions administration*, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study and other licensed routine childhood vaccinations.
  - *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced if, necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Administration of long-acting immune-modifying drugs from birth or planned administration at any time during the study period (e.g., infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives 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 milligram/kilogram (kg)/day, or equivalent. Inhaled, intra-articular and topical steroids are allowed.
- Previous vaccination against RV.
- Previous vaccination against poliomyelitis.

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug, vaccine or invasive medical device).

5.2.4. Other exclusions

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

5.3. Lifestyle considerations

This section is not applicable.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not entered in the study/randomized to a study intervention.

Limited data for screening failures (including reason for screening failure) will be collected and reported in the eCRF.

5.5. Criteria for temporarily delaying enrolment and/or study intervention administration

Enrolment/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Non-rotavirus GE within 7 days preceding the study intervention administration.
- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA (Section 1.3) for fever definition and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or vaccinated at the discretion of the investigator.
- Participants with known COVID-19 positive contacts within the past 14 days.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 7 Study interventions administered

Study intervention name:	Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) (IPV)	*Rotarix* PCV-free (HRV PCV-free)
Study intervention formulation:	CCI [redacted] CCI [redacted]	HRV RIX4414 CCI [redacted] Sterile water
Presentation:	CCI [redacted]	CCI [redacted]
Type:	Co-administered	Study
Product category:	Combination product*	Combination product*
Route of administration:	Intramuscular	Oral
Administration site:		
• **Location**	Refer to the Pharmacy Manual for more details	NA
• **Directionality**	Refer to the Pharmacy Manual for more details	NA
• **Laterality**	Refer to the Pharmacy Manual for more details	NA
Number of doses to be administered:	3	2
Volume to be administered by dose:	0.5 mL	1.5 mL
Packaging and labeling:	Refer to the Pharmacy Manual for more details	Refer to the Pharmacy Manual for more details
Manufacturer:	Beijing Biological Products Institute Co.,Ltd.	GSK

DAgU: D antigen unit; HRV: human rotavirus; IPV: inactivated poliovirus vaccine; mL: milliliter; NA: Not applicable; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used
*Combining a biological product and device
Refer to Section 6.1 for schedule of study intervention administration.

Study participants must be observed closely for at least 30 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.2. Preparation, handling, storage, and accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the Pharmacy Manual for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to each study center.

6.3.2. Randomization to study intervention

Approximately 400 eligible participants will be randomly assigned (1:1) to the 2 study groups (Co-administration and Staggered).

The numbering of *Rotarix* PCV-free and IPV supplies will be performed at GSK, using a block scheme randomization in MATerial EXcellence, a program developed 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 in this study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

6.3.3. Intervention allocation to the participant

The system's randomization algorithm will use a minimization procedure accounting for center and the study as a whole as minimization factors. Minimization factors will have equal weight in the minimization algorithm.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (Source Data Base for Internet Randomization [SBIR]).

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

Refer to the Pharmacy Manual for additional information about the study intervention number allocation.

6.3.4. Blinding and unblinding

The study will be conducted in an open-label manner with respect to *Rotarix* PCV-free and IPV.

6.4. Study intervention compliance

Study intervention administration will be performed under medical supervision. The date of each dose administered in the study center will be recorded in the source documents and in the eCRF.

6.5. Dose modification

This section is not applicable.

6.6. Continued access to study intervention after the end of the study

This section is not applicable.

6.7. Treatment of overdose

This section is not applicable.

6.8. Concomitant therapy

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

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 following each dose of study interventions (Day 1 to Day 31).
- All concomitant vaccinations from Visit 1 up to the Visit 7 (blood sample visit).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines (Please refer to the sections 5.2.2 and 9.2.1 for further details).

- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the study intervention administration) e.g., an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥37.5°C. The preferred location for measuring temperature in this study will be the axilla].
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.3.1 and 10.3.6.1. These must also be recorded in the Expedited AE report.

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTIONS AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study interventions

'Discontinuation' of study interventions refers to any participant who has not received all planned doses of the study interventions. A participant who discontinued the study interventions may continue other study procedures (e.g., safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study interventions will be documented on the eCRF as follows:

- AE requiring expedited reporting to GSK
- Unsolicited nonserious AE
- Solicited AE
- Protocol deviation
- Not willing to be vaccinated
- Migrated/moved from study area
- Other (specify).

7.1.1. Contraindications to subsequent study interventions administration

The eligibility for subsequent study interventions administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in Section 5.2.1, Section 5.2.2, Section 5.2.3 and Section 5.2.4 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.6.3). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Anaphylaxis following the administration of study interventions.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for them since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who did not return for the concluding visit planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- Adverse events requiring expedited reporting to GSK (please refer to the section 10.3.8.1 for the details)
- Unsolicited nonserious AE
- Solicited AE
- Protocol deviation
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up

- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because the participant's parent(s)/LAR(s) has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.6.3).

7.3. Lost to follow-up

Participants will be considered 'lost to follow-up' if their parent(s)/LAR(s) fail to return for scheduled visits and cannot be contacted by the study site.

Please refer to the Pharmacy Manual for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the SoA (Section 1.3). 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 the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g., hematologic profiles), and obtained before the participant's parent(s)/LAR(s) signed the Informed Consent Form (ICF), may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA [Section 1.3]).

The Pharmacy Manual provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

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:

- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol, then the interval may be extended up to a maximum length of 60 days (see Table 3 and Table 4).
- If despite best efforts it is not possible to administer Dose 2 of *Rotarix* PCV-free according to the intervals defined in Table 3 and Table 4, a maximum age of 24 weeks as per the label used outside of China may be used.

  *It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets International Council on Harmonization (ICH) Good Clinical Practice (GCP) requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 5, 10 February 2022) for more details.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant's parent(s)/LAR(s).

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

Per participant, an overall volume of at least 6 mL (not more than 7.5 mL) will be collected during the entire study period. Refer to Table 8 and SoA (Section 1.3) for details of volumes collected for different assessments.

Table 8 Biological samples

Group	Sample type	Quantity	Unit	Timepoint
Co-administration	Blood*	At least 2**	mL	Visit 2 (Month 0.5)
				Visit 6 (Month 2.5)
				Visit 7 (Month 3.5)
Staggered group	Blood*	At least 2**	mL	Visit 1 (Day 1)
				Visit 5 (Month 2)
				Visit 7 (Month 3.5)

mL: milliliter
*Blood sampling to be done before study intervention administration.
**Volume of the blood sample should be between 2 and 2.5 mL.

8.1.2. Laboratory assays

Table 9 Laboratory assays

Test Classification	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	Rotavirus Ab, IgA	ELISA	GSK designated lab in China
		IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3	Microneutralization assay	GSK designated lab in China

Ab: Antibody; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; ELISA: Enzyme Linked Immunosorbent Assay
*Refer to the list of clinical laboratories for details.

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

8.1.3. Immunological read-outs

Table 10 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-first Dose administration	Staggered group	200	Rotavirus Ab, IgA IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3
Visit 2 (Month 0.5)	Pre-first Dose administration	Co-administration group	200	Rotavirus Ab, IgA IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3
Visit 5 (Month 2)	Post Dose 2 of *Rotarix* PCV-free	Staggered group	200	Rotavirus Ab, IgA
Visit 6 (Month 2.5)	Post Dose 2 of *Rotarix* PCV-free	Co-administration group	200	Rotavirus Ab, IgA
Visit 7 (Month 3.5)	Post Dose 3 of IPV	All participants (Co-administration group + Staggered group)	400	IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3

Ab: Antibody; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

8.1.4. Immunological correlates of protection

No recognized immunological correlate of protection (CoP) has been established for the antigen used as part of the HRV vaccine. However, an analysis by Cheuvart et al. in 2014 showed that post-vaccination anti-RV IgA seropositivity (Ab concentration ≥ 20 U/mL, measured by ELISA) is a correlate of vaccine efficacy in clinical trials of *Rotarix* [Cheuvart, 2014]. This was confirmed by an independent research group in 2020 [Baker, 2020].

Antibodies against poliovirus types 1, 2 and 3 will be determined by a virus microneutralization test adapted from the WHO Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO position paper, 1993]. Titers will be expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. The lowest dilution at which serum samples will be tested is 1:8. Antibody titers greater than or equal to 1:8 will be considered as protective.

The immunological assay results will be communicated to the investigator after the end of the study.

8.2. Safety assessments

The investigator(s) and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, or that caused the participant's withdrawal from the study interventions or study.

Note: Details of COVID-19 infection-related signs and symptoms will be recorded in a separate eCRF page.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Record demographic data such as date of birth including gestational age, gender, race and ethnicity in the participants' eCRF.

Collection of race and ethnicity data is necessary to meet the inclusion criteria of the study participants, and to determine if the study participants are truly representative of the impacted population.

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the parent(s)/LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention administration in the eCRF.

8.2.1.3. Physical examination

- Axillary body temperature* of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. If the participant has fever (defined as temperature ≥37.5°C) on the day of administration of the study intervention, the study visit will be rescheduled within the allowed interval for this visit (see Table 3 and Table 4).

  *Axilla is the preferred route to measure temperature in China. If temperature is taken by other routes, conversion can be made as per local guidelines:

  – Axillary temperature = oral temperature - 0.2℃;

  – Axillary temperature = rectal temperature - 0.3℃.
- Weight and height must be collected at Visit 1 and recorded in the eCRF.
- Physical examination at each study visit subsequent to the first study intervention administration visit will be performed only if the participant's 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 participant's health on the day of study intervention administration temporarily precludes dosing, 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.

8.2.1.4. Warnings and precautions to administration of study interventions

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention as specified in SoA (Section 1.3).

Refer to the approved product label/package insert.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

An overview of the protocol required reporting periods for safety information and for AEs/SAEs leading to withdrawal is given in Table 11 and Table 12.

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.8. 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 periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and if the investigator considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 13.

Table 11 Timeframes for collecting and reporting of safety information

Event	V1[+] D1	V2[+] M0.5	V3[+] M1	V4[+] M1.5	V5[+] M2	V6[+] M2.5	V7[+] (Study Conclusion) M 3.5
Solicited events Co-ad group		■	■	■	■		
Solicited events Staggered group	■	■	■	■	■		
Unsolicited AEs Co-ad group*		■	■	■	■	■	
Unsolicited AEs Staggered group*	■	■	■	■	■		
AEs that led to withdrawal from the study	■	■	■	■	■	■	■
SAEs	■	■	■	■	■	■	■
SAEs related to study participation** or concurrent GSK medication/ vaccine	■	■	■	■	■	■	■

AE: Adverse Event; Co-ad: Co-administration group; V: Visit; D: Day, M: Month; SAE: Serious Adverse Event
* Unsolicited AEs will be collected only post *Rotarix* administration.
** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant's parent(s)/LAR consents to participate in the study.
[+] Refer to Table 3 (for Co-administration group) and Table 4 (for Staggered group) for information about optimal interval.

8.3.2. Method of detecting AEs and SAEs

Detection and recording of AE/SAE are detailed in Section 10.3.6.1.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.7.

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of participants' parent(s)/LAR(s) is the preferred method of acquiring information related to an AE/SAE.

8.3.3. Regulatory reporting requirements for SAEs

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 12. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.7.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reaction (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Please refer to Section 10.3.8 for further details regarding the reporting of SAEs.

Table 12 Timeframes for submitting SAE and other events reports to GSK

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

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee).
‡‡ For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.3.3.1. Contact information for reporting SAEs

Table 13 Contact information for reporting SAEs

Study contact for questions regarding SAEs Refer to the local study contact information document
Back up study contact for reporting SAEs Available 24/24 hours and 7/7 days: **GSK Global Safety** Outside US & Canada sites: Email address: ogm28723@gsk.com

8.3.4. Treatment of expedited adverse events (SAE)

Any medication administered for the treatment of an SAE should be recorded in the Expedited AE Report of the participant's eCRF screen (refer to Section 10.3.8.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant's parent(s)/LAR(s) must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.3.6. Medical device deficiencies

Both study groups have study interventions that are a combination product constituted of a device CCI [redacted] and biologic product. Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

8.3.6.1. Detection, follow-up, and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or relatedness of the device deficiency to the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

Medical device deficiencies and any associated AE/SAEs for associated person (i.e., spouse, caregiver, site staff) will also be collected. The associated person will be provided with a safety reporting information and authorization letter.

Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.

8.3.6.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 10.6.3 for details of reporting.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements linked to the reporting of device deficiencies to the IRB/IEC.

8.4. Pharmacokinetics

This section is not applicable.

8.5. Genetics

This section is not applicable.

8.6. Biomarkers

This section is not applicable.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

This section is not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The study includes 1 confirmatory objective. The non-inferiority margin associated with the objective is provided in Table 14.

Table 14 Study objective and null hypothesis

Primary objective	Null hypothesis
• To demonstrate the immunological non-inferiority of IPV when co-administered with *Rotarix* PCV-free compared with IPV administered alone.	• The difference in seroconversion rate between the Co-administration group and (minus) the Staggered group is below -10% for at least 1 of the anti-poliovirus types 1, 2 and 3 Abs.

Ab: Antibody; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*

The global type I error will be 2.5%. The primary objective will be achieved if the lower limit of the 2-sided 95% CI for the group difference (Co-administration group minus Staggered group) in seroconversion rate is greater than or equal to -10% for each of the anti-poliovirus types 1, 2 and 3 antibodies.

9.2. Analysis sets

Table 15 Analysis sets

Analysis set	Description
Screened	All participants who were screened for eligibility.
Enrolled Set	• All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). • Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Set as they did not enter the study.
Exposed Set (ES)	All participants with at least 1 dose of any of the 2 study interventions documented. Analysis per group is based on the administered intervention.
Per Protocol Set (PPS)	All eligible participants from the ES who meet all the following requirements: • who received the study interventions according to their random assignment and the expected study intervention administration schedule (see Table 3 and Table 4), and without intercurrent conditions* that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. . • for anti-poliovirus types 1, 2 and 3 analyses at 1 month post Dose 3 of IPV, participants should have pre- and post-vaccination immunogenicity results for at least 1 antigen and should have complied with interval between IPV Dose 3 and the post IPV Dose 3 blood sample. • for anti-RV IgA analyses at 1 month post Dose 2 of *Rotarix* PCV-free, participants should have pre- and post-vaccination immunogenicity results and should have complied with the interval between *Rotarix* Dose 2 and the post *Rotarix* PCV-free Dose 2 blood sample.

* immunosuppressive or immunodeficient conditions identified before Visit 7.

9.2.1. Criteria for elimination from analysis

If a participant meets one of the criteria mentioned in Table 15 or ones listed in the Section 7.1.1, they may be eliminated from PPS.

9.3. Statistical analyses

The statistical analysis will be detailed in the statistical analysis plan (SAP), which will be developed and finalized prior to the first subject first visit (FSFV). This section is a summary of the planned main statistical analyses of the primary/secondary immunogenicity, reactogenicity and safety endpoints and the descriptive analyses of demography summaries.

The analysis of immunogenicity will be primarily based on the PPS. The analysis of safety will be based on the ES.

9.3.1. Primary endpoint analysis

The primary endpoints are described in Section 3. The Mittienen and Nurminen 95% CI for the group difference (Co-administration group minus Staggered group) in the seroconversion rate of anti-poliovirus types 1, 2 and 3 antibodies at Visit 7 will be computed. Refer to Section 9.1 for details on how this will be used to conclude whether the primary objective is reached.

9.3.2. Secondary immunogenicity endpoints analysis

The secondary endpoints are described in Section 3.

Anti-RV IgA Ab seroconversion rate and the percentage of participants with anti-RV IgA antibody concentration ≥90 U/mL at 1 month post Dose 2 of *Rotarix*; and the percentage of participants with poliovirus types 1, 2 and 3 neutralizing antibody titers ≥1:8 and ≥1:64 at 1 month post Dose 3 of IPV will be summarized by group with 95% CI.

For all antigens and timepoints as applicable, GMT/GMC will be computed with 95% CI. The 95% CI will assume that log transformed titer/concentration is normally distributed. For the purpose of GMT/GMC computation, titer/concentration below the assay cut-off will be assigned half of the cut-off.

For each of the anti-poliovirus types 1, 2 and 3, group GMT ratio at Visit 7 will be computed with 95% CI using an analysis of variance (ANOVA) model on log transformed titer in order to characterize the impact of co-administration on the IPV response. The group GMC ratio, the difference in seroconversion rates and the difference in the percentage of participants with concentration ≥90 U/mL will not be computed for anti-RV IgA antibody because a difference may be either attributed to co-administration of *Rotarix* PCV-free with IPV, or to the difference in administration schedule for *Rotarix* PCV-free (Month 0.5 and Month 1.5 in the Co-administration group, and Day 1 and Month 1 in the Staggered group).

Reverse cumulative curve will be provided for each antigen and timepoint as applicable.

9.4. Analysis of safety

Safety analysis will be performed on the ES.

Participants who missed reporting events (solicited/unsolicited AEs or concomitant medications) will be treated as participants without the events (solicited/unsolicited AEs or concomitant medications, respectively).

9.4.1. Within groups assessment

The following calculations will be performed for each group:

- The percentage of doses and participants reporting at least 1 AE (solicited or unsolicited) during the 14-day (Day 1 to Day 14) solicited follow-up period 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 and for AEs leading to a medically attended visit.
- The percentage of doses and participants reporting each individual solicited systemic event will be computed, over the 14-day (Day 1 to Day 14) solicited follow-up period, following study intervention administration, along with exact 95% CI. The same calculations will be done for each individual solicited systemic event rated as Grade 3 in intensity and events leading to a medically attended visit. Temperature above specific thresholds will also be summarized with threshold defined by half degree increment.

*Note: Intensity of fever will be assessed by considering the grading scales recommended by the Chinese authorities [*NMPA*, 2019b].*

- The verbatim reports of unsolicited AEs will be reviewed by a physician and will be coded according to MedDRA. Every verbatim term will be matched with the appropriate preferred term. The percentage of participants with unsolicited AEs occurring within 31-day (Day 1 to Day 31) follow-up period after any dose with its exact 95% CI will be tabulated by preferred term. The same calculations will be done for each AE rated as Grade 3 in intensity, for AEs leading to a medically attended visit and for AEs causally related to HRV as per the investigator assessment.
- The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), from Day 1 to Day 14 after study intervention administrations will be tabulated with exact 95% CI. The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), within 1 month after each dose will also be tabulated with exact 95% CI.
- SAEs and dropouts due to AEs will be described in detail.

9.5. Other analyses

9.5.1. Demographic and baseline characteristics analyses

The median, mean, range and standard deviation of age (in weeks) for each dose of study intervention and for gestational age (in weeks) will be computed by group. Median, mean and standard deviation of height in centimeter and weight in kg at Visit 1 will be computed by group. The geographical ancestry and sex composition will be presented.

9.6. Interim analyses

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

9.7. Sample size determination

A maximum of 400 participants (200 in the Co-administration group and 200 in the Staggered group) will be randomized such that approximately 160 evaluable participants complete the study, in each group for the evaluation of the primary objective assuming that approximately 20% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

The power calculation is based on the positive conversion rates of the Beijing Biological Products Institute Co.,Ltd. IPV, as mentioned in the package insert [Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) package insert, 2019].

The positive conversion rate is defined as the percentage of participants at 1 month post Dose 3 of immunization with:

- Neutralizing antibody titer $\geq$ 1:8 for participants with titer < 1:8 pre-immunization or
- At least 4 times increase in neutralizing antibody titer for participants with titer $\geq$ 1:8 pre-immunization.

The definition of seroconversion used in this protocol differs slightly from the above definition of positive conversion by taking into account the expected decline in maternal antibodies between the pre-vaccination blood sample and the post IPV Dose 3 blood sample. By definition, the seroconversion rate will be at least equal to the positive conversion rate. Therefore, as a worst-case scenario, the observed positive conversion rates are used in the following sample size computations.

The power presented in Table 16 is based on PASS 2019 (one-sided Non-Inferiority Tests for the Difference Between Two Proportions), under the alternative hypothesis of a 96.23% (Polio 1), 93.83% (Polio 2), and 97.60% (Polio 3) seroconversion rate for the Staggered group and a true difference of 0% between the Co-administration group and Staggered group, using Miettinen and Nurminen's Likelihood Score Test of the Difference. Under these conservative assumptions the overall power is above 90.4% (i.e., global type II error is conservatively computed as the sum of nominal type II errors).

Table 16 Probability that the lower limit of the 95% CI around group difference in the percentage of participants with anti-poliovirus types 1, 2 and 3 antibody seroconversion 1 month post Dose 3 of IPV (Co-administration group minus Staggered group) is greater than or equal to -10%

Ag	True seroconversion rate (Co-administrationgroup) *	True seroconversion rate (Staggered group) *	N evaluable (each group)	Power	Alpha
Polio 1	96.23%	96.23%	160	98.2%	0.025
Polio 2	93.83%	93.83%	160	92.5%	0.025
Polio 3	97.60%	97.60%	160	99.7%	0.025
	Overall			90.4%	

Ag: Antigen; N: number of participants
* Observed positive conversion rate from the Beijing Biological Products Institute Co.,Ltd. IPV package insert [**Inactivated Poliomyelitis Vaccine Made From Sabin** Strains (Vero Cells) package insert, 2019].

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 protocol amendments 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 participants.
- 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.

10.1.2. 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 interests during the study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study to the participant's parent(s) or participant's LAR(s) and answer all questions regarding the study.

Participants' parent(s)/LAR(s) must be informed that their participation is voluntary.

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

The content of the ICF 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 or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

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

If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

10.1.4. Data protection

Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

The participants' parent(s)/LAR(s) must be informed that:

- Their child's/ward's study-related data will be used by the sponsor in accordance with local data protection law.
- Their child's/ward's 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.

The participants' parent(s)/LAR(s) must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF**.**

10.1.5. Committees structure

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country. This includes IRBs/IECs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers. Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and 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 participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. 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 participant data related to the study will be recorded on printed or 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 physically or electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants that supports 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 for such review and inspection.

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 in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be predefined in the Study Management Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These predefined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 15 years from issuance of the final 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.

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any 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.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

First act of recruitment

The start of study is defined as FSFV.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur 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 enough notice 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 participants by the investigator

- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the LSLV for interventional studies and follows the guidance from the International Committee of Medical Journal Editors (ICMJE).

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol required immunogenicity laboratory assessments

Anti-RV IgA antibody determination:

The anti-RV antibody concentrations are determined by a validated anti-RV IgA ELISA. Microtiter plates (96-well) are coated with an anti-RV monoclonal antibody. The wells are washed and incubated with (positive wells) or without (negative wells) RV. Following incubation, the plates are washed and serum, standard and control dilutions are incubated in both types of wells (positive and negative). Bound anti-RV IgA in the wells are detected by incubation with peroxidase conjugated anti-human IgA polyclonal antibodies. Color development proportional to the quantity of bound anti-RV IgA occurs in the presence of a chromogen, TetraMethylBenzidine, and measured spectrophotometrically. Specific optical densities are calculated for each sample/control/standard dilution by measuring the difference between positive and negative wells, the use of negative wells allowing to assess non-specific IgA binding. The concentrations of the samples expressed in units per milliliter are calculated relative to the four-parameter logistic function generated from the standard curve.

Anti-IPV type 1, type 2 and type 3 antibodies determination:

The polio microneutralization assay measures neutralizing antibody titers to poliovirus types 1, 2, and 3 using 96-well microtiter plates. The principle of the test is that the anti-poliovirus antibodies in a serum sample will bind to the virus and block infection of susceptible cells. Because poliovirus is cytopathic, virus that is not bound by antibody infects and lyses cells. The amount of neutralizing antibody is quantitated as a titer based on the last serum dilution to protect susceptible cell culture wells from poliovirus infection and cytopathic effect.

10.3. Appendix 3: AE: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an AE

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- 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.
- AEs to be recorded as solicited AEs are described in Section 10.3.3. All other AEs after administration of *Rotarix* 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.

10.3.1.2. Events NOT Meeting the AE 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 participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an 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 participant 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 participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is 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 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.

e. Other situations. Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should 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; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

Definition of solicited event
• Solicited events are predefined events-administration site events and systemic events for which the participant's parent(s) /LAR(s) is specifically questioned, and which are noted by the participant's parent(s) /LAR(s)] in their diary/eDiary. Note: for this study solicited systemic events will be collected post Dose 1 and Dose 2 of study interventions administration.

The following events will be solicited:

Table 17 Solicited systemic events

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

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

10.3.4. Unsolicited AE

Definition of unsolicited AE
• An unsolicited AE is an AE that is either not included in the list of solicited events or is included in the list of solicited events but has an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must be communicated by participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.

- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's parent(s) /LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant's parent(s)/LAR(s) will be collected during an interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Note: for this study unsolicited AEs will be collected post Dose 1 and post Dose 2 of *Rotarix* administration.

10.3.5. SAEs related to Study Participation

Any SAEs related to study participation (e.g., SAEs due to study mandated procedures, invasive tests or change in existing therapy) should be reported as per Section 8.3.3.

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments (e.g., clinical chemistry, hematology, urinalysis) or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

The investigator must exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.6.1. Recording and follow-up of AEs and SAEs

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

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the electronic Expedited Adverse Events Report. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the electronic Expedited Adverse Events Report.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers with the exception of the participant number, will be redacted on 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 instead of individual signs/symptoms.

A Paper Diary, hereafter referred to as Participant Diary will be used in this study to capture solicited systemic events. The participant should be trained on how and when to complete each field of the Participant Diary.

Any individual(s) who performs the measurements of systemic events and who will enter the information into the Participant Diary should be trained on the use of the Diary. This training must be documented in the participant's source record. If any individual other than the participant's parent(s)/LAR(s) is making entries in the Participant Diary, their identity should be documented in the Participant Diary/participant's source record.

- Collect and verify completed diary cards during discussion with the participant's parent(s)/LAR(s) as presented in the SoA Section 1.3.
- Any unreturned diary cards will be sought from the participant's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

The investigator or delegate will transcribe the required information into the eCRF in English.

All solicited events and unsolicited AEs, SAEs, and AEs that led to withdrawal from the study will be collected and recorded in the eCRF.

The verbatim reports of unsolicited AEs, SAEs and AEs leading to withdrawal will be reviewed by a physician and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Every verbatim term will be matched with the appropriate preferred term.

10.3.6.2. Time period for collecting and recording AEs and SAEs

All AEs and SAEs must be recorded into the appropriate section of the eCRF according to the timelines described in Table 11 of Section 8.3.1, irrespective of intensity or whether or not they are considered related to the study intervention.

10.3.6.3. Follow-up of AEs, SAEs or any other events of interest

After the initial AE/SAE or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until 30 days after the last study intervention administration or until the participant is lost to follow-up.

10.3.6.3.1. Follow-up during the study

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

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.6.3.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE using an electronic Expedited Adverse Events Report. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE as fully as possible.

10.3.6.4. Updating of SAE information after removal of write access to the participant's eCRF

When additional SAE information is received after write access to the participant's eCRF is removed, 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 Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 12).

10.3.7. Assessment of intensity and causality

10.3.7.1. Assessment of intensity

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

Table 18 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Infant		
Adverse Event	**Intensity grade**	**Parameter**
Fever*		Record temperature in °C
Diarrhea $		Record the number of looser than normal stools/day
Vomiting §		Record the number of episodes of vomiting/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
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

Infant		
Adverse Event	**Intensity grade**	**Parameter**
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

*Refer to the SoA for the definition of fever and the preferred location for temperature measurement.
$ 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 19 Intensity scales for diarrhea, vomiting and fever in infants

Infant		
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	Normal (< 37.5°C)
	1	37.5°C – < 38.0°C
	2	38.0°C – < 39.5°C
	3	≥39.5°C
	4	≥39.5°C, lasts more than 5 consecutive days

+ The intensity of fever using the grading scale as defined by Chinese authorities [NMPA, 2019b].

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 1 of the following categories:

1 (mild) = An AE which is easily tolerated by the participant, 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 school/kindergarten/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 1 of the predefined outcomes as described in the Section 10.3.2.

10.3.7.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or PI for marketed products while making their assessment.

Causality 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 intervention?

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

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator 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 study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

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 to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator(s) may change their opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.7.3. Medically attended visits

For each solicited (post administration of Dose 1 and Dose 2 of *Rotarix* and IPV) and unsolicited symptom (post *Rotarix* administration) the participant experiences, the participant's parent(s)/LAR(s) will be asked if the participant 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.

Medical attention received for SAEs will have to be reported using the normal AE reporting process in the eCRF.

10.3.7.4. Assessment of outcomes

The investigator will assess the outcome of all serious (post *Rotarix* and IPV administration) and nonserious unsolicited AEs (post *Rotarix* administration) recorded during the study as:

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

10.3.8. Reporting of SAEs and other events

10.3.8.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited AEs Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report. Refer to the Table 12 for the details on timeframes for reporting of SAEs.

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

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited AEs Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK Global Safety department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

This section is not applicable.

10.5. Appendix 5: Genetics

This section is not applicable.

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.6.1. Definition of medical device AE and ADE

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. 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 medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An ADE is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (i.e., user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. – Chronic disease (MDR 2017/745).
c. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the IB.

10.6.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Refer to paper 'Medical device or combination product with device deficiency/incident report form' for details on transmission of this information to the sponsor.
- GSK will review all device deficiencies, determine, and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting in Section 8.3.3.1.

10.6.4. Reporting of Medical Device Deficiencies for Associated Person

- If an Associated Person (i.e., e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the safety reporting information and authorization to contact physician letter.
- If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.
- Medical device deficiencies should be reported using the medical device deficiency report form.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.7. Appendix 7: Country-specific requirements

This section is not applicable.

10.8. Appendix 8: Abbreviations and glossary of terms

10.8.1. List of abbreviations

Ab	Antibody
ADE	Adverse Device Effect
AE	Adverse event
ANOVA	Analysis of variance
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CoP	Correlate of protection
COVID-19	Coronavirus disease 2019

CSR	Clinical study report
eCRF	electronic Case Report Form
EEA	European Economic Area
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EoS	End of study
ES	Exposed set
EU SmPC	European Union Summary of Product Characteristics
FSFV	First subject first visit
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric mean antibody concentration
GMT	Geometric mean titer
GSK	GlaxoSmithKline Biologicals SA
HRV	Human rotavirus
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IPV	Inactivated poliovirus vaccine
IRB	Institutional Review Board
IS	Intussusception
Kg	Kilogram

LAR	Legally acceptable representative
LML	Local medical lead
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NIP	National immunization programme
OPV	Oral poliovirus vaccine
PCD	Primary Completion Date
PCV	*Porcine circovirus*
PI	Prescribing Information
PPS	Per Protocol set
QTL	Quality tolerance limit
RV	Rotavirus
RVGE	Rotavirus gastroenteritis
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SBIR	Source data Base for Internet Randomization
SoA	Schedule of activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
US	United States
USADE or UADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

10.8.2. Glossary of terms

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

An adverse event (AE) can therefore be any 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 study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event

In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.

Caregiver: A ‘caregiver’ is someone who

- lives in the close surroundings of a participant and has a continuous caring role or
- has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).

In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.

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.
Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device, and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
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 studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	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 participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.

Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Legally acceptable representative:	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant 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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.

Protocol amendment:	The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' 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, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
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.

10.9. Appendix 9: Protocol Amendment change history

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

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