A descriptive analysis of the distribution of values observed for each variable will be provided. Search for outliers, logical errors and necessary corrections will be made. The following indicators will be computed (for each hospital and by year, if relevant):

- Number of AGE cases in children age-eligible to be vaccinated with ROTATEQ®;
- Number of RVGE cases in children age-eligible to be vaccinated with ROTATEQ®;
- Number of G1, G2, G3, G4, G9 AGE cases in children age-eligible to be vaccinated with ROTATEQ®.

The study will also describe baseline characteristics (gender, age, locations and month of onset) of cases and controls.

Vaccine effectiveness (VE)

VE will be estimated among children eligible to be vaccinated with ROTATEQ® once the sample size is sufficient to reach 80% statistical power.

In order to measure the VE against RVGE receiving treatments in hospitals, conditional logistic regression will be used to compare the likelihood of ROTATEQ® vaccination (defined as three doses of ROTATEQ® plus 14 days) among RVGE cases to that of RV negative AGE.

VE will be stratified if number allows according to and adjusted for age, gender, calender time, location (urban/rural) and hospital.

The progress report may include the descriptive analysis using the data from the first peak season, check the assumptions (e.g. ROTATEQ® coverage, circulation of serotypes G2/G3/G4 combined) for study size calculation and VE will be estimated once the sample size is sufficient to reach 80% statistical power.

7.8 Quality Control

By signing this protocol, the investigator agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

The investigator will supervise the selected hospitals using the standardized method to collect, store and ship stool samples to a central lab which is qualified for Group A RV antigen testing using ELISA kit for the virus identification and Multiplex RT-PCR for characterizing G and P types.

For vaccination status collected from regional immunization registers/APPs, two trained persons will cross check linkage results and double entry.

For vaccination status collected from vaccination cards, the information will be validated by reviewing the photographs of the vaccination cards.

7.9 Limitations of the Research Methods

The sample size calculation is based on several assumptions. The sample size might be lower than expected due to the uncertainty of those assumptions. There is a risk that the number of RVGE cases due to serotypes G2/G3/G4 will be lower than expected due to a lower than expected circulation of these strains in the upcoming years. Also ROTATEQ® vaccine coverage might be lower than expected in the selected hospital catchment areas or other rotavirus vaccines might be used more frequently making a 1 to 4 ratio impossible

and resulting in decreased statistical power. If this is the case, the study will not be adequately powered to assess the VE against G2/G3/G4 .

As ROTATEQ® is a type 2 vaccine, not covered by the Chinese Health Insurance, there may be a difference in the socioeconomic status between vaccinated and unvaccinated children, resulting in differences in their health care seeking behavior. Children with AGE from families with higher socio-economic status may be more likely to be admitted to hospitals compared to children from families with lower socio-economic status. Therefore, AGE cases occurring in children from families with lower socio-economic status (and thus not vaccinated with ROTATEQ®) might be missed.

7.10 Other Aspects

Not applicable

8 PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study and data will be de-identified at the time of analysis. The privacy of all participants will be well protected and database management will follow local requirements.

The study protocol will be submitted for review and approval by an Independent Ethics Committee.

8.1 Informed Consent

The informed consent will comply with ethic's committee reguirements, applicable laws and regulations and Sponsor requirements. Only data from children whose parents provide informed consent to participate in the study will be collected.

8.1.1 Consent and Collection of Specimens for Future Biomedical Research

Not applicable

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional primary data collection study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

9.1 Adverse Event and Product Quality Complaint Reporting

9.1.1 INVESTIGATOR RESPONSIBILITY:

If adverse events (AEs) or product quality complaints (PQCs) are identified following use of ROTATEQ®, or any other Merck product, then the AE* and/or PQC must be reported according to Table 3.

*For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 9.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Special situations
- Study-specific Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR or special situation

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 3.

The investigator must evaluate each SAE for causality and record causality on the report form for each SAE and NSAR reported.

Table 3. AE and PQC Reporting Timeframes and Process for Investigators and Suppliers

AEs AND PQCs	INVESTIGATOR TIMEFRAMES	SUPPLIER TIMEFRAMES
	Investigator to Supplier [1], [2]	Supplier to Merck [3]

SAE regardless of causality (including study-specific HOIs that meet criteria for SAE) Serious Special Situation, regardless of causality	24 hours from receipt	24 hours from time of receipt from investigator
NSAR (including study-specific HOIs that meet criteria for NSAR) Non-serious Special Situation, regardless of causality	10 CD from receipt	24 hours from time of receipt from investigator
PQC with or without an AE (SAE/NSAR/Special situation)	24 hours from receipt	24 hours from time of receipt
Spontaneously reported AEs/PQCs for Merck products-submit using above timeframes		
Follow-up to any AE/PQC-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
If the investigator elects to submit AEs/PQCs for **non-Merck products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.		
[1] Investigator to Supplier: AEs and PQCs for Merck study product and *other* Merck products are submitted to Supplier via fax or secure email **[2]** Supplier enters AEs for Merck study product into study database (or equivalent repository) for tabulation in study report **[3] Supplier to Merck:** Supplier submits AEs and PQCs for Merck study product and *other* Merck products to Merck for reporting to worldwide regulatory agencies as appropriate		
Submitting AE reports to MSD Local China PV: All AEs and PQCs must be submitted to PPD **in English/Chinese using an AE/PQC form (attached) for reporting to worldwide regulatory agencies as appropriate.**		

9.1.2 STUDY REPORT:

The final study report, and any planned interim analysis, will include aggregate listings of all AEs collected for ROTATEQ® and will be provided to regulatory agencies by the sponsor as required.

The Risk Management Sub-team (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

9.1.3 PERIODIC SAFETY UPDATE REPORTS:

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

9.2 DEFINITIONS

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

9.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

9.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 9.2.3.

9.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

9.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnoses, treatment or procedures. Examples of HOIs include syncope, disease progression, or hypoglycaemia collected as study endpoints. HOIs may meet the criteria of an SAE/SAR, NSAR or special situation, and if so, must be collected as such, in addition to being collected as an HOI. Specifically, collected HOI data must be assessed for the criteria described herein and reported accordingly.

9.2.7 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

9.2.8 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

9.2.9 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.10 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection
The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

9.3 Sponsor Responsibility for Reporting Adverse Events (Optional)

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

9.4 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs and PQCs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs and PQCs will be reconciled on a periodic basis.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

This study will produce a final report to be submitted [redacted] Merck also intends to publish the results after the final report has been accepted [redacted]. For any publication in a peer-reviewed journal, authorship should follow guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/).

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Annex 1 List of stand-alone documents

Not applicable

ANNEX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Adopted by the ENCePP Steering Group on 15 OCT 2018

http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml
ENCePP checklist

The ENCePP checklist must be completed for all EU PASS and non-EU PMSS. The current version of the ENCePP checklist can be obtained on the CORE DRC page.

Annex 3 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

name, address, telephone number and e-mail address;

hospital or clinic address and telephone number;

curriculum vitae or other summary of qualifications and credentials; and

other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

Additional Annexes Should be Added as Necessary

Guidance:

- Annexes and attachments can include but not limited to the product circular, algorithms for defining health outcomes of interest, tables shells for results and standard operating procedure, Future Biomedical Research).
- In addition, dated amendments should be appended. This includes significant changes from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, should be documented in writing and appended to the protocol.
- Any changes made after data analysis has begun should be documented as such and the rationale provided and appended to the protocol.
- It is recommended that amendments be kept to a minimum.
- All protocols that collect DNA (blood) must include the Future Biomedical Research sections unless a waiver is obtained from the Head of Clinical Pharmacogenomics at Merck. Please also consult with the Clinical Pharmacogenomics group at Merck regarding policies/procedures for collection and storage of biomedical specimen and include details in this section. This section applies to prospective studies where DNA samples are being collected and does not apply to retrospective analyses of samples that have already been collected.

12 APPENDICES

Guidance:

- Appendices and attachments can include but not limited to the product circular, algorithms for defining health outcomes of interest, tables shells for results and standard operating procedure, Future Biomedical Research.
- In addition, dated amendments should be appended. This includes significant changes from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, should be documented in writing and appended to the protocol.
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- Please Ensure The Criteria In The Document Below Is Incorporated In Development Of The Protocol Or Model Development Plan (As Appropriate) In Support Of HCEI Evidence Intended For Use In US Promotion Under FDAMA 114

13 ATTACHMENTS

Links to MSD Adverse Event and Product Quality Compliant Report Form and Instructions

MSD Adverse Event and Product Quality Complaint Reporting Form

MSD Adverse Event and Product Quality Complaint Reporting Form Instructions

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