Statistical Analysis Plan

Protocol Title:

An Open-label, Randomized, Controlled, Single Centre, Phase IIb Study to Assess the Immunogenicity, Reactogenicity and Safety of Three Live Oral Rotavirus Vaccines, ROTAVAC®, ROTAVAC 5CM and Rotarix® in Healthy Zambian Infants.

Sponsor: Centre for Infectious Disease Research in Zambia, Zambia

Protocol: CVIA 066

Clinicaltrial.gov reference: NCT03602053

Phase IIb

Effective Date: 11-JUL-2018

Protocol Version: 01

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Protocol	Version 01, dated 11 July, 2018
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eCRF	Version 2.0, dated 14 December, 2018
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List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BBIL	Bharat Biotech International Limited
BMGF	Bill & Melinda Gates Foundation
CCHMC	Cincinnati Children's Hospital Medical Center
CCID	Cell Culture Infectious Dose
CI	Confidence Interval
CIDRZ	Centre for Infectious Disease Research in Zambia
CMC	Christian Medical College
CRO	Contract Research Organization
CRF	Case Report Form
CS	Clinically Significant
DOB	Date of Birth
DTwP	Diphtheria, Tetanus, Pertussis (whole cell)
ELISA	Enzyme-Linked immune sorbent Assay
EPI	Expanded Program on Immunization
ET	Early Termination
FA	Full Analysis
FFU	Focus Forming Units
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
H_0	Null Hypothesis
H_1	Alternative Hypothesis
HepB	Hepatitis B
Hib	Haemophilus influenzae type B
IAE	Immediate Adverse Event
ICF	Informed Consent Form
Kg	Kilogram
LLOQ	Lowest Limit of Quantitation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

Min	Minimum
mL	milliliter
Non-TEAE	Non Treatment Emergent Adverse Event
n	Number of Participants
NCS	Not Clinically Significant
PD	Protocol Deviations
PI	Principal Investigator
PT	Preferred Term
PIDC	Post-Immunization Diary Card
PP	Per Protocol
PSRT	Protocol Safety Review Team
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCID	Severe combined immunodeficiency
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLGs	Tables, Listings, and Graphs
ULOQ	Upper Limit of Quantification
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

SAP

Table of Contents

1. Introduction

1.1 Statistical Analysis Plan

A statistical analysis plan (SAP) is intended to be a comprehensive and detailed description of the methods for data analyses to be used in a clinical trial. A clear detailed SAP will avoid post hoc decisions that may affect the interpretation of the data. This SAP includes details on the procedures for creating Tables, Listings, and Graphs (TLGs) from the results of a phase IIb study which is being carried out to evaluate and compare the immunogenicity of three rotavirus vaccines ROTAVAC®, ROTAVAC 5D® and Rotarix in Zambian Infants.

This is a separate document apart from statistical section of the protocol. Any changes in the statistical analysis / methods planned in the protocol and even if any additional statistical analysis is planned which is not part of the protocol will be explained in this detailed statistical analysis plan of the study CVIA 066.

This SAP:

- Includes a statement of the objectives of the trial, as stated in the protocol.
- Identifies all primary and secondary end-points.
- Specifies the hypotheses to be tested and any parameters that are to be estimated, in order to meet the trial objectives.
- Defines the analysis populations to be used
- Provides a full and detailed description of the methods of analysis including details of handling of missing data, drop outs, derived variables, etc.

1.2 Rationale for Study CVIA 066

This study has been designed to compare ROTAVAC 5D® with the newly World Health Organization (WHO) prequalified vaccine ROTAVAC® among infants in Africa. The main purpose of this study is to assess the immunogenicity of a full course of the two formulations of ROTAVAC®, i.e., ROTAVAC® and ROTAVAC 5D® and to assess the safety and reactogenicity of the vaccine among African infants. Rotarix® has been included as the third arm since it is being used for routine immunization of children in Zambia and holds the vast majority of the GAVI-eligible country market share. This arm will act as an internal control to validate immune response of ROTAVAC® and ROTAVAC 5D®, which are being tested for the first time in African continent. The study will also assess the safety and reactogenicity of a full immunization course and of each dose of the study vaccines, with the aim of describing its safety in Zambian infants.

This trial will generate immunogenicity and safety data on ROTAVAC® and ROTAVAC 5D® outside of India to support WHO Strategic Advisory Group of Experts on Immunization (SAGE) policy recommendations and country-level decision-making. At the conclusion of the study, PATH, public health leaders and site investigator(s), together with Bill & Melinda Gates Foundation (BMGF) officers will support Bharat Biotech International Limited (BBIL) in Communication of results to global and national policymakers and to the global public health community. Presentation of data to Zambian Ministry of Health, WHO and in peer reviewed open access publications will be key audiences targeted for communication of results.

2. Study Design and Objectives

Four hundred and fifty healthy infants, 6-8 weeks of age will be enrolled and randomized to receive either three doses of ROTAVAC® or ROTAVAC 5D®, four weeks apart, at 6, 10 and 14 weeks of age or two doses of Rotarix® (current standard of care in Zambia), four weeks apart at 6 and 10 weeks of age.

2.1 Study Objectives

2.1.1 Primary Objective

The Primary objective of the study is:

Immunogenicity: To evaluate and compare the immunogenicity of ROTAVAC® and ROTAVAC 5D®, 28 days after the last dose of the vaccine, when administered to infants in a three-dose schedule at 6, 10 and 14 weeks of age.

2.1.2 Secondary Objectives

Secondary objectives are:

Safety : To assess the reactogenicity 7 days after each vaccination and safety 4 weeks after the last vaccination of the ROTAVAC® and ROTAVAC 5D®, when administered to infants in a three-dose schedule at 6, 10 and 14 weeks of age and Rotarix®, when administered to infants in a two-dose schedule at 6 and 10 weeks of age.

Immunogenicity: To evaluate the immunogenicity of Rotarix® 28 days after the last dose of the vaccine, when administered to infants in a two-dose schedule at 6 and 10 weeks of age.

2.1.3 Exploratory Objectives

The Exploratory objective of the study is:

Immunogenicity: To evaluate the immunogenicity of the three vaccines by ELISA using 89-12 (G1P8 virus) as a substrate in a subset of the samples collected.

2.2 Assessment of Objectives

2.2.1 Primary Endpoints

2.2.1.1 Primary Immunogenicity Endpoints

Primary Immunogenicity Endpoints is Geometric mean concentrations (GMCs) of serum anti-rotavirus IgA antibodies 28 days after the last dose of a study vaccine, as measured by enzyme-linked immunosorbent assay (ELISA) using WC3 as the viral lysate.

2.2.2 Secondary Endpoints

2.2.2.1 Secondary Safety Endpoints:

The secondary safety endpoints are:

- Immediate adverse events, within 30 minutes post-vaccination.
- Solicited post-vaccination reactogenicity (fever, diarrhea, vomiting, decreased appetite, irritability, decreased activity level) during the 7 day period (Day 0-6) after each vaccination.

- Unsolicited AEs 4 weeks after each vaccination.
- SAEs, including intussusception from first vaccination through 4 weeks after the last vaccination of each study participant.

2.2.2.2 Secondary Immunogenicity Endpoints:

The secondary immunogenicity endpoint (anti-rotavirus IgA using WC3 as the Lysate) are as follows:

- Seroconversion rate 28 days after last dose of study vaccine (Day 84 for ROTAVAC® and ROTAVAC 5D®; and Day 56 for Rotarix®). Seroconversion is defined as a post-vaccination serum anti-rotavirus IgA antibody concentration of at least 20 U/mL if a baseline concentration is < 20 U/mL or a post-vaccination serum antirotavirus IgA antibody concentration of ≥ 2-fold baseline level if a baseline concentration is ≥ 20 U/mL.
- Seropositivity rate at baseline and 28 days after last dose of study vaccine (Day 84 for ROTAVAC® and ROTAVAC 5D® and Day 56 for Rotarix®). Seropositivity is defined as serum anti-rotavirus IgA Antibody concentration ≥ 20 U/mL.
- Seroresponse rate 28 days after last dose of study vaccine (Day 84 for ROTAVAC® and ROTAVAC 5D® and Day 56 for Rotarix®). Seroresponse will be assessed as a four-fold, three-fold and two- fold rise in antibody concentration from baseline.
- Geometric Mean Fold Rise (GMFR) that is a ratio of GMCs at 28 days after last dose of study vaccine (Day 84 for ROTAVAC® and ROTAVAC 5D® and Day 56 for Rotarix®) with reference to baseline.

2.2.2.3 Exploratory Endpoints:

The exploratory endpoints based on anti-rotavirus IgA antibodies measured by ELISA using 89-12 as the viral lysate in a subset of samples are as follows:

- GMCs of serum anti-rotavirus IgA antibodies 28 days after the last dose of study vaccine.
- Seroconversion rate 28 days after last dose of study vaccine. Seroconversion is defined as a post-vaccination serum anti-rotavirus IgA antibody concentration of at least 20 U/mL if a baseline concentration is < 20 U/mL or a post-vaccination serum anti-rotavirus IgA antibody concentration of ≥ 2-fold baseline level if a baseline concentration is ≥20 U/mL.
- Seropositivity rate at baseline and 28 days after last dose of study vaccine. Seropositivity is defined as serum anti-rotavirus IgA antibody concentration ≥ 20 U/mL.
- GMFR that is a ratio of GMCs at 28 days after last dose of study vaccine with reference to baseline.

Method of Endpoint assessment:

To evaluate the Rotavirus vaccine immunogenicity a blood sample will be obtained from all the participating infants before first vaccination and four weeks (+1 week) after the last vaccine dose. This would mean that the blood sample will be collected at approximately 14 weeks of age for infants in the Rotarix® arm and 18 weeks for infants in the ROTAVAC®

Groups. Serum anti-rotavirus IgA antibodies will be analyzed by a validated ELISA assay using WC3 as the viral lysate at Wellcome Trust Research Laboratory, Christian Medical College, Vellore, India.

To evaluate the Rotavirus vaccine immunogenicity by ELISA, using 89-12 as the viral lysate, a subset of 50 sample pairs per arm (total 150 pairs) will be randomly selected from the samples collected. These will then be tested at Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, USA by a validated ELISA which uses 89-12 as a lysate

Also safety will be monitored by recording immediate adverse events within 30 minutes post-vaccination, solicited post vaccination reactogenicity (fever, diarrhea, vomiting, decreased appetite, irritability, and decreased activity level) daily for 7 days after each vaccination, unsolicited adverse events through 4 weeks after each vaccination and serious adverse Events (SAEs) (including Intussusception), spontaneously reported as untoward events occurring in a participant up to visit 4 i.e. four to six weeks after third vaccination.

The study will compare the immunogenicity of the two formulations of ROTAVAC® i.e. ROTAVAC® vs. ROTAVAC 5D® in terms of GMCs and will describe without comparing the immune response to Rotarix®.

2.3 Change in the Planned Analysis from Protocol during the conduct of the study

Sr. No	Section	As Per Protocol	Change in SAP
1.	Secondary Safety Endpoints	Unsolicited AEs from first vaccination through 4 weeks after the last vaccination	Unsolicited AEs 4 weeks after each vaccination
2.	Demographics	Demographic and baseline characteristics (age, ethnicity, sex, length, and weight) will be tabulated by vaccine group on the FA population	Demographic and baseline characteristics (age, ethnicity, sex, length, and weight) will be tabulated by vaccine group on the Enrolled and FA populations

2.4 Study Design

This study is designed as a Phase IIb, single-center, randomized, active-controlled, open-label study enrolling a total of 450 healthy infants 6-8 weeks (42-56 days) of age. Prospective participants, whose parent or legal guardian sign an informed consent form and pass the test of understanding, will be assessed for eligibility to participate in the study. Screening for eligibility will include solicitation of medical history, assessment of vital signs, and physical examination.

If the participant is found to be eligible, the infants will be allocated to one of the three groups in a ratio of 1:1:1 (n=150 per group) to receive either three doses of ROTAVAC®, three doses of ROTAVAC 5D® or two doses of Rotarix®, 4 weeks apart (minimum interval of 4 weeks and maximum of 5 weeks). Allocation of treatment to individual participants will be based on a randomization schedule developed in co-ordination with the data management organization for unbiased randomization of participants to the treatments. Three doses of ROTAVAC® and ROTAVAC 5D® will be administered at 6, 10 and 14 weeks of age whereas two doses of Rotarix® will be administered at 6 and 10 weeks of age (see table below).

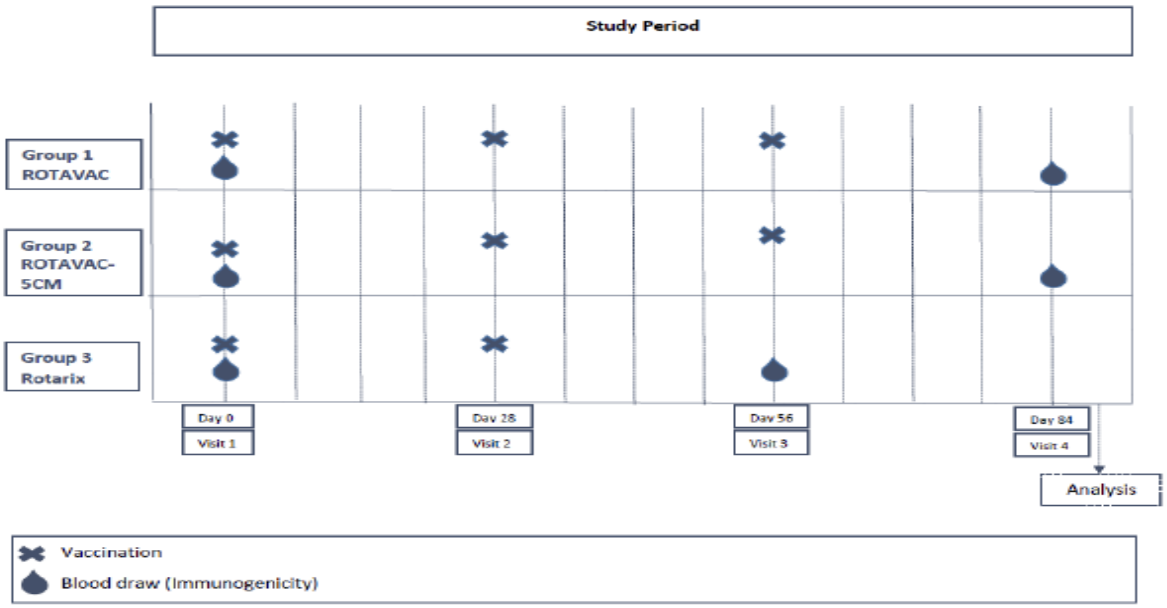
All vaccines will be administered concomitantly with EPI vaccines including Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type B and Hepatitis B vaccine (DTwP-Hib-HepB), Pneumococcal conjugate vaccine and OPV at 6, 10 and 14 weeks and IPV at week 14 (when switched to in Zambia). Should any changes to the EPI schedule in the Zambia occur before or during the study the vaccines given alongside the study vaccines will be allowed to reflect the current program without a protocol amendment unless this is considered to interfere with the assessment of the study endpoints in any way.

The participants will be monitored for 30 minutes following vaccine administration for immediate adverse events like anaphylaxis, vomiting etc.

Group	No. of Participants	Visit 1 (6-8 weeks)	Visit 2* V1+28 (+7) days	Visit 3* V2+28 (+7) days
A	150	ROTAVAC®	ROTAVAC®	ROTAVAC®
B	150	ROTAVAC 5D®	ROTAVAC 5D®	ROTAVAC 5D®
C	150	Rotarix®	Rotarix®	NA

The study will compare the immunogenicity of the two formulations of ROTAVAC® i.e. ROTAVAC® vs. ROTAVAC 5D® in terms of GMCs and will describe without comparing the immune response to Rotarix®. To evaluate the immune responses, a blood sample will be obtained from all the participating infants before first vaccination and four weeks (+1 week) after the last vaccine dose. This would mean that the blood sample will be collected at approximately 14 weeks of age for infants in the Rotarix® arm and 18 weeks for infants in the ROTAVAC Groups. To evaluate the Rotavirus vaccine immunogenicity all the available paired samples will be testing an ELISA using WC3 as the viral lysate at Wellcome Trust Research Laboratory, Christian Medical College, Vellore. The immune responses will also be tested in a subset of participants using an ELISA using 89-12 as the viral lysate. This test uses a strain specific to Rotarix vaccine and will be conducted at Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, USA.

Study Schema



Enhanced passive/Active surveillance for vaccine reactogenicity (solicited reactions) over the 7- day period after each vaccination will be conducted on all infants. In addition, surveillance for unsolicited AEs, SAEs including intussusception will be carried out over the period between first vaccination and four weeks after the last vaccination on all infants.
Participants will be evaluated for:

- Immediate adverse events within 30 minutes post-vaccination.
- 7-days post-vaccination reactogenicity, i.e., the occurrence of solicited reactions (fever, diarrhea, vomiting, decreased appetite, irritability, decreased activity level) after each vaccination.
- Unsolicited AEs four weeks after each vaccination.
- Incidence of serious adverse events (SAEs) including intussusception, from first vaccination through four weeks after the last vaccination.

For evaluation of post-vaccination reactogenicity, the parent will be given a digital thermometer and a Post-Immunization Diary Card (PIDC) covering Days 0-6 (Day 0 = day of vaccination). They will be instructed to record their child's axillary temperature as well as other solicited reactions on the PIDC for 7 days post-vaccination. Study staff will make a home visit on Days 2 (+1 day) and Day 7 (+1 day) to determine health status and to support completion of the PIDC as well as capture information on the PIDC recorded to-date. Completed PIDC will be collected by the field officer on the Day 7 (+1 day) following vaccination. The data in the PIDC collected by the parents will be reviewed by the study physician/designee and entered in the CRF.

2.5 Sample Size and Power Considerations

The immunogenicity of the study vaccines will be primarily assessed by geometric mean concentrations (GMCs) of serum anti-rotavirus IgA antibodies at 28 days after the last dose of the study vaccine, along with its two-sided 95% confidence interval (CI), by exponentiating the corresponding log10-transformed mean and its two-sided 95% CI limits.
Table 1 below presents the precision of the 95% CI of the GMC in log10-transformed scale per group under different assumptions of group sizes and assumed standard deviation (SD) of log10-transformed anti-rotavirus IgA concentrations.

Table 1. The half width of a two-sided 95% CI of the GMC in log10-transformed scale based on various group sizes and assumed standard deviation (SD) of log10-transformed anti-rotavirus IgA concentrations

Assumed SD of log10-transformed anti-rotavirus IgA concentrations	Number of evaluable participants per group		
	120	**135**	150
0.50	0.090	0.085	0.081
0.55	0.099	0.094	0.089
0.60	0.108	**0.102**	0.097
0.65	0.117	0.111	0.105
0.70	0.127	0.119	0.113

With a sample size of 150 for each group and an assumed SD of log10-transformed anti-rotavirus IgA concentrations of 0.60, the half width of a two-sided 95% CI for anti-rotavirus IgA GMC will be 0.102 in log10-transformed scale for each group, assuming a dropout rate of 10%.

Power to show that the ratio of anti-rotavirus IgA GMCs in ROTAVAC 5D® group to that in ROTAVAC® group is at least 0.5 was calculated using two-sample t-test according to various group sizes, different assumed SDs of log10-transferred anti-rotavirus IgA concentrations and equal true underlying geometric mean and is provided in Table 2.

Table 2. Power to show comparability of immune response in terms of GMCs for rotavirus-specific serum IgA antibody concentrations between ROTAVAC 5D® **and ROTAVAC® groups, based on various group sizes, different assumed SD of log10 anti-rotavirus IgA concentrations, and equal true geometric mean**

Assumed SD of log10 anti-rotavirus IgA concentrations	**Number of evaluable participants *per* group**	**Power to demonstrate that the lower limit of 95% CI of the ratio of GMC between groups is > 1/2**
0.50	120 vs. 120	>99%
	135 vs. 135	>99%
	150 vs. 150	>99%
0.55	120 vs. 120	99%
	135 vs. 135	99%
	150 vs. 150	>99%
0.60	120 vs. 120	97%
	135 vs. 135	**98%**
	150 vs. 150	99%
0.65	120 vs. 120	95%
	135 vs. 135	97%
	150 vs. 150	98%
0.70	120 vs. 120	91%
	135 vs. 135	94%
	150 vs. 150	96%

Assuming the true standard deviation of log10-transformed anti-rotavirus IgA concentration is below than or equal to 0.60, with a sample size of 150 and a dropout rate of 10% per group (135 evaluable participants per group), the study has power of 98% to detect at least 0.5 of GMC ratio between ROTAVAC 5D® and ROTAVAC® groups.

With 150 infants vaccinated per group, this study design allows a greater than 90% chance of observing at least one AE if true incidence is 1.53%. Conversely, if no AEs are observed in 150 vaccine recipients, the study will be able to rule out AEs occurring at a rate of approximately 2.5% or above based on the upper bound of the two-sided 95% CI.

2.6 Randomization

Healthy infants will be randomized to receive one of the three study vaccines (ROTAVAC 5D® or ROTAVAC® or Rotarix®) in a 1:1:1 ratio. For vaccine allocation, a randomization blocking scheme will be used in order to ensure that balance between vaccine groups will be maintained. Infants will be randomized sequentially in the order that they are enrolled. The randomization scheme that contains a participant identification number and the corresponding randomization assignment will be generated using computer software prior to the initiation of the study and provided to the designated site personnel.

2.7 Blinding

The study will be conducted under open-label condition. This means that the patient, clinical site, Contract Research Organization (CRO), sponsor and PATH will be unblinded to the treatment assignments. Therefore, unblinding procedures are not applicable. The study laboratory will be kept blinded for the treatment administered until the end of testing.

2.8 Random Sample selection for CCHMC

Out of 450 participants enrolled in the study i.e 150 participant s, a subset of the samples 50 participants /arm (50 paired sample /arm) collected will also be tested by a validated ELISA which uses strain 89-12 (G1P8 virus) as a substrate. Strain 89-12 was the isolated strain that was used to develop the Rotarix® Vaccine. Since no correlation between the two assays has been established and it is expected that tests employing heterologous strains as substrate may give lower concentrations, no within-group or between assays comparisons will be done. To avoid any bias in selecting subset that will be tested using ELISA using 89-12 at Cincinnati, the random sample list will be generated using the following criteria:

- No major protocol deviation affecting immunogenicity i.e. In eCRF module “PROTOCOL DEVIATION / VIOLATION”, field “Is this a protocol deviation or violation” marked as “Protocol violation” will not be considered only if it’s impacting immunogenicity. If “Protocol Violation” is related to safety and not impacting immunogenicity then the participant will be considered for extracting random sample.
- Paired sample for Cryotube 2 should be available with minimum sample in both pre and post vaccination sample to be 0.3 ml. (For Rotarix arm, “Visit 3” will be considered as “Post Vaccination” and for ROTAVAC® and ROTAVAC 5D® arm, “Visit 4” will be considered as “Post Vaccination”).
- Quality of sample in Cryotube 2 should be good.
- Equal number of paired sample from each of the three arms i.e. 50 paired samples from each of the three arms.

3 General Analysis Requirements

3.1 Study Duration

Participant will be followed for approximately 3 - 4.5 months (28 (+7) days after the last vaccination).

Actual study duration = Last participant last visit date - First participant first visit date + 1.

Actual study duration of each participant = Last visit date of the participant / withdrawal date whichever is later - First visit date of respective participant + 1.

3.2 Schedule of Study Visits, Visit windows and Procedures

Table 3: Time and Events Table

Visit	V1	V2	V3	V4
Time point	**D0**	**D28**	**D56**	**D84**
Interval	**6-8 weeks**	**V1+28 (+7) days**	**V2+28 (+7) days**	**V3+28 (+7) days**
Information process and written informed consent	X			
Collect baseline demographic data	X			
Collect/review medical history	X			
Perform physical and vital signs examination	X[a]	X	X	X
Check inclusion/ exclusion criteria	X			
Check withdrawal criteria		X	X	X
Participant enrollment and Randomization	X			
Collect blood sample for immunogenicity testing	X (Pre-dosing)		X[c]	X[b]
Study vaccination along with EPI vaccination	X	X	X[b]	
Check contraindications, warnings and precautions to vaccine receipt		X	X[b]	
Observe for immediate adverse events for 30 minutes post vaccination	X	X	X[b]	
Perform post-vaccination Vital examination and targeted physical examination if required.	X	X	X[b]	
Issue and Instruct participant's Parent/LAR on use of diary card	X	X	X[b]	
Record solicited AEs for 7 days post-vaccination	X	X	X[b]	
Safety follow up post vaccination by social worker	X[d]	X[d]	X[db]	
Record unsolicited AEs , including SAEs	X	X	X	X[b]
Record any concomitant medications/vaccinations	X	X	X	X[b]
Review interim medical history and record any intercurrent medical conditions		X	X	X[b]
Participant completion of study			X[c]	X[b]

Visit	V1	V2	V3	V4
D = day; PRE = pre-vaccination; AE = adverse events, SAE = serious adverse event. [a] Symptom-based PE to be performed if screening is being repeated and there is any change in health since last screening. [b] Not applicable for participants in Rotarix arm [c] Applicable only for participants in Rotarix arm [d] This includes visit by the health worker to the parent on day 2 and 7 after vaccination.				

3.3 Study Population

The sufficient number of healthy infants' aged 6-8 (42-56 days; both inclusive) weeks will be screened with parental consent to enroll 450 infants in the study.

Participants' parents who have signed informed consent and those who satisfy all the inclusion and exclusion criteria will be targeted for enrollment in the study. During screening visit, review of eligibility criteria will be performed. Screening procedures will be conducted to determine eligibility for randomization. At Visit 1 (Day 1), a participant will be randomized if he or she fulfills all eligibility criteria as reviewed against the inclusion and exclusion criteria. The participant will be vaccinated for Dose 1 within 24 hours from randomization. A listing of Participant Eligibility Criteria will be provided.

3.3.1 Inclusion Criteria

Fulfillment of all of the following criteria is required to accept an infant in the study:

1. Healthy infant as established by medical history and clinical examination before entering the Study.
2. Age: 6-8 weeks (42-56 days, both days inclusive) confirmed by Immunization Record.
3. Infants received age-appropriate EPI vaccines till enrolment.
4. Ability and willingness to provide informed consent as per local consenting procedures.
5. Parent can be contacted on phone and confirms intention to remain in the study area with the participant during the study period.

3.3.2 Exclusion Criteria

Any of the following will exclude an infant from the study:

1. Presence of diarrhea or vomiting in the previous 72 hours or on the day of enrolment (temporary exclusion).
2. Presence of fever on the day of enrolment (temporary exclusion).
3. Acute disease at the time of enrolment (temporary exclusion).
4. Concurrent participation in another clinical trial throughout the entire timeframe of this study.
5. Presence of severe malnutrition (weight-for-height z-score < -3SD median).
6. Any systemic disorder (cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrine, immunological, dermatological, neurological, cancer or autoimmune disease) as determined by medical history and/or physical examination which would compromise the child's health or is likely to result in non-conformance to the protocol.
7. History of congenital abdominal disorders, intussusception, abdominal surgery
8. Known or suspected impairment of immunological function based on medical history and physical examination.
9. Prior receipt or intent to receive rotavirus and other age specified EPI vaccines outside of the study center and during study participation.

10. A known sensitivity or allergy to any component of the study vaccine.
11. Clinically detectable significant congenital or genetic defect.
12. History of persistent diarrhea (defined as diarrhea more than 14 days).
13. Participant's parents not able, available or willing to accept active follow-up by the study staff.
14. Has received any immunoglobulin therapy and/or blood products since birth or planned administration during the study period.
15. History of chronic administration (defined as more than 14 days) of immunosuppressant's including corticosteroids. Infants on inhaled or topical steroids may be permitted to participate in the study.
16. History of any neurologic disorders or seizures.
17. Any medical condition in the parents/infants that, in the judgment of the investigator, would interfere with or serves as a contraindication to protocol adherence or a participant's parent's/legally acceptable representative's ability to give informed consent.
18. Participant is a direct descendant (child or grandchild) of any person employed by the Sponsor, the CRO, and the Principal Investigator (PI) or study site personnel.

After informed consent has been obtained and the child is identified as meeting inclusion and exclusion criteria for enrollment, the child will be enrolled in the study.

3.3.3 Continued Eligibility Confirmation for Subsequent Vaccination

The following events constitute absolute contraindications to rotavirus vaccination and all participants should be evaluated for these before further administration of the study vaccine. If any of these events occur during the study, the participant must not receive additional doses of the vaccine but should be appropriately followed up for safety by the Investigator.

- Hypersensitivity reaction following the administration of the study vaccine.
- Any uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) which is diagnosed after the first vaccination and that would predispose for intussusception.
- Infants with any history of intussusception.
- Severe combined immunodeficiency (SCID).
- Detection of one or more of the exclusion criteria during dosing period.

The following events constitute contraindications to administration of the study vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the participant may be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the Investigator.

- Acute disease and / or fever at the time of vaccination.
    - Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection without fever.
    - Fever is defined as temperature ≥37.5°C (99.5°F) on axillary setting.

- Gastroenteritis within 72 hours preceding the study vaccine administration.

3.3.4 Withdrawal / Discontinuation Criteria

Participants have the right to decline study treatment or procedures for any reason and at any time during the study. If a participant declines further vaccination or study procedures (but continues in the study for safety assessment) this will be recorded as a study deviation and the reason will be clearly documented in the source document. The participant will be encouraged to complete the remaining applicable safety-related follow-up to complete safety follow-up for at least 28 days after last dose and immunogenicity blood draw at the end of safety follow-up. If the participant does not wish to remain in the study by declining any follow-ups or procedures, the participant can choose to withdraw consent and be withdrawn from the study.

The participants may be withdrawn from the study for any of the following reasons:

- If parent of participant wishes to withdraw consent.
- If the Principal Investigator (PI) decides that withdrawal is in the best interest of the participant.
- Significant non-compliance with treatment regimen or trial requirements
- Participant is lost to follow-up.
- The sponsor/manufacturer recommends to terminate the study

In all cases, where the participant is withdrawn from the study the reason for withdrawal will be documented in an appropriate section of the eCRF. However, the data collected up to the last contact will be part of the analysis. In the event of withdrawal from study, reasonable efforts should be made to conduct the following procedures:

- Review diary card if still in use prior to withdrawal
- Updating any ongoing AE/SAEs that remain ongoing at time of participant's last visit prior to withdrawal
- Query about AEs, SAEs and concomitant medications if the interval between the participant's last visit and the time of withdrawal is within the protocol-defined reporting period.
- Conduct physical examination.
- Collect blood for immunologic testing if withdrawal occurs before end of study
- Update contact information.

3.4 Treatment Assignment and Study arms

Based on a central computer-generated randomization schedule, participants will be randomized to either of the three ROTAVAC®, ROTAVAC 5D® and Rotarix® study arms in the ratio 1:1:1

- ROTAVAC® (Frozen formulation)
    - Vaccine is a live, attenuated G9P[11] monovalent vaccine at a dose of 0.5 mL containing NLT $\log10^{5.0}$ focus forming units (FFU) per dose. The vaccine should be stored at -20°C. Before administration, liquid frozen

vaccine vial will be shifted from -20°C to room temperature for thawing. The liquid vaccine will be administered per oral.

- ROTAVAC 5D® (Liquid formulation)
    - Vaccine is a live, attenuated G9P[11] monovalent vaccine to be administered in a dose of 0.5 mL containing NLT log $10^{5.0}$ focus forming units (FFU) per dose. Since this is a fully liquid vaccine stored at 2-8^{0}C, no thawing is required before administration. The liquid vaccine will be administered per oral.
- Rotarix®
    - Live attenuated RIX4414 strain of human rotavirus of the G1P[8] type containing not less than $10^{6.0}$ CCID50 (cell culture infectious dose 50%) of the RIX 4414 strain of human rotavirus. 1.5 ml of the liquid vaccine will be administered per oral.

4 Statistical Methods

4.1 Analysis Populations

4.1.1 Enrolled Population

The enrolled population is defined as all screened participants who provide informed consent and are eligible for study participation, regardless of the participant's randomization and treatment status in the study.

4.1.2 Safety Population

The safety population is defined as all participants in the enrolled population who received a study vaccination and had any safety data available. Participants in the safety population will be analyzed as "treated", i.e. according to the actual vaccine received at the first dose. All safety analyses will be performed using this population.

4.1.3 Full Analysis (FA) Population

The full analysis population is defined as all participants in the enrolled population who were randomized, received a study vaccination, and provided at least one evaluable serum sample.

This population will be mainly used for immunogenicity analyses. The immunogenicity analysis based on this population will serve as supportive results for all immunogenicity objectives.

Participants in the Full Analysis (FA) population will be analyzed "as randomized", i.e. according the vaccine a participant was designated to receive, which may be different from the vaccine that the participant actually received at the first dose of vaccination.

4.1.4 Per Protocol (PP) Population

The per-protocol population is defined as all participants in the FA population who correctly received study vaccine per randomization with no major protocol deviations that are determined to potentially interfere with the immunogenicity assessment of the study vaccines. This population will serve as the primary analysis population for all immunogenicity objectives.

Any major protocol deviation specified as "Yes" in the column "Affects immune response" of External PD listing will be excluded from Per Protocol (PP) population.

Due to unpredictability of some irregularities, the criteria for exclusion of participants from the Per Protocol (PP) population will be determined before the database is locked.

4.1.5 ELISA - Strain 89-12 Per Protocol Population

ELISA - Strain 89-12 Population is defined as a subset of 150 paired samples of participants with no major protocol deviations (i.e. protocol violations) affecting immunogenicity who are randomly selected for testing using ELISA using strain 89-12 as viral lysate. This population will be used for exploratory immunogenicity endpoints related to strain 89-12 and will be used to compare the results obtained in this population using the two assays.

4.1.6 Protocol Deviations and Violations

A Protocol Violation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the study which may affect the safety of trial participants or the study outcomes e.g. wrong kit administered leading to wrong randomization, Enrolment of participants that do not meet inclusion / exclusion criteria and may impact immunogenicity analysis.

A Protocol Deviation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes. Examples of deviations include a protocol visit date outside the study visit window or an isolated incident of a missed or incomplete study procedure or study evaluation.

All deviations will be categorized as Protocol Deviations and Protocol Violations and will be summarized and listed as finalized in approved mock TLGs. The analysis of protocol deviation and violation will be based on safety population

Specific criteria for exclusion of data from the Per Protocol and Immunogenicity analyses are shown in the Table 4.

Table 4 Analysis Population Inclusion / Exclusion

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
1.	Did not meet I-E criteria but randomized	Participant did not meet inclusion criterion	Participant did not meet inclusion criterion 1: Healthy infant as established by medical history and clinical examination before entering the study.	No PD review	Exclude
2.	Did not meet I-E criteria but randomized	Participant did not meet inclusion criterion	Participant did not meet inclusion criterion 2: Age: 6-8 weeks (42-56 days, both days	No PD review	Exclude

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			inclusive) confirmed by Immunization Record.		
3.	Did not meet I-E criteria but randomized	Participant did not meet inclusion criterion	Participant did not meet inclusion criterion 3: Infants received age-appropriate EPI vaccines till enrolment.	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing performed prior to database lock
4.	Did not meet I-E criteria but randomized	Participant did not meet inclusion criterion	Participant did not meet inclusion criterion 4: Ability and willingness to provide informed consent as per local consenting procedures.	No PD review	Exclude
5.	Did not meet I-E criteria but randomized	Participant did not meet inclusion criterion	Participant did not meet inclusion criterion 5: Parent can be contacted on phone and confirms intention to remain in the study area with the participant during the study period.	No PD review	Include

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
6.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 1: Presence of diarrhea or vomiting in the previous 72 hours or on the day of enrolment (temporary exclusion).	No PD review	Exclude
7.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 2: Presence of fever on the day of enrolment (temporary exclusion).	No PD review	Include
8.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 3: Acute disease at the time of enrolment (temporary exclusion).	No PD review	Include
9.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 4: Concurrent participation in another clinical trial throughout the entire timeframe of this study.	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing performed prior to database lock

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
10.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 5: Presence of severe malnutrition (weight-for-height z-score < -3SD median).	No PD review	Exclude
11.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 6: Any systemic disorder cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrine, immunological, dermatological, neurological, cancer or autoimmune disease) as determined by medical history and/or physical examination which would compromise the child's health or is likely to result in non-conformance to the protocol.	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing performed prior to database lock
12.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 7: History of congenital abdominal disorders, intussusception,	No PD review	Include

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			abdominal surgery		
13.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 8: Known or suspected impairment of immunological function based on medical history and physical examination.	No PD review	Exclude
14.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 9: Prior receipt or intent to receive rotavirus and other age specified EPI vaccines outside of the study center and during study participation.	No PD review	Exclude
15.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 10: A known sensitivity or allergy to any component of the study vaccine.	No PD review	Include
16.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 11: Clinically detectable significant congenital or	PD review	Decision will be taken on the case by case basis during the review of final protocol

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			genetic defect.		deviation listing performed prior to database lock
17.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 12: History of persistent diarrhea (defined as diarrhea more than 14 days).	No PD review	Exclude
18.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 13: Participant's parents not able, available or willing to accept active follow-up by the study staff.	No PD review	Include
19.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 14: Has received any immunoglobulin therapy and/or blood products since birth or planned administration during the study period.	No PD review	Exclude
20.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 15: History of chronic administration (defined as more than 14 days)	No PD review	Exclude

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			of immunosuppressants including corticosteroids. Infants on inhaled or topical steroids may be permitted to participate in the study.		
21.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 16: History of any neurologic disorders or seizures.	No PD review	Include
22.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 17: Any medical condition in the parents/infants that, in the judgment of the investigator, would interfere with or serves as a contraindication to protocol adherence or a participant's parent's/legally acceptable representative's ability to give informed consent.	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing performed prior to database lock
23.	Did not meet I-E criteria but randomized	Participant met exclusion criterion	Participant met exclusion criterion 18: Participant is a direct descendant (child or grandchild) of any	No PD review	Include

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			person employed by the Sponsor, the CRO, the PI or study site personnel.		
24.	Randomized to wrong treatment arm	Dosed with wrong treatment arm at visit 1	Received vaccine which is not as per randomization schedule generated for the study	No PD review	Exclude
25.	Wrong IP administered	Wrong vaccine of other arm administered at Dose 2 / Dose 3	Due to wrong IP allocation, the participant received vaccine which is not as per randomization schedule generated for the study	No PD review	Exclude
26.	Wrong IP administered	Damaged / Expired / Quarantined IP used without prior approval	Participant received expired / damaged / quarantined vaccine	No PD review	Exclude
27.	Received Prohibited Medication /Vaccinations / Therapies	Receipt of blood products/ immunoglobulins outside the study center	Receipt of Prohibited Medication / immunoglobulin therapy and / or blood products during the study period.	No PD review	Exclude
28.	Received Prohibited Medication /Vaccinations / Therapies	Received Licensed Rotavirus vaccine during the study	Administration of any protocol prohibited vaccine including Licensed Rotavirus vaccine (outside of the	No PD review	Exclude

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			study centre) during the study period.		
29.	Missed Visit Procedure	Post vaccination assessment missed	Study Procedure related to Medical History / Physical Examination / Vital signs / AE / SAE / 30 mins observation post vaccination is not performed.	No PD review	Include
30.	Missed Visit Procedure	Post-vaccination blood sample missed to be collected from eligible participant	Post-vaccination blood Sample collection is not performed for immunogenicity	No PD review	Exclude
31.	Missed Visit Procedure	Assessments (e.g. PE, vitals) at scheduled Visits	Study Procedure related to Medical History / Physical Examination / Vital signs / AE / SAE were not performed at scheduled visits.	No PD review	Include
32.	Deviation to allowable window period	Post vaccination assessment done beyond protocol specified timeline	Study Procedure related to Medical History / Physical Examination / Vital signs / AE / SAE / 30 min observation post vaccination is not performed within specified window period	No PD review	Include

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
33.	Deviation to allowable window period	Study Procedure Not Performed as per Protocol Visit Schedule	First Dose of vaccine/placebo is not administered orally at 6-8 weeks (42- 56 Days) of life of infant.	No PD review	Exclude
34.	Deviation to allowable window period	Blood sample collected outside specified window period	Blood Sample Collection done after 4 (+1) weeks after last dose of study vaccination	No PD review	Exclude
35.	Deviation to allowable window period	Dose 1 administration beyond 24 hours of randomization	Dose 1 is administration after 24 hours of randomization	No PD review	Include
36.	Deviation to allowable window period	Out of Window Dose 2 Vaccine Administration	Second Dose of vaccine is not administered as per window period (28 to 35 days from Dose 1)	No PD review	Exclude
37.	Deviation to allowable window period	Out of Window Dose 3 Vaccine Administration	Third Dose of vaccine is not administered as per window period (28 to 35 days from Dose 2)	No PD review	Exclude
38.	Study vaccine administration	Any of the study vaccine dose not administered	Any of the study vaccine dose not administered	No PD review	Exclude
39.	Temperature excursion	Temperature excursion: transit/ storage (IP)	Vaccine has been administered despite a storage temperature deviation not approved by the sponsor or vaccine has been	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
			administered from a batch where the temperature was not monitored.		performed prior to database lock
40.	Inappropriate Blood Collection / Processing	Blood sample not processed correctly as per requirement	Blood sample for immunogenicity not processed correctly as per requirement	PD review	Decision will be taken on the case by case basis during the review of final protocol deviation listing performed prior to database lock
41.	Study vaccine administration	Incorrect route of vaccine administration	Incorrect route of vaccine administration	No PD review	Exclude
42.	Study drug administration	Vaccine has been administered out of the expiration date at the time of administration without sponsor's approval.	Vaccine has been administered out of the expiration date at the time of administration without sponsor's approval.	No PD review	Exclude
43.	Informed Consent Not Taken	--	Informed Consent is Not Taken at screening visit	No PD review	Exclude
44.	Incorrect/Unapproved ICF version used	--	Incorrect/Unapproved ICF version is used at screening visit	No PD review	Include
45.	Incorrect Informed consent process followed	Impartial Witness not used	Impartial Witness is not used at screening visit	No PD review	Include

Number	Protocol Deviation Category	Protocol Deviation Subcategory	Detailed Exclusion Description	PD Assessment	Decision for Per Protocol Population
46.	Dosed when withdrawal / discontinuation criteria met.	Dosed when withdrawal / discontinuation criteria met. (except discontinuation reason - Prohibited Medication)	Participant is discontinued from the study with any reason except discontinuation reason - Prohibited Medication	No PD review	Include
47.	SAE not reported within timelines	Initial SAE reporting not done within the timelines	Initial SAE reporting is not done within the timelines	No PD review	Include
48.	Due Analysis not reported within timelines	Due analysis report not shared within the timelines	Due analysis report is not shared within the timelines	No PD review	Include
49.	Immunogenicity result not available	Serological results unavailability	Serological results not available for any of the antigens tested (including lost samples, blood sample not done, unable to test, absence of parallelism).	No data review. This exclusion will be filtered at "Analysis Level"	Exclude
50.	Study vaccine administration	Vomiting after repeat dose administration	Subjects who had vomiting/ regurgitation within 5 minutes of repeat dose vaccine administration	No data review. This exclusion will be filtered at "Analysis Level"	Exclude

4.2 Timing of Analysis

No interim analysis is planned. A final analysis on all safety and immunogenicity data will be performed after the end of study participation for all participants and database is cleaned and locked.

4.3 Methods for Handling Missing Data

4.3.1 Handling of Missing Data of Study Completed Subjects

Generally no imputation will be made for missing values in immunogenicity analyses, the data will be treated as missing at random and will not be analyzed, except for the following:

- Serum anti-rotavirus IgA antibody concentrations below the lower limit of quantitation (<LLOQ) (i.e., below the starting dilution of assay recorded as "< LLOQ") will be set to half that limit (i.e., LLOQ / 2).

LLOQ value will be obtained from laboratory responsible for performing immunogenicity analysis and will be documented in approved "Data Transfer Specification" document. This will be used as reference document to do programming related to external Immunogenicity data transferred by Data Management team.

For all other safety endpoints except AE the missing data will be treated as missing at random and will not be imputed.

4.3.2 Handling Missing Data of Dropouts

For any participant who withdraws prematurely from the study, all available data up to the time of discontinuation will be included in the analyses as appropriate. Data are assumed to be missing at random and therefore missingness is ignorable.

A listing of discontinued participants by study groups will be provided.

The Early Termination (ET) visit data (if ET visit is performed) will always be mapped with end of study visit for safety analysis.

Thus, if data is missing after applying re-test and ET visit criteria then that data will be treated as missing at random and no imputation techniques will be applied. The ET visit data will be used for safety Analysis.

Unsolicited Adverse Events Data:

If partial data is missing then following rules will be followed:

- Unsolicited AEs / SAEs with a missing severity will be treated as "Missing".
- Missing / Unknown relationship to study vaccine will be regarded as "Missing" to study vaccine
- If for Start date - day of event / condition is missing for any adverse event then it will be imputed as the first day of the month or the previous vaccination day whichever is later.
- If for Start date - day and month of any adverse event is missing then it will be imputed as the date of previous dose of study vaccine administered to participant.
- If Stop date of any adverse event is missing then it will be treated as missing.

Thus missing data for safety will be treated as missing at random except for Start date of AE.

4.3.3 Handling of Screen Failures / Ineligible subjects

Participants failing to meet inclusion criteria and those who meet exclusion criteria at screening visit will not be randomized to either of the three study arms. A listing of screen-failure participants will be provided with the following reasons of screen failure along with details if available:

- Participant not fulfilling inclusion criterion / criteria only
- Participant fulfilling the exclusion criterion / criteria only
- Participant not fulfilling inclusion criterion / criteria and fulfilling the exclusion criterion / criteria
- Other
- Participant not fulfilling inclusion criterion / criteria along with Other
- Participant fulfilling the exclusion criterion / criteria along with Other
- Participant not fulfilling inclusion criterion / criteria and Participant fulfilling the exclusion criterion / criteria along with other

4.4 Statistical Analysis

All statistical analysis relating to the study will be performed on statistical software, Statistical Analysis System (SAS), version 9.4 or later.The quantitative variables will be summarised by study vaccine groups as Number of participants (n), Missing data [n (Missing)], Mean, Standard Deviation [Mean (SD)], Median, Range - Minimum and Maximum [Range (Min, Max)]. The qualitative variables will be summarised by study vaccine groups as Number of participants (n) and percentage (%) [n (%)]. All data used to provide summaries will be listed.

4.4.1 Derived Data

- **Baseline Values:**

Baseline value of any parameter is defined as the latest non-missing value of the parameter on or before the date of administration of first dose of study vaccine

- **Date of birth:**

The “Date of Birth (DOB)” is mandatory field in the eCRF.

Based on Date of birth the age will be calculated using following formula:

Age at screening (weeks) = (Date of screening visit – Date of birth) / 7

Age at Dose j (weeks) = (Date of Vaccine administration at Dose j – Date of birth) / 7, where j =1, 2, 3

- **End of Study value:**

End of Study value is defined as the latest available value after the date of first dose of the study vaccine and prior to the Date of last clinic visit / Date of last contact whichever is the later date.

- **Assessment window:**

In general, visit-specific evaluations will be taken as nominal visit value in days without any consideration of window days around the visit Days. The only exception is with ET visit evaluations, which will be windowed with End of the study visit for safety analysis as specified in section 4.3.2.

4.4.2 Multiplicity Consideration

No multiplicity adjustment will be carried out as ROTAVAC 5D® and ROTAVAC® will be primarily compared based on a single primary endpoint.

4.4.3 Transformed Data

Other than log-transformations for the immunogenicity data, no other data transformations are planned.

4.4.4 Covariates

For immunogenicity analysis baseline concentrations will be evaluated as covariate in analysis of covariance (ANCOVA). This adjusted analysis will be considered as supportive.

4.4.5 Study Centre's

This study was conducted at a single center at George Health Centre in Lusaka working under the Centre for Infectious Disease Research in Zambia (CIDRZ), Zambia.

4.4.6 Subject Disposition

The number of screened participants will be provided without reference to study vaccine groups. The Number and percentage of participants who were screen failures, along with the reason of screen failure will be provided.

"Participants Randomized in the Study" include all participants to whom a randomization number is allotted irrespective of whether they receive first dose of the study vaccine. The number and percentage of participants randomized to each study vaccine groups, will be provided.

"Participants Eligible but not Randomized" are those screened participants who are eligible for the study but are not randomized to any of the study vaccine group.

"Participants Randomized but not Vaccinated" are those participants who have been randomized to one of the study vaccine groups but had not received first dose of the study vaccine. Thus randomized participants may include dropouts before first dose administration of the study vaccine. These discontinuations from the study prior to vaccination will be summarized by study vaccine group along with reasons for discontinuation, using enrolled population.

"Participants who completed the Study", are those participants who received all doses planned in the protocol based on vaccine group and completed last scheduled clinic visit as specified in the protocol [i.e. visit 4 for ROTAVAC 5D® and ROTAVAC® or visit 3 for ROTARIX®, i.e. participant did not prematurely discontinue the study up to the visit 4/visit 3 and received all three/two doses of study vaccine of ROTAVAC 5D® and ROTAVAC® or ROTARIX® respectively].

"Participants who completed the Safety Follow-up but Discontinued from Study Vaccination" are those participants who did not receive all doses planned in the protocol based on vaccine group but completed last scheduled clinic visit as specified in the protocol i.e. completed visit 4 for ROTAVAC 5D® and ROTAVAC® or completed visit 3 for ROTARIX®.

Premature/ Vaccine discontinuation from the study will be summarized by study vaccine group along with reasons for discontinuation, using enrolled population.

The summary of protocol deviations and protocol violations will be provided by study vaccine group using the enrolled population. All protocol deviations and protocol violations captured during the study conduct will be provided as listing. The protocol deviations and protocol violations listing will be provided for enrolled population.

The number and percent of participants in each analysis population will be provided by study vaccine group.

4.4.7 Baseline Characteristics

The baseline analyses will be presented for Enrolled population except for Demographic data. For the demographic analysis, Enrolled and FA populations will be used. Baseline immunogenicity data in terms of GMC of serum anti-rotavirus IgA antibodies measured by ELISA will be presented along with planned immunogenicity analyses at 28 days after the last dose of a study vaccine.

4.4.7.1 Demographics

Demographic and baseline characteristics (age, ethnicity, sex, length, and weight) will be tabulated by vaccine group on the Enrolled and FA populations. If more than 10% of the FA population is excluded from the PP population, the description and comparability of the vaccine groups at baseline will be repeated on the PP population if analyzed for demographics. Continuous variables, such as age, length, and weight, will be described as number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables, such as ethnicity, Race and sex, will be described by number of participants and percentage for each vaccine group.

Vaccine group comparison will be performed to confirm whether the vaccine groups are similar with regard to demographic and baseline characteristics. Continuous variables will be compared among using Analysis of Variance (ANOVA) and categorical variables will be compared among groups using Fisher's exact test / Monte Carlo method as appropriate.

The type of demographic variables and the corresponding analysis will be presented by study vaccine group as per details provided in the table given below:

Variable	Type of Variable	Type of Analysis	Unit of Measurements	Formulae for Derived Variable
Age at Baseline	Quantitative	Summary Statistics by study vaccine groups and P Value by ANOVA	Weeks	Age at Baseline = (Date of Vaccine administration at Dose 1 – Date of birth) / 7, where j =1 Age at baseline is Age at Dose 1
Gender	Qualitative (Male/ Female)	Frequency and Percentage by study vaccine group and p-value by Fishers Exact test	Not applicable	--
Weight at birth	Quantitative	Summary Statistics by study vaccine group and p-value by ANOVA	Kilogram (Kg.)	--
Ethnicity	Qualitative	Frequency and Percentage by study vaccine group and	Not applicable	--

Variable	Type of Variable	Type of Analysis	Unit of Measurements	Formulae for Derived Variable
		P Value by Fishers Exact test / Monte Carlo method as appropriate		
Race	Qualitative	Frequency and Percentage by study vaccine group and P Value by Fishers Exact test / Monte Carlo method as appropriate	Not applicable	--
Current weight	Quantitative	Summary Statistics by study vaccine group and p-value by ANOVA	Kilogram (Kg.)	--
Current length	Quantitative	Summary Statistics by study vaccine group and p-value by ANOVA	Centimeter (cm)	--
Weight-for-height z-score ≥ -3SD median	Qualitative (Yes/No)	Frequency and Percentage by study vaccine group and p-value by Fishers Exact test	Not applicable	--

4.4.7.2 Medical History

Participants will be assessed at screening visit for any medical conditions under medical history and pre-existing conditions.

Medical History will be those medical events which occurred during past (Start Date of Medical Condition <= Screening Visit Date) and stopped before administration of dose 1 of the study vaccine (Stop date of medical condition should be < First Vaccination Date).

Pre-existing conditions are those medical events which occurred during past (Start Date of Medical Condition <= Screening Visit Date) and are ongoing at the time of administration of dose 1 of the study vaccine i.e. (Stop date of condition should be ≥ First Vaccination Date). If the stop date is missing or partial such that the stop date of the event could not be determined unambiguously with respect to date of administration of dose 1 of investigational vaccine, the event will be considered as Pre-existing condition.

Medical history and pre-existing conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 21.1 or higher.The exact version of the dictionary will be mentioned in the footnote of the respective Listings and/or Tables. Medical history and pre-existing conditions of all the participants will be summarized for each vaccine group by System Organ Class (SOC) and Preferred Term (PT). For this analysis, Enrolled and randomized

analysis population will be used. For at least one Medical history and pre-existing conditions, 95% confidence interval using Clopper-Pearson method will be provided for each vaccine group.

4.4.7.3 Prior Medications/Therapies

Medications will be coded as per the World Health Organization Drug Dictionary (WHO-DD). The Listing will be presented with the 1st Level ATC term, 3rd level Anatomical Therapeutic Chemical (ATC) and Preferred Name as finalized in approved mock TLGs. The prior Medication/ therapies will be analysed using ATC Class as 1st Level and 3rd level in the order of ATC Level 1 within that ATC level 3. The version of the WHO DD used will be Version September - 2018 or higher. The exact version will be mentioned in the footnote of the respective Listings and/or Tables.

Prior medications/therapies are medication / therapies started prior to first dose of the study vaccination (Dose 1 Date).

In Dataset "**PAST AND ONGOING MEDICATION RECORD**", field "**Medication was taken"** marked as "Prior to Dose 1" will be considered as Prior Medications.

Prior medications/therapies will be classified as follows:

- Prior medications/therapies stopped before first dose of study vaccination.

Prior Medications/Therapies that were stopped before administration of first dose of the study vaccine, are referred as Prior medications/therapies stopped before treatment start.

Stop date of medication should be ≤ First Vaccination Date in CRF.

- Prior medications/therapies ongoing at the time of first vaccination.

Prior Medications/Therapies that were started before the administration of first dose of study vaccine and were continuing at the time first dose of study vaccination are referred as Prior medications/therapies ongoing at the time of first vaccination.

If the stop date is missing or partial such that the stop date of the medication could not be determined unambiguously with respect to date of administration of dose 1 of the study vaccine the medication will be considered as Prior medications/therapies ongoing at the time of first vaccination.

Stop date of medication should be > First Vaccination Date in CRF.

Prior medications/therapies for each of the above classifications will be summarized as n (%), E where n = Count of Participants (at least one Prior Medication i.e. participants counted only once), % = (n / N) *100 where N=Number of participants in the Safety Population and E = Count of Prior Medication (One participant may be counted more than once) by ATC class and by study groups. For at least one Prior medications/therapies, 95% confidence interval using Clopper-Pearson method will be provided for each vaccine group.

For this analysis, Enrolled and randomized population will be used.

4.4.8 Immunogenicity Analysis

Immunogenicity analysis of this study will be based on serum anti-rotavirus IgA antibody immune response measured by enzyme-linked immunosorbent assay (ELISA). PP population will serve as the primary analysis population while FA population will serve as supportive analysis for all immunogenicity objectives. Participants will be analyzed as per randomized vaccine group.

4.4.8.1 Primary Immunogenicity Analysis

The primary immunogenicity analysis is for the comparison of Geometric mean concentrations (GMCs) of serum anti-rotavirus IgA antibodies 28 days after the last dose of a study vaccine, as measured by enzyme-linked immunosorbent assay (ELISA) using WC3 as the viral lysate.

1. GMCs of Serum Anti-Rotavirus IgA Antibody between the ROTAVAC® and ROTAVAC 5D®

Serum anti-rotavirus IgA antibody Geometric Mean Concentration (GMC) of serum anti-rotavirus IgA antibody assessed at 28 days (+4 to +6 weeks) from third dose of vaccination of participants will be evaluated for the ROTAVAC® and ROTAVAC 5D®. The primary immunogenicity analysis is for the evaluation and comparison of GMC of serum anti-rotavirus IgA antibody between ROTAVAC® and ROTAVAC 5D®. The GMCs will be calculated along with its two-sided 95% CI, by exponentiating the corresponding log10-transformed arithmetic mean and its two-sided 95% CI limits.

Hypothesis:-

To compare the immunogenicity of ROTAVAC® and ROTAVAC 5D® at baseline and 28 days following the last dose of the study vaccine, the following hypothesis will be tested,

Null Hypothesis (H_0): $GMC_{ROTAVAC\ 5D®} / GMC_{ROTAVAC®} \leq ½$

Alternative Hypothesis (H_1): $GMC_{ROTAVAC\ 5D®} / GMC_{ROTAVAC®} > ½$

The GMC will be calculated as:

GMC = antilog (mean [log10 x])

Where x is the serum anti-rotavirus IgA antibody immune response as measured by enzyme-linked immunosorbent assay (ELISA) and 10 is the base of logarithm.

The test will be done at baseline and 28 days following the last dose of ROTAVAC 5D® and ROTAVAC® and will be conducted with one-sided with a type I error rate of 0.025. The ratio of the post-vaccination anti-rotavirus IgA GMCs between the ROTAVAC 5D® and ROTAVAC® groups will be provided with its two-sided 95% CI. The log10-transformed anti-rotavirus IgA concentrations will be used to construct a two-sided 95% CI for the mean difference between the two study groups using t-distribution. The mean difference and corresponding 95% CI limits will be exponentiated to obtain the GMC ratio and the corresponding 95% CI. If the lower limit of the 95% CI of the ratio of GMCs between the ROTAVAC 5D® and ROTAVAC® groups is larger than 1/2, ROTAVAC 5D® is considered to be non-inferior to ROTAVAC®.

The comparison of the GMCs between the two study vaccines will be also performed using Analysis of covariance (ANCOVA) method with log10-transformed anti-rotavirus IgA concentrations 28 days post last dose of vaccination as the dependent variable, the vaccine group as the explanatory variable, and log10-transformed baseline concentrations as a covariate. This adjusted analysis will be considered as supportive.

2. Seroconversion rate 28 days after last dose between the ROTAVAC® and ROTAVAC 5D®

Seroconversion is defined as serum anti-rotavirus antibody IgA concentration, 28 days post last dose of vaccination is

- at least 20 U/mL if a baseline concentration is < 20 U/mL

  OR
- ≥ 2-fold baseline level if a baseline concentration is ≥ 20 U/mL.

The percentage of participants with seroconversion will be computed for the ROTAVAC 5D® and ROTAVAC® groups along with exact two-sided 95% CIs based on Clopper-Pearson method. The difference in the percentage between the two groups will be provided along with its two-sided 95% CI obtained by Miettinen and Nurminen method.

3. Seropositivity rate at baseline and 28 days after last dose between the ROTAVAC® and ROTAVAC 5D®

Seropositivity at any visit is defined as serum anti-rotavirus IgA antibody concentration ≥ 20 U/mL at that respective visit.
The percentage of participants with seropositivity will be computed for the ROTAVAC 5D® and ROTAVAC® groups along with exact two-sided 95% CIs based on Clopper-Pearson method. The difference in the percentage between the two groups will be provided along with its two-sided 95% CI obtained by Miettinen and Nurminen method.

4. Seroresponse rate 28 days after last dose between the ROTAVAC® and ROTAVAC 5D®

Seroresponse will be assessed as a four-fold, three-fold and two- fold rise in antibody concentration from baseline.
n-fold response at 28 days after last dose from baseline is defined as ratio of serum anti-rotavirus IgA antibody concentration at 28 days after last dose to serum anti-rotavirus IgA antibody concentration at baseline ≥ n i.e. [serum anti-rotavirus IgA antibody concentration at 28 days after last dose / Serum anti-rotavirus IgA antibody concentration at baseline] ≥ n and the participant is referred as n-fold responder at 28 days after last dose.
The percentage of participants with Seroresponse will be computed for the ROTAVAC 5D® and ROTAVAC® groups along with exact two-sided 95% CIs based on Clopper-Pearson method. The difference in the percentage between the two groups will be provided along with its two-sided 95% CI obtained by Miettinen and Nurminen method.

5. Geometric Mean Fold Rise (GMFR) at 28 days after last dose between the ROTAVAC® and ROTAVAC 5D®

The Geometric Mean Fold Rise (GMFR; GMC post vaccination / GMC at baseline) will be provided with its two-sided 95% CIs, by exponentiating the difference in means of log10-transformed anti-rotavirus IgA concentrations between post vaccination and baseline and its two-sided 95% CI that will be obtained by paired t-test method.

In addition for each visit when immunogenicity data is assessed, a reverse cumulative distribution (RCD) curve will be created by vaccine group.

4.4.8.2 Secondary Immunogenicity Analysis

The secondary immunogenicity analysis is to evaluate the immunogenicity of Rotarix® 28 days after the last dose of the vaccine, when administered to infants in a two-dose schedule at 6 and 10 weeks of age. This will be descriptive analysis.

1. GMCs of serum anti- rotavirus IgA antibody of Rotarix® at 28 days after last dose

The GMCs will be calculated along with its two-sided 95% CI, by exponentiating (to the Power of 10) the corresponding log10-transformed arithmetic mean and its two-sided 95% CI limits.
The GMC will be calculated as:
GMC = antilog (mean [$\log_{10}$ x])
Where x is the serum anti-rotavirus IgA antibody immune response as measured by enzyme-linked immunosorbent assay (ELISA) and 10 is the base of logarithm.

2. Seroconversion rate 28 days after last dose of Rotarix®

Seroconversion is defined as serum anti-rotavirus antibody IgA concentration, 28 days post last dose of vaccination is

- at least 20 U/mL if a baseline concentration is < 20 U/mL

  OR
- ≥ 2-fold baseline level if a baseline concentration is ≥ 20 U/mL.

The percentage of participants with seroconversion will be computed for the Rotarix® group along with its exact two-sided 95% CIs based on Clopper-Pearson method.

3. Seropositivity rate at baseline and 28 days after last dose of Rotarix®

Seropositivity at any visit is defined as serum anti-rotavirus IgA antibody concentration ≥ 20 U/mL at that respective visit.
The percentage of participants with Seropositivity will be computed for the Rotarix® group along with its exact two-sided 95% CIs based on Clopper-Pearson method.

4. Seroresponse rate 28 days after last dose of Rotarix®

Seroresponse will be assessed as a four-fold, three-fold and two- fold rise in antibody concentration from baseline.
n-fold response at 28 days after last dose from baseline is defined as ratio of serum anti-rotavirus IgA antibody concentration at 28 days after last dose to serum anti-rotavirus IgA antibody concentration at baseline ≥ n i.e. [serum anti-rotavirus IgA antibody concentration at 28 days after last dose / Serum anti-rotavirus IgA antibody concentration at baseline] ≥ n and the participant is referred as n-fold responder at 28 days after last dose.
The percentage of participants with Seroresponse will be computed for the Rotarix® group along with its exact two-sided 95% CIs based on Clopper-Pearson method.

5. Geometric Mean Fold Rise (GMFR) at 28 days after last dose of Rotarix®

The Geometric Mean Fold Rise (GMFR; GMC post vaccination / GMC at baseline) will be provided with its two-sided 95% CIs, by exponentiating the difference in means of log10-transformed anti-rotavirus IgA concentrations between post vaccination and baseline and its two-sided 95% CI that will be obtained by paired t-test method.
In addition for each visit when immunogenicity data is assessed, a reverse cumulative distribution (RCD) curve will be created for Rotarix® group.

4.4.8.3 Exploratory Immunogenicity Analysis

The exploratory immunogenicity analysis is based on anti-rotavirus IgA antibodies measured by ELISA using 89-12 (G1P8 Virus) as the viral lysate in a subset of samples. This will be descriptive analysis.

1 GMCs of serum anti-rotavirus IgA antibodies measured by ELISA using 89-12 (G1P8 Virus) as the viral lysate, 28 days after the last dose of study vaccine of each study Vaccine

The GMCs will be calculated along with its two-sided 95% CI, by exponentiating (to the Power of 10) the corresponding log10-transformed mean and its two-sided 95% CI limits.
The GMC will be calculated as:

GMC = antilog (mean [$\log_{10}$ x])

Where x is the serum anti-rotavirus IgA antibody immune response as measured by enzyme-linked immunosorbent assay (ELISA) using 89-12 (G1P8 virus) and 10 is the base of logarithm.

2 Seroconversion rate 28 days after last dose of each study Vaccine

Seroconversion is defined as serum anti-rotavirus antibody IgA concentration measured by ELISA using 89-12 (G1P8 Virus) as the viral lysate, 28 days post last dose of vaccination is

- at least 20 U/mL if a baseline concentration is < 20 U/mL

  OR
- ≥ 2-fold baseline level if a baseline concentration is ≥ 20 U/mL.

The percentage of participants with seroconversion will be computed for each study vaccine along with its exact two-sided 95% CIs based on Clopper-Pearson method.

3 Seropositivity rate at baseline and 28 days after last dose of each study Vaccine

Seropositivity at any visit is defined as serum anti-rotavirus IgA antibody concentration measured by ELISA using 89-12 (G1P8 Virus) as the viral lysate ≥ 20 U/mL at that respective visit.

The percentage of participants with Seropositivity will be computed for each study vaccine along with its exact two-sided 95% CIs based on Clopper-Pearson method.

4 Geometric Mean Fold Rise (GMFR) at 28 days after last dose of each study Vaccine

The Geometric Mean Fold Rise (GMFR; GMC post vaccination / GMC at baseline), measured by ELISA using 89-12 (G1P8 Virus) as the viral lysate, will be provided with its two-sided 95% CIs, by exponentiating the difference in means of log10-transformed anti-rotavirus IgA concentrations between post vaccination and baseline and its two-sided 95% CI that will be obtained by paired t-test method.

4.4.9 Safety Analysis

Safety events are reported from the time of the first study vaccination through completion of the study at 4 weeks after the final vaccination. Specifically,

- Immediate adverse events will be collected for 30 minutes after each vaccination.
- Solicited AEs to assess systemic reactogenicity will be collected for 7 days after each vaccination. If a solicited AE started during the 7 days (Day 0-6) post vaccination and continues beyond the 7 days it will continue to be reported as a solicited AE.
- Unsolicited AEs and SAEs will be collected from day 0 up to four weeks after last vaccination inclusive. Analysis of unsolicited AEs will be limited to within 28 days after each vaccination whereas for SAEs, all SAEs collected after first vaccination up to 28 days after last vaccination will be included. Unsolicited AEs and SAEs occurred after 28 days of any vaccination will be presented only in Listing and will not be summarized in Table. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not

reported as an AE. AEs characterized as intermittent require documentation of onset and duration of each episode. No specific safety laboratory tests are planned in the study; however, clinical and laboratory investigations conducted in order to diagnose or treat a condition in a study participant will warrant documentation of all the key laboratory results. Events will be followed for outcome information until resolution or stabilization.

For these analyses, safety population will be used and the summaries will be produced by study vaccine group.

The percentage calculation will be based on number of participants in the safety population for whom specific safety endpoint data is available. Thus, the denominators for different safety endpoints may vary according to the number of participants with available data for the specific endpoint. For instance, the solicited systemic adverse event endpoints will be based only on those who have received scheduled dose with the corresponding CRF data regardless of other safety follow-up data.

This population will be used for different safety end points such as solicited AEs, unsolicited AEs, SAEs, Deaths (as per data availability). Once a participant is determined to be in the safety population, the participant will be included in all safety analyses regardless of the availability of individual endpoint data but will be evaluable / analyzed if specific safety endpoint is available.

Thus, to find out the missing safety data of each safety endpoint and thus to fix the denominator of respective safety endpoint the following fields of the eCRF will be used as follows:

- Solicited Adverse Event –Dose 1, Dose 2 and Dose 3: To find out the missing data for each Solicited AE, the field provided in PIDC related to each solicited AE will be used. If the field in the PIDC is blank for all 7 days then Solicited AE data will be treated as missing for that respective dose. Therefore, even though the participant is dosed as per planned schedule still related Solicited AE data of that participant for that respective dose will be treated as missing data. Hence, the participant will not be counted in the denominator of “Solicited AE” analysis of that particular solicited event for that particular dose even if participant is part of safety population.
- Solicited Adverse Event –Any Dose: If Solicited AE data is present for any one dose for that particular solicited AE then participant will be counted for Solicited AE analysis – “Any Dose”. If Solicited AE data is missing for all doses then only “Solicited AE” data will be treated as missing data and the participant will not be counted in the denominator for that particular solicited AE even though participant is part of safety population.
- Unsolicited Adverse Event –Dose 1, Dose 2 and Dose 3: To find out the missing data, the field “Has the participant experienced any Adverse Events since last visit?” will be used. This scheduled visit will be subsequent visit post each dose. If this field is blank along with no data in the “Adverse Event” form of the eCRF then even though the participant is dosed as per planned schedule still related unsolicited AE data of that participant will be treated as missing data and the participant will not be counted in the denominator for that particular dose even though participant is part of safety population.
- Unsolicited Adverse Event / SAEs – Any Dose: To find out the missing data, the field “Has the participant experienced any Adverse Events since the last visit?” will be used. If this field is blank for each scheduled/Unscheduled visit throughout the study along with no data in the “Adverse Event” form of the eCRF then even though the participant is part of the safety population and the participant will not be counted in the denominator of “Unsolicited AE / SAE” analysis. i.e. If unsolicited AE data is present for any one dose then

participant will be counted for Unsolicited AE / SAE analysis – “Any Dose”. If unsolicited AE data is missing for all doses then only “Unsolicited AE” data will be treated as missing data and the participant will not be counted in the denominator for that particular dose even though participant is part of safety population.

- Concomitant Medication – Any Dose: To find out the missing data, the field “Has the participant experienced any Concomitant Medication since the last visit?” will be used. If this field is blank for each scheduled visit throughout the study along with no data in the “Concomitant Medication” form of the eCRF then even though the participant is part of the safety population and the participant will not be counted in the denominator of “Concomitant Medication” analysis.
- For rest of Safety endpoints corresponding CRF data from respective Form will be used for Percentage Calculation. If Data is present then it will be considered for percentage calculation otherwise it will be treated as missing and hence will not be considered for percentage Calculation.

4.4.9.1 Adverse Events

AEs will be coded using the MedDRA dictionary, Version 21.1 or higher except solicited AEs. The exact version of the dictionary will be mentioned in the footnote of the respective Listing and/or Table.

For Solicited AEs, following data will be derived at analysis level for particular event using PIDC data entered in the eCRF and then further required calculations will be done.

- Maximum severity grading

  For Reactions (Protocol specified terms), severity grading of each day will be derived for analysis based on data captured in PIDC table. Where Maximum Severity of Reactions will be considered from Severity of all Days.
- Onset date of the solicited AE

  If Severity (Intensity) of solicited AE > 0 for any event between Day 0 to Day 6 then Onset/Start Date of that event will be derived as Date of last dose received before Event + Earliest Day when the Severity (Intensity) of Solicited AE > “Grade 0”

  E.g. If on Day 0, Severity (Intensity) of solicited AE = “Grade 0” and on Day 1 Severity (Intensity) of solicited AE > “Grade 0” then Onset/Start date of that Solicited AE = Last Dose Date before Event + 1.
- Resolution date of the Solicited AE

  If any Solicited AE is ongoing (as captured in PIDC form) beyond Day 6 then Resolution/Last Symptom Date = End Date captured in PIDC form

  Else if event is resolved on or before Day 6 then Resolution/Last Symptom Date of event will be derived as

  Date of last dose received before Event + Latest Day (i.e. last day between Day 0 to Day 6) when the Severity (Intensity) of Solicited AE > “Grade 0” or the last day when the Severity (Intensity) of Solicited AE is “Missing” or “Not available” during the solicitation period and the Severity (Intensity) of Solicited AE was above “Grade 0” prior to the occurrence of “Missing” or “Not available”.

  E.g. If on Day 3, Severity (Intensity) of solicited AE > “Grade 0”and on Day 4 Severity (Intensity) of solicited AE = Grade 0 then Resolution/Last Symptom date of that Solicited AE = Date of last dose received before Event + 3.

If on Day 3, Severity (Intensity) of solicited AE > “Grade 0”and on Day 4, Severity (Intensity) of solicited AE = “Missing or Not available” and on Day 5 and Day 6 Severity (Intensity) of solicited AE = Grade 0 then Resolution/Last Symptom date of that Solicited AE = Last Dose Date before Event + 4.

- Outcome of Solicited AE

Outcome of Solicited AEs will be derived as follows:
If in eCRF field “Ongoing on Day 6” is “No” then outcome will be considered as “Recovered/Resolved”.
Else if in eCRF field “Ongoing on Day 6” is “Yes” and Resolution date of Solicited Event is present then outcome will be considered as “Recovered/Resolved”
Else if in eCRF field “Ongoing on Day 6” is “Missing” and Solicited Event is resolved earlier than Day 6 then outcome will be considered as “Recovered/Resolved”
Else if in eCRF field “Ongoing on Day 6” is “Yes” and Resolution date is missing then outcome will be considered as “Ongoing”.
The unsolicited AEs / SAEs will be coded using the categories of Preferred Term (PT) and System Order Class (SOC) from MedDRA. In case the preferred term for any event is not available / coded then Preferred Term by the Investigator Reported Term of respective AE will be considered as Preferred Term in the tables and for identification it will be marked as “#”. SOC term will contain mainly Primary SOC Term. If Primary SOC terms are missing, then SOC will contain the text like “Code Not Available”.
For solicited reactions coding will not be performed so, protocol specified term will be used for analyses.
All safety analysis will be summarized by study vaccine group and by visits (if applicable). Listings for all the AEs (Reactogenicity and Unsolicited Adverse Event), Immediate Adverse Event (IAEs) and SAEs will be provided for each participant as finalized in approved mock TLGs. IAEs and SAEs will be included in “Unsolicited AEs”. Any AE will be summarized as frequency and percentages [n (%), E], by study groups.
Where
n is the number of participants who experienced that particular AE post each vaccination and overall study.
% Percentages w.r.t. number of participants who experienced event post that particular vaccination and overall study
E is the number of times that particular AE experienced by participants post each vaccination and overall study.
For Solicited AEs, 95% confidence interval using Clopper-Pearson method will be provided for each vaccine group.
Thus any type of AEs will be summarized as n (%), E where n = Count of Participants (at least one event i.e. participants counted only once), % = (n / N) *100 where N=Number of participants in the Safety Population for whom specific safety endpoint data is available and E = Count of Events (One participant may be counted more than once) for each dose and for overall.

4.4.9.1.1 Immediate Post-vaccination Reactions (IAEs) (within 30 min post vaccination)

IAEs at each dose are defined as adverse events occurring within 30 minutes post study Vaccination. IAEs will be captured on “Adverse Event form” of the eCRF.

The IAEs will be summarized as n (%) E along with 95% CI, by study vaccine groups for each vaccine dose and for overall study (all doses combined) as follows:

- IAEs by SOC, PT and Severity
- IAEs by SOC, PT and Relatedness

4.4.9.1.2 7-Days Post-vaccination Solicited Reactogenicity

The solicited AEs - diarrhea, vomiting, fever, decreased appetite, decreased activity level, irritability will be observed for 7-days post each vaccination. The Solicited AEs will not be coded. Protocol specified terms will be used for analyzing solicited AEs.

For Solicited AEs, severity grading of each day will be derived for analysis based on following table:

Solicited AEs with Maximum Severity as “Grade 0” will be treated as “No Solicited AE” in analysis.

Severity grading of adverse events/reactions

Reactions (Protocol specified terms)	Intensity grade	Parameter
Fever (°C)	0/Normal	Axillary temperature < 37.5°C
	1/ Mild	Axillary temperature ≥ 37.5 – ≤ 38.0°C
	2/Moderate	Axillary temperature > 38.0 – ≤ 39.0°C
	3/ Severe	Axillary temperature > 39.0°C
Diarrhea	0/Normal	0 - 2 looser than normal stools / day
	1/ Mild	3 looser than normal stools / day
	2/Moderate	4 - 5 looser than normal stools / day
	3/ Severe	≥ 6 looser than normal stools / day
Vomiting	0/Normal	Normal (no emesis)
	1/ Mild	1 episode of vomiting / day
	2/Moderate	2 episodes of vomiting / day
	3/ Severe	≥ 3 episodes of vomiting / day
Decreased appetite	0/Normal	Appetite as usual
	1/ Mild	Eating/breast feeding less than usual / no effect on normal activity
	2/Moderate	Eating/breast feeding less than usual / interferes with normal activity
	3/ Severe	Not eating/breast feeding at all
Decreased activity level	0/Normal	Normal (Behavior as usual)
	1/ Mild	Crying more than usual with no effect on normal activity
	2/Moderate	Crying more than usual that interferes with normal activity
	3/ Severe	persistent crying and the child could not be comforted and that prevents normal activity
Irritability	0/Normal	Behavior as usual
	1/ Mild	Drowsiness easily tolerated

Reactions (Protocol specified terms)	Intensity grade	Parameter
	2/Moderate	Drowsiness that interferes with normal activity
	3/ Severe	Drowsiness that prevents normal activity

Solicited AEs will be summarized as n (%) E along with 95% CI, by study vaccine groups for each vaccine dose and for overall study (all doses combined) as follows:

- Solicited AEs by Protocol Specified Term and Maximum Severity
- Solicited AEs by Protocol Specified Term and Action Taken
- Ongoing on Day 6 Solicited AEs by Protocol Specified Term and Maximum Severity.
- Solicited AEs by Protocol Specified Term and Outcome
- Solicited AEs by Protocol Specified Term and Duration. Duration (Days): (Resolution Date of AE - Start Date of AE) +1. Duration = 1 implies that AE resolved on the day of Onset of an AE.
- Solicited AEs by Protocol Specified Term and Onset Day. Onset Day from Dose j (Days): Start Date of AE - Vaccine administration Date of dose j, where j = Dose 1, 2 or 3. Onset = 0 implies that event started on the same day of vaccination and Start Date of AE is the first sign & symptom Date of AE and is derived from PIDC

For each Solicited AE along with frequency and percentage, an exact two-sided 95% CI will also be provided for “At Least one <<Solicited AE>> and overall. Two-sided 95% CI for each vaccine group will be calculated using Clopper-Pearson method.

4.4.9.1.3 Unsolicited Adverse Event

All Adverse Events reported by the parents of the participants or apparent from their physical appearance or vital signs (except for axillary temperature which will be reported under reactogenicity) will be captured on the “Adverse Event Form” of the eCRF, throughout the study. Further, the Immediate Solicited AEs and SAEs (solicited or unsolicited) will also be captured on the “Adverse Event Form” of the eCRF and all these AEs will be referred as unsolicited AEs only. Thus, unsolicited AE analysis will include immediate solicited AEs and SAEs (solicited or unsolicited).

However, unsolicited AEs, including IAEs and SAEs (including intussusception) reported through 4 weeks after each vaccination will be provided by vaccine group, severity, and causality. For each SOC along with frequency and percentage, an exact two-sided 95% CI will also be provided. Two-sided 95% CI for each vaccine group will be calculated using Clopper-Pearson method. AEs after 28 days post last dose will not be analyzed and will be reported only in unsolicited AE listing.

Unsolicited AEs/SAEs analysis will be presented in tables as follows:

- AEs from Dose 1 to up to 28 days Post Dose 1.
- AEs from Dose 2 to up to 28 days Post Dose 2.
- AES up to 28 Days Post Dose 3 (Not Applicable for Rotarix® group).
- AEs of All Dose Combined

Note: Above analysis is not applicable for Immediate Adverse Events. Immediate Adverse events will be presented by Dose wise only.

Grade of Severity of unsolicited reactions, Relatedness categories and Outcome categories captured in the eCRF will be as follows:

- **Severity for unsolicited AE**
    - Grade 1 / Mild - Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.
    - Grade 2 / Moderate - Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.
    - Grade 3 / Severe - Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
    - Grade 4 / Potentially Life Threatening - Potentially life-threatening symptoms with intervention indicated to prevent permanent impairment, persistent disability, or death (the Investigator should not grade a reaction as life-threatening if had it occurred in a more severe form then it might have caused death).
    - Grade 5 / Death- All AEs leading to death are Grade 5 events.
- **Relatedness for unsolicited AE**
    - Related
    - Not Related
- **Outcome for unsolicited AE**
    - Recovered/resolved without sequelae
    - Recovered/resolved with sequelae
    - Ongoing at the end of study
    - Death
    - Stabilized
    - Unknown

The Unsolicited AEs will be overall summarized as n (%) E along with 95% CI, by study vaccine groups for each vaccine dose and for overall study (all doses combined), according to the following categories:

- Any unsolicited AEs
- Related unsolicited AEs
- SAEs
- Related SAEs
- Unsolicited AEs leading to withdrawal from the study
- Unsolicited AEs leading to withdrawal from study vaccination but remaining in the study
- Unsolicited AEs leading to hospitalization

- Any AEs leading to death.

An unsolicited AE leading to withdrawal from study vaccination but remaining in the study will be filtered when on “End of Study Form”, the question “Did the participant complete vaccination?” is ticked as “No” along with reason for vaccine discontinuation is ticked as “Adverse Event” with event code provided, the question “Did the participant complete study?” is ticked as “Yes”.

An unsolicited AE leading to withdrawal from the study will be filtered when on “End of Study Form”, the question “Did the participant complete study?” ticked as “No” along with reason for premature discontinuation ticked as “Adverse Event” with event code provided.

Unsolicited AEs will be tabulated by study vaccine groups, SOC, PT, and severity and by study vaccine groups, SOC, PT and relatedness for each vaccine dose and all doses combined.

When an adverse event occurs more than once for a participant, the severity analysis will be presented as follows

- Within each severity participant will be counted once but could be counted more than once per Unsolicited Event in different Severity

When an adverse event occurs more than once for a participant, the relationship analysis will be presented as follows

- Within each relationship participant will be counted once but could be counted more than once per Unsolicited Event in different relationship

The outcome, onset day, duration, and action taken (action taken for further dose and other action taken for treatment) of the unsolicited AEs will be summarized by study vaccine groups for each vaccine dose and all doses combined. The onset day and duration of the unsolicited AEs will be calculated as follows

- Onset Day from Dose j (Days): (Start Date of AE - Vaccine administration Date of dose j), where j = Dose 1, 2 or 3
- Duration (Days): (Resolution Date of AE - Start Date of AE) + 1

All reported AEs that start after vaccination will be tabulated. If a given disease is already reported as ongoing at the first visit on the medical history pages, it will be counted and tabulated as a vaccine emergent adverse event only if it worsens after the immunization with the study vaccine.

Listing of Unsolicited AEs will be presented.

4.4.9.1.4 Deaths, Serious Adverse Events

AEs which are marked “Yes” for the field “Serious” will be considered as SAEs and will be analyzed and tabulated separately.

SAEs will be captured throughout the study.

Tables of SAEs will be part of Serious Adverse Event section in the table presented during analysis.

The SAEs will be summarized as n (%) E along with 95% CI, by study vaccine groups for each vaccine dose and for overall study (all doses combined), as follows:

- SAEs by SOC, PT and Severity
- SAEs by SOC, PT and Relatedness
- Related SAEs by SOC, PT and Severity

- SAEs by Outcome, Onset Day, Duration, Action Taken (Action taken for further dose and Other action taken for treatment), and Seriousness Criteria
- Fatal SAEs by SOC and PT

Similarly, the onset day and duration of the SAEs will be obtained as follows,

- Onset Day from Dose j (Days): (Start Date of SAE - Vaccine administration Date of dose j), where j = Dose 1, 2 or 3
- Duration (Days): (Resolution Date of SAE - Start Date of SAE) + 1

The Seriousness Criteria of the SAEs is classified as follows,

- 1 - Results in death
- 2 - Is life threatening
- 3 - Requires inpatient hospitalization/ prolongation of existing hospitalization
- 4 - Results in persistent or significant disability/ incapacity
- 5 - Is a congenital anomaly/birth defect
- 6 - Is an important medical event

Listing of Death and SAEs will be provided as finalized in approved mock TLGs.

4.4.9.2 Vital Signs

The vital signs captured in CRF are Weight, Length, Axillary Temperature, Heart Rate and Respiratory Rate.

Listing of vital signs will be provided as finalized in approved mock TLGs.

All the Vital signs will be tabulated and analyzed by study vaccine groups. All quantitative variables will be summarized as Number of participants (n), Missing data [n (Missing)], Mean, Standard Deviation [Mean (SD)], Median, Range, Minimum and Maximum [Range (Min, Max)] by study vaccine groups and visit wise.

Qualitative data i.e. the categories of Axillary Temperature, Heart Rate and Respiratory Rate: Vital signs will be categorized as “Normal (N)”, “Abnormal- Not Clinically Significant (NCS)”, “Abnormal- Clinically Significant (CS)”, “Not Done” or “Missing” and summarized as n (%) by study vaccine groups and visit wise.

Qualitative results of vital sign will be derived using following Reference Ranges and for Clinical Significance “CS” and “NCS” investigator assessment will be used.

The Reference Ranges considered for vital signs are as follows:

Parameter	Units	Lower reference range	Upper reference range
Axillary temperature	Celsius	35.5	37.4
Heart rate	Beats per minute	90	160
Respiratory rate	Breaths per minute	30	55

4.4.9.3 Physical Examinations

Physical examination includes assessment of head, eyes, ears, nose, oropharynx, neck, chest (auscultation), lymph nodes (neck, supraclavicular, axillary, inguinal), abdomen (auscultation and palpation), genitourinary, musculoskeletal, skin (especially injection sites), and neurological is captured in CRF for each clinical visit.

Listing of physical examinations will be provided as finalized in approved mock TLGs.

All these examinations are qualitative results and will be classified as “Normal (N)”, “Abnormal- Not Clinically Significant (NCS)”, “Abnormal- Clinically Significant (CS)”, “Not Done” or “Missing” and will be summarized as n (%) by study vaccine groups and visit wise.

4.4.9.4 Concomitant Medications

Medications/therapies will be coded as per the WHO DD. The Listing will be presented with the Preferred Name, 3rd level ATC, 1st Level ATC term and Modified Term as finalized in approved mock TLGs. The Concomitant Medication will be analysed using ATC Class as 1st Level and 3rd level in the order of ATC Level 1 within that ATC level 3. The Version of the WHO DD used will be Version September 2018 or higher. The exact version will be mentioned in the footnote of the respective Listing. If any 1St Level or 3rd Level ATC Class is missing then ‘Code Not Available#’ will be used.

Medications/Therapies that were started on or after the start of the study treatment are referred to as Concomitant Medications (CM). In Dataset “**PAST AND ONGOING MEDICATION RECORD**”, field “**Medication was taken”** marked as “After Dose 1/ After Dose 2/ After Dose 3” will be considered as Concomitant Medications.

Details of concomitant medications including each medication such as, dose, frequency, route, etc. will be contained in the data listing and will not be summarized / tabulated.

Concomitant Medications/therapies for each of the above classifications will be summarized as n (%), E where n = Count of Participants (at least one Concomitant Medication i.e. participants counted only once), % = (n / N) *100 where N=Number of participants in the Safety Population and E = Count of Concomitant Medication (One participant may be counted more than once) by ATC class by study groups. For at least one Concomitant medications/therapies, 95% confidence interval using Clopper-Pearson method will be provided for each vaccine group.

For this analysis, safety population will be used.

4.4.9.5 Past and Ongoing Vaccination Record

The vaccines received from birth or during the study but not received concomitantly along with study vaccine will be reported in “Past and Ongoing Vaccination” form of the eCRF.

The Listing will be presented with the Preferred Name, 3rd level ATC, 1st Level ATC term and Modified Term as finalized in approved mock TLGs. Details of Past and Ongoing Vaccination such as, Site, route, etc. will be contained in the data listing and will not be summarized / tabulated.

Past and Ongoing Vaccination will be summarized using Preferred Name and Anatomical Therapeutic Chemical (ATC) Class as 1st Level and 3rd level ATC in the order ATC Level 1 within that ATC level 3 and then Preferred Name, by each study groups.

If Preferred Name is missing/ Not Available then Modified preferred term will be presented and if modified preferred term is also missing then investigator reported term will be used in the table instead of Preferred Name term and will be identified as "#" in the related table.

Past vaccination" / "Ongoing vaccination for will be summarized as n (%) where n = Number of Participants (i.e. participant counted only once), % = (n / N) *100 where N=Number of participants in the enrolled and randomized Population. For this analysis, enrolled population will be used.

4.4.9.6 Concomitant Vaccination Record

Concomitant and other vaccines used during the study will be reported in the Concomitant vaccination section of the CRF. Listing of EIP vaccines will be provided separately. Vaccine names will be coded as per the WHO DD. The Listing will be presented with the Preferred Name, 3rd level ATC, 1st Level ATC term and Modified Term as finalized in approved mock TLGs. The Concomitant Vaccination will be analyzed using Preferred Name and Anatomical Therapeutic Chemical (ATC) Class as 1st Level and 3rd level ATC in the order ATC Level 1 within that ATC level 3 and then Preferred Name, by each study groups.

If Preferred Name is missing/ Not Available then Modified preferred term will be presented and if modified preferred term is also missing then investigator reported term will be used in the table instead of Preferred Name term and will be identified as "#" in the related table.

The Version of the WHO DD used will be Version September 2018 or higher. The exact version will be mentioned in the footnote of the respective Listing.

Vaccination that were taken on or after the dose 1 of the study vaccine and received along with study vaccine are referred to as Concomitant Vaccination. Concomitant Vaccination will be captured using the "Concomitant Vaccine Administration Record" form of the eCRF.

Details of concomitant vaccination such as, Site, route, etc. will be contained in the data listing and will not be summarized / tabulated.

The Concomitant Vaccines will be summarized as n (%), by study vaccine groups for each vaccine dose

Where n = Number of Participants (i.e. participant counted only once), % = (n / N) *100 where N=Number of participants in the Safety Population. For this analysis, safety population will be used.

5 Evaluation of Treatment Compliance and Exposure

5.1 Compliance to Study Drug

Treatment compliance is defined as having received all three doses of ROTAVAC® or ROTAVAC 5D® or Two doses of ROTARIX®. Participants with less than full compliance, other than those who discontinued early or were lost to follow-up, will be listed. The compliance column be categorised as follows:

"Full": Participants having received all three doses of ROTAVAC® or ROTAVAC 5D® or Two doses of ROTARIX® and completed Study

"Early Withdrawal": Participants who received less than three doses of ROTAVAC® or ROTAVAC 5D® or less than two doses of ROTARIX® and discontinued early by investigator due to safety reason (AE / SAE) or reason other than lost to follow-up.

"Lost To follow-up": Participants who received less than three doses of ROTAVAC® or ROTAVAC 5D® or less than two doses of ROTARIX® and not completed study due to Lost to follow-up.
"Full but Early Withdrawal": Participants having received all three doses of ROTAVAC® or ROTAVAC 5D® or two doses of ROTARIX® but not completed the study
"Less": Participants who received less than three doses of ROTAVAC® or ROTAVAC 5D® or less than two doses of ROTARIX® and discontinued early by investigator due to reason other than safety (AE / SAE) and reason suggesting noncompliance to protocol or discontinued due to Consent withdrawal by parents or improper vaccine administration i.e. reason for discontinuation of vaccine other than "AE / SAE" or Loss to follow up.

5.1.1 Drug Accountability

Vaccine Accountability records will be maintained throughout the course of the study. The amount of investigational vaccine administered to the study participants and the amount received from and returned to sponsor / designee will be documented at site level. Thus vaccine accountability data will not be provided at analysis level, only the vaccine administration details will be provided.

5.2 Exposure to Study Drug

5.2.1 Extent of Exposure

The number of participants who received number of doses of either of doses of ROTAVAC® or ROTAVAC 5D® or ROTARIX® vaccine will be summarized as frequency and percentage in disposition Table. Tables will be presented for Safety population as finalized in approved mock TLGs.
Listing of vaccine administration for individual participant will be provided along with randomized and actual vaccine received along all details as finalized in approved mock TLGs.

5.3 Subgroup / Exploratory Analysis

Subgroup analysis is not planned as this study is conducted at one site.

5.4 Statistical Analytical Issues

Based on approval received post initiation of study, the vaccine name of "ROTAVAC 5CM" will be replaced by "ROTAVAC 5D" for the analysis in line with addendum to Protocol No. 02 dated 11OCT2019.

6 Interim Analysis and Safety Monitoring Analysis

6.1 Interim Analysis

Not Applicable.
One final statistical analysis will be performed on the data collected during the trial at the end of the study. The external data will be integrated in the database. The data collected will be cleaned and then database lock will be performed and data will be transferred for analysis.

6.2 Safety Monitoring Analysis

The study site Investigators will be responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if concerns arise or if criteria for expedited review of safety data are met.

6.2.1 Protocol Safety Review Team (PSRT)

An internal team, the PSRT, will be established to examine safety at periodic intervals. The Protocol Safety Review Team (PSRT), a group of physicians which includes the principal investigator, other physicians from the site and the medical officer(s) from PATH will routinely monitor safety throughout the duration of the trial. The PSRT will be chaired by a PATH Medical Officer and may seek additional independent expert medical opinion as dictated by needs. The CRO statistician with assistance from the data management staff will provide safety TLGs as per finalized mock TLGs approved by sponsor for the review of safety data by the PSRT. These TLGs will provide at a minimum the following information: 1) accrual and participant status data with regard to completion of study vaccinations and study visits; and 2) summaries of solicited and unsolicited adverse events during the review period 3) Reported SAEs. The PSRT safety review will be conducted by teleconference occurring approximately fortnightly to monthly (depending on rate of enrolment) during the vaccination phase of the study and as needed thereafter for the remainder of the study. An expedited safety review will be carried out within 36 hours of submission of the safety information for the safety events listed below:

Event and relationship to study agent*	**Severity Grade**
SAE, related	All grades
A case of Intussusception	All grades
Unsolicited AE, related	4 and above

* As assessed by investigator or Medical Monitor

The analysis of PSRT will be performed as per mock PSRT tables finalized by sponsor.

6.2.2 Data and Safety Monitoring Board

Not Applicable.

7 Statistical Tables to be generated

Unless otherwise specified,

Decimals places will be provided as follows:

- Percentages will be presented with one decimal place
- Mean and Confidence Interval with one decimal place if raw data is an integer OR to one decimal place more than that used in raw data for fractional numbers (numbers with decimal places).
- Standard Deviations to one decimal more than that used for the mean; median, minimum and maximum will be in the same format as that of raw data
- P-value will be rounded to four decimal places and if it's <0.0001 then will be presented as it is.

14.1 Demographic and Baseline Data Summary

Table 14.1.1 Summary of Participant Disposition – Screened Population

Table 14.1.2 Summary of Reason for Screen Failure

Table 14.1.3 Summary of Participant Disposition by Study Group – Enrolled[1] Population

Table 14.1.4 Summary of Participant Discontinuation – Enrolled Population who received at least one Dose of Investigational Product

Table 14.1.5 Summary of Protocol Deviation and Protocol Violations by Study Groups - Enrolled Population

Table 14.1.6A Summary of Baseline Characteristics: Demographics and Other Characteristics- Enrolled Population

Table 14.1.6B Summary of Baseline Characteristics: Demographics and Other Characteristics - FA Population

Table 14.1.7 Summary of Baseline Characteristics: Medical History by Study Groups – Enrolled Population

Table 14.1.8 Summary of Baseline Characteristics: Pre-Existing Conditions by Study Groups – Enrolled Population

Table 14.1.9 Summary of Quantitative Baseline Vital Signs by Study Groups - Enrolled Population

Table 14.1.10 Summary of Qualitative Baseline Vital Signs by Study Groups - Enrolled Population

Table 14.1.11 Summary of Baseline Physical Examinations by Study Groups - Enrolled Population

Table 14.1.12 Summary of Baseline Characteristics - Prior Medication Stopped Before Study Vaccination - Enrolled Population

Table 14.1.13 Summary of Baseline Characteristics - Prior Medication Ongoing at the Time of Study Vaccination – Enrolled Population

Table 14.1.14 Summary of Baseline Characteristics - Past and ongoing Vaccination – Enrolled Population

14.2 Immunogenicity Data Summary

14.2.1 Primary Immunogenicity Tables

Table 14.2.1.1A Summary of GMCs of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate 28 Days Post-Vaccination–
PP Population

Table 14.2.1.1B Summary of GMCs of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate 28 Days Post-Vaccination–
FA Population

14.2.2 Secondary Immunogenicity Tables

Table 14.2.2.1A Summary of Seroconversion, Seroresponse and GMFR of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate, 28 Days Post-Vaccination – PP Population

Table 14.2.2.1B Summary of Seroconversion, Seroresponse and GMFR of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate, 28 Days Post-Vaccination – FA population

Table 14.2.2.2 Summary of Seropositivity rate at Baseline and 28 Days Post Last Dose of ROTAVAC and ROTAVAC 5D for Serum Anti-Rotavirus IgA Antibody Concentration Measured by ELISA - WC3 Viral Lysate – FA and PP Population

Table 14.2.2.3 Summary of GMCs of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate 28 Days Post-Vaccination for ROTARIX – PP and FA Population

Table 14.2.2.4A Summary of Seroconversion, Seroresponse and GMFR of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate 28 Days, Post-Vaccination for ROTARIX – PP Population

Table 14.2.2.4B Summary of Seroconversion, Seroresponse and GMFR of Serum Anti-Rotavirus IgA Antibody Concentrations Measured by ELISA - WC3 Viral Lysate 28 Days, Post-Vaccination for ROTARIX – FA Population

Table 14.2.2.5 Summary of Seropositivity Rate at Baseline and 28 Days After Last Dose of ROTARIX for Serum Anti-Rotavirus IgA Antibody Concentration Measured by ELISA - WC3 Viral Lysate for ROTARIX – FA and PP Population

14.2.3 Exploratory Immunogenicity Tables

Table 14.2.3.1 GMCs of Serum Anti-Rotavirus IgA Antibodies Measured by ELISA - 89-12 (G1P8 Virus) Viral Lysate at Baseline and 28 Days After Last Dose of Study Vaccine – ELISA - Strain 89-12 PP Population

Table 14.2.3.2 Summary of Seroconversion Rate 28 Days After Last Dose of Study Vaccine for Serum Anti-Rotavirus IgA Antibody Concentration Measured by ELISA - 89-12 Viral Lysate – ELISA - Strain 89-12 PP Population

Table 14.2.3.3 Summary of Seropositivity Rate at Baseline and 28 Days After Last Dose of Study Vaccine for Serum Anti-Rotavirus IgA Antibody Concentration Measured by ELISA - 89-12 Viral Lysate – ELISA - Strain 89-12 PP Population

Table 14.2.3.4 Summary of Geometric Mean Fold Rise (GMFR) at 28 Days After Last Dose of Study Vaccine for Serum Anti-Rotavirus IgA Antibody Concentration Measured by ELISA - 89-12 Viral Lysate – ELISA - Strain 89-12 PP Population

14.3 Safety Data Summary

14.3.1 Immediate Adverse Events (Immediate Vaccine Reactions)

Table 14.3.1.1A Overview of All Immediate Adverse Events: All Dose Combined– Safety Population

Table 14.3.1.1B Overview of All Immediate Adverse Events: After Dose 1– Safety Population

Table 14.3.1.1C Overview of All Immediate Adverse Events: After Dose 2– Safety Population

Table 14.3.1.1D Overview of All Immediate Adverse Events: After Dose 3– Safety Population

Table 14.3.1.2 Summary of Immediate Adverse Events by SOC, PT and Severity – Safety Population

Table 14.3.1.3 Summary of Immediate Adverse Events by SOC, PT and Causality – Safety Population

14.3.2 Solicited Adverse Events (Post-vaccination Reactions)

Table 14.3.2.1A Summary of Solicited Adverse Events by Maximum Severity – All Doses Combined – Safety Population

Table 14.3.2.1B Summary of Solicited Adverse Events by Severity – After Dose 1 – Safety Population

Table 14.3.2.1C Summary of Solicited Adverse Events by Severity – After Dose 2 – Safety Population

Table 14.3.2.1D Summary of Solicited Adverse Events by Severity – After Dose 3 – Safety Population

Table 14.3.2.2A Summary of Solicited Adverse Events ongoing on Day 6 by Maximum Severity – All Doses Combined – Safety Population

Table 14.3.2.2B Summary of Solicited Adverse Events ongoing on Day 6 by Maximum Severity – After Dose 1 – Safety Population

Table 14.3.2.2C Summary of Solicited Adverse Events ongoing on Day 6 by Maximum Severity – After Dose 2 – Safety Population

Table 14.3.2.2D Summary of Solicited Adverse Events ongoing on Day 6 by Maximum Severity – After Dose 3 – Safety Population

Table 14.3.2.3A Summary of Solicited Adverse Events by Action Taken – All Doses Combined – Safety Population

14.3.3 Unsolicited Adverse Events

Table 14.3.3.4D Summary of Unsolicited Adverse Events by Outcome, Onset Day, Duration, and Action Taken – After Dose 3 – Safety Population

Table 14.3.3.5A Summary of Related Unsolicited Adverse Events by SOC, PT and Severity - All Doses Combined – Safety Population

Table 14.3.3.5B Summary of Related Unsolicited Adverse Events by SOC, PT and Severity – After Dose 1 – Safety Population

Table 14.3.3.5C Summary of Related Unsolicited Adverse Events by SOC, PT and Severity – After Dose 2 – Safety Population

Table 14.3.3.5D Summary of Related Unsolicited Adverse Events by SOC, PT and Severity – After Dose 3 – Safety Population

14.3.4 Serious Adverse Events

Table 14.3.4.1 Summary of Serious Adverse Events by SOC, PT and Severity - Safety Population

Table 14.3.4.2 Summary of Serious Adverse Events by SOC, PT and Causality - Safety Population

Table 14.3.4.3 Summary of Related Serious Adverse Events by SOC, PT and Severity - Safety Population

Table 14.3.4.4 Summary of Serious Adverse Events by Outcome, Onset Day, Duration, Action Taken and Seriousness Criteria - All Doses Combined – Safety Population

Table 14.3.4.5 Summary of Fatal Serious Adverse Events by SOC, PT and Severity - Safety Population

14.3.6 Other Safety Information

Table 14.3.6.1 Summary of Quantitative Vital Signs by Study Groups

Table 14.3.6.2 Summary of Qualitative Vital Signs by Study Groups – Safety Population

Table 14.3.6.3 Summary of Physical Examination Results by Study Groups

Table 14.3.6.4 Concomitant Medications Taken Post Study Vaccination by Study Groups – Safety Population

Table 14.3.6.5A Concomitant Vaccinations Taken Post Study Vaccination by Study Groups: All Doses Combined – Safety Population

Table 14.3.6.5B Concomitant Vaccinations Taken Post Study Vaccination by Study Groups: After Dose 1 – Safety Population

Table 14.3.6.5C Concomitant Vaccinations Taken Post Study Vaccination by Study Groups: After Dose 2 – Safety Population

Table 14.3.6.5D Concomitant Vaccinations Taken Post Study Vaccination by Study Groups: After Dose 3 – Safety Population

Table 14.3.6.6 Drug Compliance – Safety Population – Safety Population

Table 14.3.6.7 Summary of Spit or Regurgitate after ROTAVAC / ROTAVAC 5D / ROTARIX administration – Safety Population

8 Statistical Listings to be generated

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Listing 14.3.2.1 Listing of Fatal SAEs

Participant Data Listings

16.2.1 Participants Disposition

Listing 16.2.1.1 Details of Participants who are Screen-Failure

Listing 16.2.1.2 Discontinued Participants

16.2.2 Protocol Deviations

Listing 16.2.2.1 Protocol Violations/ Deviations during the Study

16.2.3 Participants Excluded from FA, PP, Safety Analysis Populations

Listing 16.2.3.1 Analysis Populations

16.2.4 Demographics and Baseline Characteristics

Listing 16.2.4.1 Demographic Data

Listing 16.2.4.2 Baseline Characteristics – Medical History

Listing 16.2.4.3 Baseline Characteristics – Any Other Medical and Surgical Condition

Listing 16.2.4.4 Baseline Characteristics – Prior Medications - I of II

Listing 16.2.4.4 Baseline Characteristics – Prior Medications - II of II

Listing 16.2.4.5 Past and ongoing Vaccination

16.2.5 Compliance and Study Drug Exposure Data

Listing 16.2.5.1 Study Drug Dose Exposure – Vaccine Administration Details

Listing 16.2.5.2 Total Study Drug Compliance

Listing 16.2.5.3 Concomitant Vaccination

Listing 16.2.5.4 Concomitant Medications- I of II

Listing 16.2.5.4 Concomitant Medications- II of II

16.2.6 Individual Immunogenicity Response Data

Listing 16.2.6.1 Details of Immunogenicity Data – Serum Anti-Rotavirus ELISA IgA antibody received from Analytical Laboratory

Listing 16.2.6.2 Immunogenicity Endpoint – Serum Anti-Rotavirus IgA antibody Measured by ELISA

16.2.7 Adverse Events Listings

Listing 16.2.7.1 Listings of Solicited Adverse Events - I of II

Listing 16.2.7.1 Listings of Solicited Adverse Events - II of II

Listing 16.2.7.2 Unsolicited Adverse Events Listings – I of II

Listing 16.2.7.2 Unsolicited Adverse Events Listings – II of II

Listing 16.2.7.3 Serious Adverse Events

16.4 Individual Participant Data Listings

Listing 16.4.1 Participant Eligibility Criteria

Listing 16.4.2 Listing of Vital Signs

Listing 16.4.3 Listing of Physical examination

Listing 16.4.4 Study Completion Status

Listing 16.4.5 Final Randomization List

9 Statistical Graphs to be generated

Figure 14.1 Study Flowchart

14.2 Immunogenicity Figures

Figure 14.2.1 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at Baseline for the Comparison of ROTAVAC with ROTAVAC 5D – PP Population

Figure 14.2.2 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at Baseline for the Comparison of ROTAVAC with ROTAVAC 5D – FA Population

Figure 14.2.3 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at 28 Days After Last Dose for the Comparison of ROTAVAC with ROTAVAC 5D – PP Population

Figure 14.2.4 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at 28 Days After Last Dose for the Comparison of ROTAVAC with ROTAVAC 5D – FA Population

Figure 14.2.5 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at Baseline and 28 Days After Last Dose for ROTARIX – PP Population

Figure 14.2.6 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using WC3 Viral Lysate at Baseline and 28 Days After Last Dose for ROTARIX – FA Population

Figure 14.2.7 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using 89-12 Viral Lysate at Baseline for the Comparison of ROTAVAC with ROTAVAC 5D – ELISA - Strain 89-12 Per Protocol Population

Figure 14.2.8 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using 89-12 Viral Lysate at 28 Days After Last Dose for the Comparison of ROTAVAC with ROTAVAC 5D – ELISA - Strain 89-12 Per Protocol Population

Figure 14.2.9 Reverse Cumulative Distribution Curves for IgA Antibody Immune Response Measured by ELISA using 89-12 Viral Lysate at Baseline and 28 Days After Last Dose for ROTARIX – ELISA - Strain 89-12 Per Protocol Population