PASS INFORMATION

Title	Post-marketing surveillance to monitor the incidence of intussusception after large-scale vaccination with Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ®) in Chinese infants using the Ningbo Regional Health Information Platform (NRHIP)
Protocol Version identifier	V260-075/VERSION 3.0
Date of last version of protocol	October, 13th, 2020
EU PAS Register No:	EUPAS35812
Active substance	G1：2.2×106 infectious units ；G2：2.8×106 infectious units ；G3：2.2×106 infectious units ；G4：2.0×106 infectious units ；P1A[8]：2.3×106 infectious units
Medicinal product(s):	Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell)
Joint PASS	No
Research question and objectives	The objective of this post-marketing surveillance is to assess the occurrence of intussusception (IS) among Chinese infants who have been vaccinated with ROTATEQ® during routine clinical practice.
Country(-ies) of study	China
Author	Prof. Si Yan Zhan Peking University Health Science Center, Beijing, 100083, China
Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme Corp. P.O. Box 4, West Point, PA19486, U.S.A
Merck Final Repository (RCAM) Date	
Date of Health Authority Approval of Protocol	September 14th, 2020

SUMMARY OF CHANGES

Summary of Changes for Amendment

The protocol has been updated [redacted] to protocol V2.0 to clarify the corresponding statistitical hypothesis.

The specific changes are listed in the table below:

Protocol Section	*Change*
7.7 Data Analysis	• Added null/alternative hypothesis • Added "one-sided" into the last paragraph.

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
ADR	Adverse Drug Reaction
AE	Adverse Event
AGE	Acute gastroenteritis
BCG	Bacillus Calmette-Guerin vaccine
CDE	Center for Drug Evaluation
DSUR	Development Safety Update Report
DTaP	Diphtheria, Tetanus, Pertussis vaccine
EDC	Electronic Data Collection
EMA	European Medicines Agency
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HepB	Hepatitis B vaccine
HOIs	Health Outcomes of Interest
HPV	Human papilloma virus
IPV	Inactivated poliovirus vaccine
IRB	Institutional Review Board
IS	Intussusception
JEV-I	Japanese encephalitis vaccine, live attenuated
JEV-L	Japanese encephalitis vaccine, live attenuated
LLR	Lanzhou Lamb Rotavirus Vaccine
MenA	Group A meningococcal polysaccharide vaccine
MR	Measles-Rubella vaccine
NSAR	Non-Serious Adverse Reaction
OPV	Oral Poliovirus vaccine, live attenuated
PBRER	Periodic Benefit Risk Evaluation Report
PKU	Peking University Health Science Center
PSUR	Periodic Safety Update Report
RR	Relative risk
RV	Rotavirus
RVGE	Rotavirus acute gastroenteritis
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCCS	Self-controlled cases series
SOP	Standard Operating Procedure
WHO	World Health Organization

1 RESPONSIBLE PARTIES

Principal investigator	Si Yan Zhan, PhD
Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD
Other contacts	Not applicable
Vendor/Collaborator	Si Yan Zhan, Peking University Health Science Center.
Investigators	Not applicable
Shared responsibilities	Not applicable

2 ABSTRACT

Title	Post-marketing surveillance to assess the incidence of intussusception after large-scale vaccination with Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ®) in Chinese infants using the Ningbo Regional Health Information Platform (NRHIP)
Protocol Number / Version	V260-075/VERSION 3.0
Date	October 13th, 2020
Author	Si Yan Zhan, Peking University Health Science Center, China; PPD
Rationale & Background	Rotavirus (RV) is the leading cause of severe diarrhea in infants and young children. In China, RV caused over 40% of diarrhea hospitalization and about 30% of diarrhea related outpatients visits in children aged < 5 years. ROTATEQ® is approved in China for the prevention of RV gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4,

	and G9. Following initial licensure of ROTATEQ® in 2005, intussusception (IS) is a recognized and well-characterized safety concern that is adequately addressed in the product label and is currently monitored by the Sponsor as an important identified risk. IS is a rare event in infants and its background incidence in the unvaccinated general population varies in different regions of the world from 9 to 425 cases/100,000 children <1 year per year. It has been estimated to range from 80 to 425 cases/100,000 children <1 year of age per year in China. ROTATEQ® was approved for marketing in China on April 12th, 2018. [redacted]
Research Question(s) & Objective(s)	**Feasibility objective** • To assess the overall feasibility of conducting the study using NRHIP, by assessing the IS diagnosis validity, the completeness of follow-up and the quality of linkage between immunization register and Electronic Medical Records . **Primary objective** • To assess the incidence of IS (confirmed cases, Brighton Level 1) occurring within 3 months after vaccination with ROTATEQ® in Chinese infants. **Secondary objective** • To describe the occurrence of IS (confirmed cases, Brighton Level 1) in the periods 1 to 7 days, 1 to 14 days, 1 to 21 days, 1 to 42 days and 1 day to 3 months following any dose of ROTATEQ ® in Chinese infants;

	• To assess the incidence of IS (confirmed cases, Brighton Level 1) among Chinese infants in the same age range as the infants vaccinated with ROTATEQ® but did not receive any rotavirus vaccine. • To calculate the relative risk (RR) of IS in children vaccinated with ROTATEQ ® compared to children from the same birth cohort and within the same age range who did not receive any rotavirus vaccine.
Study Design	All recipients of ROTATEQ® studied under this protocol received ROTATEQ® in the course of routine clinical practice. The design is a cohort study conducted in Ningbo, China. Infants vaccinated with ROTATEQ® and identified from the immunization registry will be linked to the Electronic Medical Record (EMR) within the Ningbo Regional Health Information Platform (NRHIP) to identify IS cases that occurred within 3 months of vaccination. The comparison group will include infants vaccinated with at least one type 1 childhood vaccine, but no rotavirus vaccine from the same data source. The incidence of IS occurring within 3 months of vaccination with ROTATEQ ® will be compared to the incidence of IS occurring in unvaccinated infants aged 6 to 45 weeks.
Population	All infants aged 6 to 45 weeks from December 2018 to June 2021 from the NRIHIP immunization register, including infants vaccinated with ROTATEQ® (“vaccinated infants”) as well as infants from the same birth cohorts, who received at least one type 1 vaccine but no rotavirus vaccine (“unvaccinated infants”).

Variables	The primary outcome variable includes confirmed IS occurring within 3 months following ROTATEQ® vaccination for vaccinated infants and IS occurring at any time during age 6 to 45 weeks old for unvaccinated infants. Additional variables include clinical and demographic information, including age, gender and resident location (rural and urban) of vaccinated infants.
Data Sources	Data for this study will be obtained via a secondary data collection from the immunization register and EMR of NRHIP. Additional data will be collected from a medical chart review.
Study Size	[redacted]. Based on the current number of vaccinated infants and assuming stable vaccine coverage over 26 study months, we expected to enroll about 16,000 infants vaccinated with at least one dose of ROTATEQ® during the study period. Assuming the annual incidence rate of naturally occurring IS in infants under age 1 in Ningbo city is 100.6-181.8/100,000, and a sample size of 16,000 infants vaccinated with ROTATEQ ®, the statistical power (expressed in percent) to detect a two fold increase in IS during the 39 week period after vaccination will be 76.6-93.1 for a ratio of vaccinated vs. unvaccinated of 1:2 and 81.1-95.2 for a ratio of 1:3.
Data Analysis	The incidence of IS occurring within 3 months after vaccination with ROTATEQ® will be estimated. The occurrence of IS cases will be described with respect to the time-interval post-vaccination and in relation to dose number.

	We will compare the incidence rate (per 100,000 person-years) of IS in vaccinated infants to unvaccinated infants during the concurrent period (December 2018 to June 2021).
Milestones	
Start of data collection:	November 27th, 2018
End of data collection:	June 30th, 2021
Interim report(s) of study results:	Not applicable
Study progress report(s):	Not applicable
Final report of study results:	March, 2022

3 AMENDMENTS AND UPDATES

Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason
<1>	June 3rd, 2020	ABSTRACT, section 5.1, 6, 7.1, 7.2.1, 7.5, 7.6, 7.8, 7.10	Amendment	To address China agency's requests
<2>	October 13rd, 2020	Section 7.7	Amendment	To address China agency's requests

4 MILESTONES

Milestone	**Planned Date**
Start of data collection	November 27th, 2018 (ROTATEQ® launch in Ningbo)

End of data collection	June 30th, 2021
<Registration in the EU PAS register>	not yet registered
Final report of study results	March, 2022

5 RATIONALE AND BACKGROUND

5.1 Background

Rotavirus (RV) is the leading cause of severe gastroenteritis in infants and young children. RV infection was responsible for an estimated 128,500 deaths and 258 million episodes of diarrhea worldwide among children younger than 5 years of age in 2016.[1] In 2009, the World Health Organization (WHO) recommended RV vaccination for all children worldwide, especially in countries with a high number of gastroenteritis-associated deaths.[2] In China, RV caused over 40% of gastroenteritis related hospitalizations and about 30% of gastroenteritis related outpatient visits in children aged < 5 years.[3] Over 50% of RV-related hospitalizations in China occurred by age 1 year and about 90% occurred by age 2 years. Therefore, a vaccine with a schedule that is completed in early infancy has the potential to prevent the majority of the burden of severe RV disease in China.[4]

Currently there are 2 types of RV vaccines available on the market in China: the Lanzhou Lamb RV vaccine (LLR, Lanzhou Institute of Biological Products) and ROTATEQ® (Merck & Co., Inc., Kenilworth, NJ, USA). The LLR vaccine has been in use in China since 2000[5] and contains the genotype G10P[15].[6] ROTATEQ® is an oral, live pentavalent (G1, G2, G3, G4, and P1A[8]) human–bovine (WC3) reassortant rotavirus vaccine. The vaccine is indicated for the prevention of RV gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G9.[7]

ROTATEQ® was approved in China on April 12th, 2018. [redacted]

In 1999, the first licensed RV vaccine, Rotashield, was withdrawn from the market less than 1 year after its introduction into the US childhood immunization program due to an association with intussusception (IS).[8]

IS is a rare event in infants and its background incidence in the unvaccinated general population varies in different regions of the world from 9 to 425 cases/100,000 children <1 year per year.[9-13] It has been estimated to range from 80 to 425/100,000 children <1 year of age in China.[14-17] 77.5% of the cases occuring in infants <1 year are occurred at age 3 to 8 months.[15] A retrospective observation in Liuzhou, Guangxi province estimated the incidence rate of IS before the introduction of ROTATEQ@ to range between 138(95% confidence interval (CI): 81, 221) and 172 (95% CI: 111, 257) per 100,000 person years (py) (unpublished).

Although clinical trials of the next generation RV vaccines, including ROTATEQ® did not show an increased risk of IS, post-marketing data indicate a potential and small elevated risk with this vaccine, particularly after the first dose.

In the Rotavirus Efficacy and Safety Trial (REST),[18] 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of IS within 7, 14, and 42 days after each dose. Overall, there were 6 cases among ROTATEQ® recipients and 5 cases among placebo recipients. The results did not suggest an increased risk of IS relative to placebo with a relative risk (RR) of 1.6 (95% CI: 0.4; 6.4). In addition, among vaccine recipients, there were no confirmed cases of IS within the 42-day period after the first dose. A systematic review and meta-analysis including 38,339 vaccine recipients and 38,363 placebo recipients from 4 clinical trials in 2006 to 2017 did not show an association between ROTATEQ® vaccination and an elevated risk of IS among neonates or infants.[19]

Large cohort studies, conducted in the US between 2006 and 2010 found no increased risk of IS after vaccination with ROTATEQ® as compared to prevaccination background incidence and/or unvaccinated infants.[20-22]

Subsequent studies using a self controlled case series (SCCS) or a self controlled risk interval (SCRI) desing, performed in several countries, indicated that RV vaccines carry

an increased risk of IS, with up to 6 additional cases per 100,000 infants within 7 days of vaccination. It remains unclear whether RV vaccines affect the overall incidence of IS based on longer periods of follow up.[23] In most studies, IS is considered potentially related to RV vaccination if it occurs within 1 month after vaccination.

A meta-analysis on the risk of IS after ROTATEQ® vaccination was performed including 4 post-marketing studies[24-27] using the self-controlled cases series (SCCS) design.[28] It indicated that the RR during 1 to 7 days after the first, second and third dose of ROTATEQ® ranged from 3.5 to 9.9, 1.4 to 2.8 and 0.7 to 1.7, respectively. The pooled estimates of the RR (95% CI) after first, second and third doses were 4.6 (3.1, 6.9), 1.6 (1.2, 2.3) and 1.1 (0.7, 1.7). A retrospective study at a single center in Korea evaluated the relationship between ROTATEQ® vaccination and the risk of IS by dividing the number of observed excess cases by the number of expected cases.[29] It indicated that the RR (95% CI) for all doses and dose 2 were respectively 1.0 (0.1, 5.1) and 3.2 (0.4, 15.6) within 4 weeks after vaccination. No IS cases were observed after dose 1 and dose 3.

To our knowledge, no data has been published as of today, evaluating the IS risk following vaccination with the local RV vaccine, LLR since its licensure in 2000.[5]

5.2 Rationale

Following initial licensure of ROTATEQ® in 2005, IS is a recognized and well-characterized safety concern that is adequately addressed in the product label and is currently monitored by the Sponsor as an important identified risk. In the Chinese label, it is indicated that "In a post-marketing observational study in the US, cases of IS were observed in temporal association within 21 days following the first dose of ROTATEQ®, with a clustering of cases in the first 7 days. "[7]

To minimize the risk of IS, ROTATEQ® has a restrictive age-indication with a first dose to be administered at age 6 to 12 weeks, subsequent doses with a 4- to 10- weeks interval and the third dose at no later than 32 weeks of age.[7]

In the phase 3 clinical trial in China,[30] a total of 4,040 healthy infants aged 6-12 weeks were enrolled and randomly assigned in a 1:1 ratio to receive ROTATEQ® or placebo. Two

IS cases were reported during the entire study period, both in the ROTATEQ® group. One case occurred on Day 32 post dose 1 and the other case on Day 53 post dose 3. Both patients recovered after appropriate treatment.

The aim of our study is to provide information on the incidence of IS after a large-scale vaccination with ROTATEQ® in Chinese infants.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Feasibility objective

- To assess the overall feasibility for conducting the study using NRHIP by assessing the IS diagnosis validity, the completeness of follow-up and the quality of linkage between immunization register and Electronic Medical Record.

6.2 Primary Objective

- To assess the incidence of IS (confirmed cases, Brighton Level 1) occurring within 3 months after vaccination with ROTATEQ® in Chinese infants.

6.3 Secondary Objective

- To describe the occurrence of IS (confirmed cases, Brighton Level 1) in the periods 1 to 7 days, 1 to 14 days, 1 to 21 days, 1 to 42 days and 1 day to 3 months following any dose of ROTATEQ ® in Chinese infants.

- To assess the incidence of IS (confirmed cases, Brighton Level 1) among Chinese infants in the same age range as the infants vaccinated with ROTATEQ® but did not receive any rotavirus vaccine.

- To evaluate the relative risk (RR) of IS in children vaccinated with ROTATEQ ® compared to children from the same birth cohort and within the same age range who did not receive any rotavirus vaccine.

7 RESEARCH METHODS

7.1 Study Design

This study does not involve active administration of ROTATEQ®. All recipients of ROTATEQ® studied under this protocol received ROTATEQ® in the course of usual clinical practice. The design is a cohort study using secondary data from NRHIP to monitor IS incidence within 3 months following ROTATEQ ® vaccination. A comparison group will include infants vaccinated with at least one type 1 childhood vaccine, but no rotavirus vaccine from the same data source. Table 3 provides an overview of the vaccination schedule in China.

All infants will be identified from the NRHIP immunization register, linked to the NRHIP Electronic Medical Records (EMR) and followed to detect a potential occurrence of IS within 3 months of receipt of the last dose (vaccinated infants) or from age 6 weeks to 45 weeks (unvaccinated children). All suspected IS cases will be reviewed by an adjudication committee to confirm IS cases according to the Brighton Collaboration criteria. In cases where the NRHIP EMR records of a suspected case do not contain all the information necessary to adjudicate the case, the medical charts if available, will be reviewed. Number of vaccinated infants, number of IS cases occurring after vaccination with ROTATEQ® overall and by dose and time interval after vaccination, and detailed case description as well as the IS incidence rate in vaccinated infants will be summarized. The relative risk (RR) will be calculated by comparing the incidence of IS that occurred in infants up to 3 months after vaccination with the last dose of ROTATEQ® that they received with the incidence of IS in “unvaccinated infants” during the age 6 to 45 weeks. An up to 1:3 vaccinated: unvaccinated ratio (if number of unvaccinated allows) will be used.

China Expanded Program on Immunization (EPI) covers children from birth to 7 years, included at least 9 type I and 5 type II vaccines. For type I vaccines only, Chinese infants under age 1 will take Bacillus Calmette-Guerin vaccine (BCG) and hepatitis B vaccine (HepB) at birth, Hep at 1 month age, Inactivated poliovirus vaccine (IPV) at 2 months

age, both Oral Poliovirus vaccine, live attenuated (OPV) and Diphtheria-tetanus-pertussis acellular vaccine (DTaP) at 3 and 4 months age respectively, DTaP at 5 months age, HepB at 6 months age, Measles-rubella vaccine, live attenuated (MR), Japanese encephalitis vaccine, live attenuated (JEV-L), and Japanese encephalitis vaccine, inactivated (JEV-I) at 8 months age, as well as Group A meningococcal polysaccharide vaccine (MenA) from 6 months to 18 months age with 2 doses.[31] As the schedule of those type I vaccines overlapped with ROTATEQ® schedule plus 3 months follow-up period, and had almost 100% coverage in China[32], their vaccination date could be considered as the indicator for the completeness of follow-up.

7.2 Setting

The study population is defined as all infants aged 6 to 45 weeks from December 2018 to June 2021 from the NRHIP immunization register, including infants vaccinated with ROTATEQ® ("vaccinated infants") as well as infants from the same birth cohorts, who received at least one type 1 vaccine but no rotavirus vaccine ("unvaccinated infants").

NRHIP is currently the only regional health data platform we can access for this study. The NRHIP was established in 2013 and certified as the "top-level regional platform" by the former China Ministry of Health in 2016. The NRHIP covers the population of Ningbo, which counted approximately 7.9 million inhabitants in 2016.

The city of Ningbo is located in the east of the Zhejiang Province, in the south wing of the Yangtze River Delta, in the middle of China's Southeastern coastline. In 2017, the number of Ningbo city's resident population was about 8.0 million. 61,258 children were born, and the crude birth rate was 10.31‰. A total of 31,873 newborns were male, with a male-to-female ratio of 108:100. In 2017, the disposable per capita income of Ningbo residents was 48,233 yuan (and therefore much higher than the national per capita income in 2017 of 25,973 yuan), with an increase of 8.0% over the previous year.

Inclusion criteria

- All infants aged 6 to 45 weeks from December 2018 to June 2021 from the NRHIP immunization register.

- Infants who received at least one dose of ROTATEQ® at age 6 to 12 weeks as recorded in the NRHIP immunization register will be considered vaccinated infants;

- Infant from the same birth cohort as the "vaccinated infants" who received at least one dose of a type 1 childhood vaccines but no rotavirus vaccine as recorded in the NRHIP immunization register will be considered unvaccinated infants.

Exclusion criteria

- Vaccinated infants:
    - Infants with IS before they received the first dose of ROTATEQ®;
    - Infants who were vaccinated out of the indicated age schedule, i.e., who received a first vaccine dose before 6 weeks or after 12 weeks of age and/or any dose after 32 weeks of age;
    - Infants who received one or more doses of LLR or any other RV vaccines in addition to ROTATEQ® during the study period;
    - Infants without any recorded type 1 vaccination at age 8 to 9 months or until their individual end of follow-up three months after their last ROTATEQ® dose (whatever comes first) as those infants are considered to be lost to follow-up.
- Unvaccinated infants
    - Infants with IS prior to 6 weeks of age;
    - Infants without any recorded type 1 vaccination at age 8 to 9 months are considered to be lost to follow-up.

7.2.1 Study period

The study will be conducted retrospectively with data collection starting at the time when ROTATEQ® became available in Ningbo on November 27th, 2018 and ending on June 30th, 2021.

7.3 Variables

This is a cohort study. All exposure, outcome and covariate variables will be extracted at the end of the study period and linked to their EMR records for a detection of potential IS occurrence.

7.3.1 Exposure

The study product of interest is ROTATEQ®, however this study does not involve active administration of ROTATEQ®. The study will include infants exposed to ROTATEQ® from routine practice and included in the NRHIP immunization registry.

7.3.2 Outcomes

The study outcome is IS occurrence. The case definition for IS for this study conforms to the level 1 criteria from the Brighton collaboration case definition.

7.3.3 Covariates

Following covariates will be abstracted from the NRHIP immunization register and EMR.

From NRHIP immunization register

- Infant's gender;
- Infant's location (urban/ rural);
- Dose number (dose 1, 2, and 3);
- Infant's age in days at dose 1, 2 and 3.

From NRHIP EMR

- Infant's age in days when IS occurred;
- Interval between IS onset and most recent dose prior to the IS onset (1-7 days, 8-14 days, 15-21 days, 22-42 days, 42days -3 months).

7.3.4 Missing data

All analyses will be carried out using all available data. A participant with missing data on one variable will be used only in calculations that do not involve that variable. This allows analysis with larger sample sizes than when using complete case report forms.

7.4 Data Sources

Data for this study will be obtained via secondary data collection from NRHIP. NRHIP contains several major databases for Ningbo residents and registers. The immunization registers and the EMR database are the data sources for the present study.

Table 1. List of variables in the NRHIP immunization register and EMR to be used in the study

Data source		Time range	Key variable
Immunization register	Children	2000- present	ID, vaccination record No., name, date of birth, gender, vaccine name, date of vaccination, age at vaccination, vaccination clinic, dosage, dose No., vaccine batch No., and vaccine manufacturer.
EMR	Outpatient	2015- present	ID, name, date of birth, gender, medical institution No., visit No., time of visit, time of onset, ICD-10[1], prescription No., drug name, dosage, unit, date of prescription, days of dispensing, lab test and its result.
	Inpatient	2015-present	ID, name, date of birth, gender, medical institution No., inpatient No., time of onset, ICD-10, date of discharge.

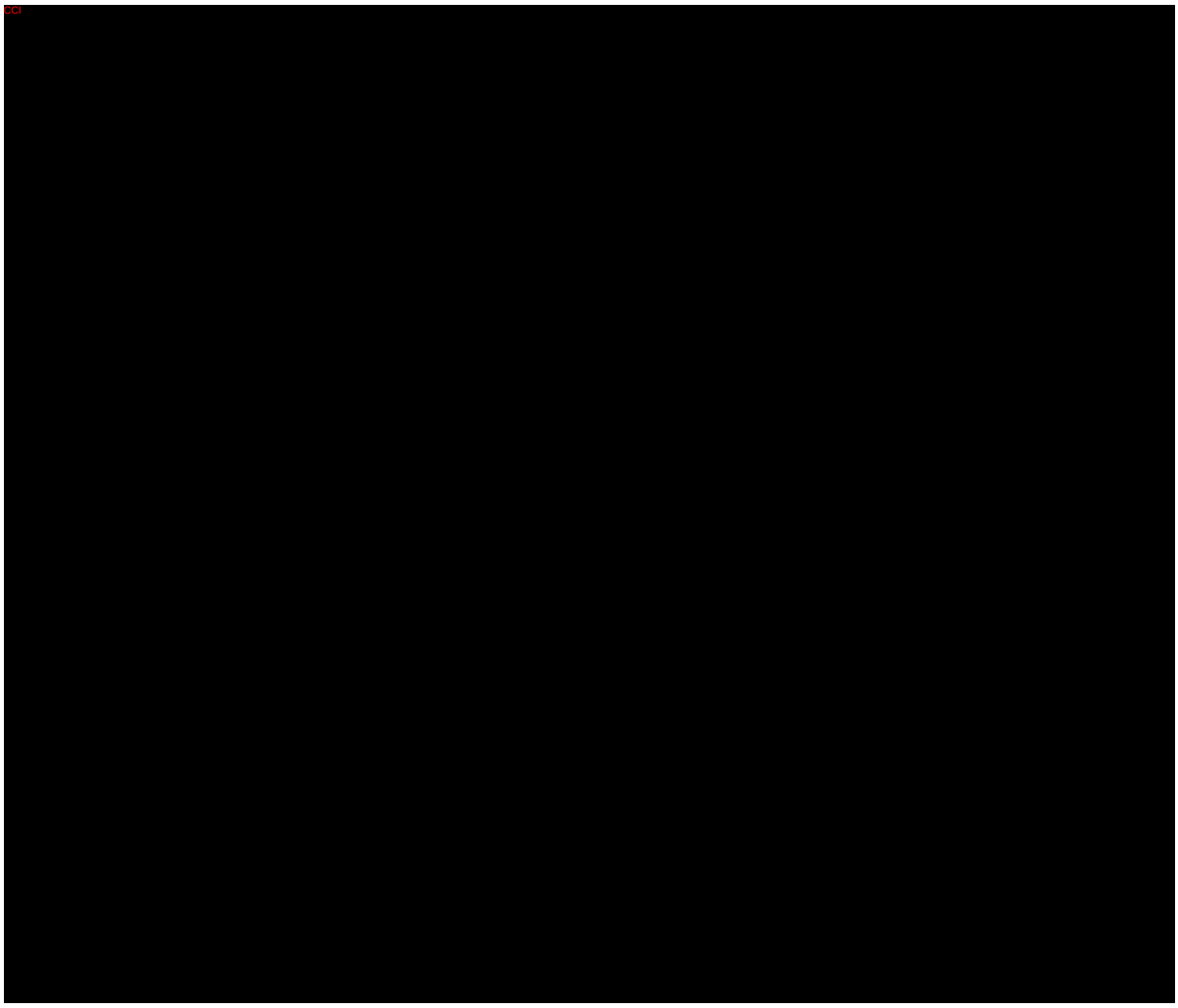
[1] The ICD code will be from 1 to 10 per visit, depends on the situation of patient. All ICD codes are visible at the platform.

NRHIP immunization register

NRHIP covers 11 Centers for Disease Control and Prevention (CDCs). In 2005, the vaccination information system of the Ningbo CDC was completed and fully

implemented covering all vaccination clinics in Ningbo city. There are 167 points of vaccination in Ningbo city, including 10 hospitals and 157 community health service centers.

The vaccination information system collects personal basic information and vaccination records in real time. Personal IDs are registered together with the vaccination records. The records contain personal basic information, vaccination information including vaccine name and lot number. Vaccination is required to be recorded in the CDC's immunization register for each vaccine recipient, including recipient's age, gender, personal ID, date of vaccination, vaccine name, injection site, vaccine batch number, dose number, manufacturer, name of the vaccination clinic, etc. (Table 1).



CCI [redacted]

NRHIP EMR database

Among more than 4,000 medical facilities that are located in Ningbo, NRHIP EMR covers the most important 249 medical institutions (46 general hospitals, 21 specialized hospitals, 11 maternity and pediatric hospitals, 6 Chinese hospitals for traditional medicine, and 160 community health centers, and 5 other institutes). Twenty-one of the hospitals are Grade A hospitals, 26 are tier 2 hospitals. Two hundred twenty-one of these hospitals are public hospitals and 28 are large private hospitals. The NRHIP EMR system contains the information that are listed in Table 1. As all pediatric and all community health centers of Ningbo are covered by HRHIP EMR, it is very likely that all IS cases that are treated in Nigbo are included in the database.

CCI [redacted].

Data linkage

The linkage between immunization register and EMR based on infant ID codes has not be assessed. The linkage rate based on infant's IDs is expected to be 70%. In case of lower availability of IDs in young infants, a linkage algorithm based on infants' name, gender and birth date will be developed and validated.

7.4.1 Study Procedures

This study is based on secondary data collection and does not involve active administration of ROTATEQ®. The study protocol will be submitted for approval to the ethnic committees at PKU and NRHIP. The study conduct encompasses the following steps:

7.4.2 Feasibility assessment

Prior to initiating the study to monitor the incidence of IS after large scale vaccination of ROTATEQ® in NRHIP, a feasibility assessment will be conducted

- To assess if IS cases can be reliably extracted from the NRHIP by evaluating if EMR data are sufficiently recorded to adjudicate the IS cases according to the Brighton criteria;
- To assess the rate of follow-up in the target population over the entire observation period (6 -45 weeks of age);
- To evaluate the linkage rate (between NRHIP EMR and immunization registry) in the target population.

IS diagnosis validity

The process of assessing the IS diagnosis validity will include about 20 IS cases regardless their ROTATEQ® vaccination status using the following procedures:

- Explore ICD codes and/or other key codes and/or text of diagnosis to identify all potential IS cases;
- Evaluate the NRHIP EMR database accessibility by extracting IS cases from infants age-eligible to be vaccinated with ROTATEQ® (born after 2018) from EMR/database, including ICD codes, clinical manifestation, imaging and demographic data, like birth date, gender, address;
- Evaluate the completeness of data for each selected IS case to adjudicate the case according to the Brighton criteria;
- Adjudicate about 20 randomly selected IS cases using the Brighton criteria following Standard Operating Procedure for the Adjudication of Cases of IS.

Rate of follow-up

- To assess the percentage of infants in the immunization register who have follow up from the time point of first childhood vaccination until any type 1 vaccination at age 8 to 9 months based on a sample of at least 30 infants.

Linkage rate

- To assess the rate of linkage for IS cases identified from NRHIP EMR to their records in the immunization register, using demographic data (infants' ID, name, gender and birth date) based on a sample of about 20 IS cases.

Completeness of NRHIP EMR

- To understand the work mechanism and the timelag in the NRHIP for the data transmission from each registered hospital to the platform.

The NRHIP will be considered not appropriate, if

- the linkage rate between the immunization register and EMR <50%; OR
- it is impossible to identify IS cases in the database; OR
- no longitudinal data (immunization records and/or health encounter data) are available to assess the completeness of follow-up; OR
- it is impossible to differentiate the LLR from ROTATEQ in the immunization register.

Other data sources would be explored for the main study if the feasibility assessment concludes that NRHIP is not appropriate for the study conduct.

7.4.3 Main study procedures

Identification of infants vaccinated with ROTATEQ®

There are 2 types of RV vaccines available in Ningbo city. In the immunization register, the LLR is recorded as "Rotavirus" (in Chinese), while ROTATEQ® is recorded as

"PENTAVALENT Rotavirus" (in Chinese). To register the vaccine in the immunization register, the bar code of the RV vaccine is scanned, therefore the probability that a wrong vaccine name is entered in the NRHIP immunization register is very low. The infants who received at least one dose of ROTATEQ® (identified through the Chinese word "PENTAVALENT Rotavirus" = vaccine name) will be identified as the vaccinated infants.

Identification of the cohort of unvaccinated infants

Infants from the same birth cohort as the infants vaccinated with ROTATEQ® will be identified, if they have received at least one dose of a type 1 vaccine before age 6 weeks and no rotavirus vaccine (any brand).

Infants with follow-up from 6 weeks to 45 weeks of age over the study period will be identified from the NRHIP immunization register. Only infants born after October 16th, 2018 (who were at least 42 days [6 weeks] old on November 27, 2018 when ROTATEQ® was launched in Ningbo) and before August 12th, 2020 (322 days [45 weeks] old on June 30th, 2021) will be included in the study.

For both infants who received at least one dose of ROTATEQ® (identified through the Chinese word "PENTAVALENT Rotavirus" = vaccine name) and infants from the unvaccinated cohort, the following information will be extracted from the NRHIP immunization register:

- Infant's ID;
- Infant's name;
- Infant's gender;
- Infant's birth date;
- Parent's name and resident address;
- Vaccine name;
- Dose number;
- Date of of vaccination for each dose;
- Lot number for each dose;

- Other rotavirus vaccines, including dose and date of vaccination at any time during the observation period
- Date of type 1 vaccines including, but not limited to DTaP (Diphtheria, Tetanus, Pertussis), HepB (Hepatitis B), MR (Measles-Rubella), MPSV-A (Meningococcal polysaccharide), at age 8 to 9 months in both cohorts to identify infants that are lost to follow-up.

Table 3. Pre-selected type 1 vaccines and their schedules from China National Immunization Programme.

Vaccine names	Scheduled vaccination age (Months)									
	birth	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**18**
HepB	1	2					3			
DTaP				1	2	3				4
MR								1		
MenA							1		2	

HepB: Hepatits B vaccine; DTaP: Diphtheria, Tetanus, Pertussis vaccine; MR: Measles-Rubella vaccine; MenA: Group A meningococcal polysaccharide vaccine

The individual age of each infant at dose 1, 2 and 3 vaccination will be computed using the date of vaccination of each dose and infant's birth date.

Linking data from the immunization register and the EMR within the NRHIP

Infants' IDs will be used for the linkage between immunization register and EMR database for enrolled children between age 6 to 45 weeks (unvaccinated infants) or 3 months after they received the last dose of ROTATEQ® (vaccinated infants). For those infants without complete IDs in the two databases, infants' name, gender and birth date will be combined into an algorithm for probabilistic linkage. Parent's name and resident address will be used to validate linkage results by comparing this information both from immunization register and EMR database. Vaccine names and lots number of each dose will be used to validate whether those infants were vaccinated with ROTATEQ®.

Identification of potential IS cases

All eligible infants will be identified in the EMR using the infant's ID or the above described algorithm. The ICD-10 code and hospital discharge diagnosis of these children will be searched to identify potential IS either through ICD-10 code K56.1 or through the hospital discharge diagnosis including the Chinese term for intussusception.

For vaccinated infants, any potential IS that occurred from Dose 1 up to 3 months following the last dose of ROTATEQ@ will be captured. The follow-up period ends at the end of data collection. For unvaccinated infants, any potential IS that occurred during their age from 6-45 weeks will be extracted.

For all identified potential IS cases, the following information will be extracted:

- Infant's ID;
- Infant's name;
- Infant's gender;
- Infant's birth date;
- Parent's name and resident address;
- IS diagnoses code (ICD-10 code: K56.1)
- Hospital discharge diagnosis;
- Date of IS onset;
- Description and conclusion of radiographic examination, including Barium and air contrast enema ultrasound;
- Description and surgical findings for each IS cases;
- Clinical symptoms records, including colicky abdominal pain, intermittent irritability/significant lethargy, fever, diarrhea, and vomiting;
- Physical examination records, including abdominal mass, rectal blood, bowel sounds, and abdominal tenderness;
- Pathology reports, including an anatomical lead point, such as intestinal polyps, lymphosarcoma, Meckel's diverticulum, and lymphoid hyperplasia (Peyer Patches);
- Plain abdominal radiographic report, describing as the target sign and the meniscus sign.

Infant's age in days at IS occurrence will be computed by infants' birth date and the date of IS onset. Date of first and last dose of ROTATEQ® vaccinations from immunization register and date of IS onset will be used to exclude IS cases which occurred before vaccination and/or more than 3 months following the last dose, as well as to calculate the interval between IS onset and preceeding dose.

Adjudication of potential IS cases

Suspected IS cases will be subject to adjudication to confirm cases and symptom onset dates. Level 1 of diagnostic certainty for IS requires surgical, radiological, or autopsy criteria. Radiologic evidence includes demonstration of intestinal invagination by either gas or liquid contrast enema, the demonstration of an intra-abdominal mass with specific features by ultrasound that is proven to be reduced by hydrostatis enema on post-reduction ultrasound.

The detailed descriptions of IS from radiographic findings and surgical intervention will be collected from the NRHIP EMR database. A medical chart review will be required when there are 1) no records of radiographic findings, surgical interventions and/or autopsy findings from the NRHIP EMR database and/or; 2) the radiographic findings, surgical interventions and/or autopsy findings are incomplete or not consistent. In this case, the medical charts available at the hospital where the suspected IS case was treated will be reviewed.

Suspected cases will be adjudicated by the Adjudication Committee (AC). There will be 3 physicians including a pediatrician being invited as AC members. The members of the AC will individually review each IS case. They will evaluate each case with respect to the pre-specified Criteria for Adjudication as defined by the Brighton collaboration and will not have access to the vaccination status of the cases. The adjudicator will determine, based on the Brighton criteria, his/her clinical judgment and the evidence at hand, if more information is needed to confirm or refute the case.

Only cases that are confirmed by AC, in accordance with the standard operating procedure, will be considered for the primary and secondary analyses. Cases that are unconfirmed or for which medical records are not available for adjudication and negatively adjudicated cases will not be considered for any analysis.

Exclusion of infants who did not receive any type 1 vaccine at age 8 to 9 months

Vaccinated infants have to be followed until 3 months after administration of the last ROTATEQ® dose. For infants receiving three doses, the follow-up time ends between the ages ~26 weeks in case of early schedule and ~44 weeks in case of late schedule. (Early schedule: dose 1 at 6 weeks, dose 2 at 10 weeks, dose 3 at 14 weeks + 3 months follow-up =~26 weeks; late schedule: dose 3 at 32 weeks + 3 months of follow-up time = ~44 weeks). Unvaccinated infants will be followed from age 6 weeks to 45 weeks.

To ensure that infants who moved out of the Ningbo region before the end of the follow-up time will be excluded from the study, all infants without diagnosed IS and who did not receive any type 1 vaccine at age 8 to 9 months or until their individual end of follow up three months after their last ROTATEQ® dose (whatever comes first) will be excluded from the study. Vaccine coverage with type 1 vaccines in China is very high, almost 100%. [32]

7.5 Study Size

[redacted], we estimate to include around 16,000 infants vaccinated with at least one dose of ROTATEQ® during the 26 months study period (from November 27th, 2018 to June 30th, 2021).

Assuming that the annual incidence rate of IS in children under age 1 in Ningbo is 100.6-181.8/100,000 ,[15, 16] the statistical power (expressed as percent) to detected a 2 fold increase in IS in the 39 week period after vaccination among 16,000 subjects vaccinated

with ROTATEQ® for the concurrent cohort design will be 76.6-93.1 for a vaccinated to unvaccinated ratio of 1:2 and 81.1-95.2 for a ratio of 1:3 (Table 4).

A total of 29,445-53,259 (9,815-17,753 vaccinated and 19,630-35,506 unvaccinated) infants need to be included in the study to detect a RR of 2 with 80% statistical power using a vaccinated to unvaccinated 1:2 ratio cohort design. If the ratio is 1:3, the sample size will be 34,120-61,716 (8,530-15,429 vaccinated and 25,590-46,287 unvaccinated)(Table 5).

Table 4. Power (expressed in percent) to detect a 1.5 to 3.0 fold increase in the occurrence of IS after vaccination of 16,000 subjects with ROTATEQ® in the concurrent control design

Ratio of vaccinated: control	IS background incidence (1/100,000)	Detectable relative risk			
		1.5	2.0	2.5	3.0
1:2	100.6	37.8	76.6	94.3	99
	181.8	54.5	93.1	99.6	100
1:3	100.6	41.8	81.1	96.2	99.4
	181.8	59.3	95.2	99.8	100

Table 5. Number of vaccinated infants needed to detected a 1.5- to 3.0 fold increase in the occurrence of IS * in the concurrent control design

Ratio of vaccinated: control	IS background incidence (1/100,000)	Detectable relative risk			
		1.5	2.0	2.5	3.0
1:2	100.6	60,181	17,753	9,088	5,784
	181.8	33,277	9,815	5,024	3,197
1:3	100.6	52,837	15,429	7,832	4,950

	181.8	29,216	8,530	4,330	2,736

*80% statistical power

7.6 Data Management

All data management activities including data capture, data storage, data cleaning, data security, and system backup processes will be undertaken under the supervision of the Peking University and Ningbo CDC, will follow all procedures detailed in a separate "Data Management Plan".

7.7 Data Analysis

Descriptive data analysis of the aggregated information will be performed and the results displayed in tabulated form. Descriptive statistics will be used to describe baseline characteristics of vaccinated infants that will be displayed in summary tables. Categorical variables will be described using frequencies and percentages, while continuous variables will be presented using medians and interquartile ranges. The following information will be summarized in tables: number of infants vaccinated with ROTATEQ® (at least 1, exact 1, 2 and 3 doses), gender and age in days when receiving dose 1, 2 and 3, as well as the overall number of IS cases among infants who received at least one dose of ROTATEQ®.

Table 6. Mock-up table: characteristics summary of vaccinated infants in the study

	ROTATEQ® Infants
N infants Dose 1	
N infants Dose 2	
N infants Dose 3	
Average Age Dose 1 2019	
Average Age Dose 1 2020	
Median (range) Age Dose 2	
Median (range) Age Dose 3	
% Female	
Overall IS cases within 3 months	

IS: intussusception

Statistical Methods

Primary objective

This study will estimate the incidence of IS occurring within 3 months after vaccination with ROTATEQ®. For each subject, the incidence of IS in the given risk period will be defined as the first occurrence of IS in the EMR, identified either through ICD-10 code or through hospital discharge diagnosis, within 3 months following the ROTATEQ® vaccination. Infants will be followed until three months after the last dose they received, i.e. three months after dose three for fully vaccinated infants, three months after dose two for those who only received two doses and three months after dose one for infants who only received one dose.

For analyses in which subjects may have more than one IS, each subject can contribute only once throughout the whole risk period (i.e. a maximum of one IS occurrence will be taken into account for each study subject). The denominator will be all infants vaccinated with at least one dose of ROTATEQ ® who are still living and getting care in Ningbo city at age 8 to 9 months or later as documented by IS diagnosis up to 3 months after vaccination or vaccinated with any type 1 vaccine at age 8 to 9 months or before individual end of follow up three months after last ROTATEQ® dose (whatever comes first).

If sample size allows the results will be stratified by age.

Secondary objective

The occurrence of IS cases will be described with respect to the time-interval post-vaccination and in relation to the dose number.

The risk period after a vaccine dose is censored when a subsequent dose is administered and the risk period of the subsequent dose starts; i.e. an IS case that occurred 10 days following the second dose of ROTATEQ® and therefore 40 days after the first dose (for a

30 days interval between dose 1 and dose 2), will only be counted in the 1-14 days range of dose 2 and NOT in the 1-42 days range of dose 1.

Table 7: Mock-up table: number of IS cases by day range in relation to dose

Day range	Dose 1	Dose 2	Dose 3	Any Dose
1-7				
1-14				
1-21				
1-42				
1-90				

To evaluate RR of IS in infants vaccinated with ROTATEQ ® compared to infants from the same birth cohort and within the same age range who did not receive any rotavirus vaccine, the hypothesis to be tested is:

H_0: RR=1.0

H_1: RR>1.0 (the study is powered for RR≥2.0)

H_0 represents the null hypothesis and H_1 represents the alternative hypothesis.

The analysis will be done once the necessary sample size (Table 5) is sufficient to reach 80% statistical power to detect a RR of the incidence of IS of 2.0 or higher in vaccinated infants compared to unvaccinated infants .

The RR and its one-sided 95% confidence interval will be calculated by comparing the incidence rate (per 100,000 person-years) of IS in infants who had received ROTATEQ® with the incidence rate (per 100,000 person-years) of IS in infants from the same birth cohort who did not receive any rotavirus vaccine. The RR estimate will be adjusted for age and other potential cofounders using multivariate regression analysis.

7.8 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

7.9 Limitations of the Research Methods

Our study has several limitations:

- IS cases might be missed for the following reasons:
    - IS cases may not present for care in one of the hospitals of the NHRIP because they choose a hospital outside NRHIP or get primary care;
    - IS cases in infants who cannot be linked to the EMR cannot be identified;
    - IS cases in infants who migrate out of Ningbo city after receiving ROTATEQ® vaccination will be missed.
- We use the Type 1 vaccines that infants get at age 8 to 9 months to ensure that infants who moved out of the Ningbo region will be excluded from the study.

Infants who received a late schedule will not have completed their follow-up at that time and IS cases from infants who move after age 8 to 9 might be missed. As no type 1 vaccine is scheduled in the Chinese vaccination calendar between ages 9 and 18 months, it was not possible to choose a later time point for verification.

7.10 Other Aspects

Not applicable

8 PROTECTION OF HUMAN SUBJECTS

All demographic and clinical information for each IS case were generated from NRHIP and will not be provided to entities outside the study.

8.1 Informed Consent

No informed consent is needed for this study as medical charts will be reviewed retrospectively.

8.1.1 Consent and Collection of Specimens for Future Biomedical Research

Not applicable

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Introduction

This is a non-interventional study based on secondary use of data collected for other purposes. 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:

Although adverse events (AEs) and product quality complaints (PQCs) are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE* or PQC to ROTATEQ® or any other Merck product is identified, the AE/PQC must be reported according to Table 8.

*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 reactions (SARs), including death
- Non-serious adverse reactions (NSARs)
- Special situations
- Study-specific Health Outcomes of Interest (HOIs) that meet criteria for SAR/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 8.

Table 8. AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	**INVESTIGATOR TIMEFRAMES Investigator to Merck [1], [2]**
SAR (including study-specific HOIs that meet criteria for SAR Serious Special Situation, regardless of causality	24 hours from receipt
NSAR (including study-specific HOIs that meet criteria for NSAR)	10 CD from receipt

Non-serious Special Situation, regardless of causality	
PQC with or without an AE (SAR/NSAR/Special situation)	24 hours from 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 Merck: AEs and PQCs for Merck study product and *other* Merck products are submitted to Merck for reporting to worldwide regulatory agencies as appropriate. **[2]** Study Lead ensures AEs for Merck study product are entered into study database (or equivalent repository) for tabulation in study report	
Submitting AEs and PQCs to MSD Local China PV: All AEs and PQCs must be submitted to PPD in English/Chinese using an AE/PQC reporting form (attached).	

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 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.

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, treatments 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 for each reported event in relationship to a Sponsor's product.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

9.2.11 Adjudication Procedures

AC will be comprised of 3 physicians with expertise in pediatric surgery and pediatric medicine and who are experienced in diagnosing IS. The AC will not otherwise be involved in the conduct of this protocol. The committee will meet on a regularly scheduled basis to review all individual cases of suspected IS identified from the study activities, but will not have access to the vaccination status of the case. The committee will adjudicate cases of IS by examining relevant information obtained by abstracting information from medical records, written results of diagnostic tests including x-rays, surgical reports, and pathology reports. Separate SOPs, which include definitive clinical,

radiographic, surgical, and pathology guidelines for the diagnosis of IS will be used by the AC for the adjudication process. The SOPs also include information about adjudication rules and clinical classification criteria.

For cases in which a death was recorded, the AC will review the medical chart and autopsy report, if available. The AC will adjudicate the cause of death and summarize the circumstances of the death in a short narrative.

Specific details regarding endpoint definitions can be found in the Standard Operating Procedure for the Adjudication of Cases of Intussuscep (detailed in apprendix).

9.3 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], as required. Merck and the University of Peking also intend to collaborate on publications after the final report has been accepted [redacted] as required. 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

None

ANNEX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Adopted by the ENCePP Steering Group on 15 Oct 2018

This checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

For each of the questions of the Checklist, indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section can be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

For additional information on the checklist, please consult: 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

Guidance: Registration is only required for PASS studies (safety and/or efficacy).

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.

ANNEX 4 QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV)

PPD

European Union Qualified Person for Risk Management and Pharmacovigilance
Office of the European Union Qualified Person for Pharmacovigilance (EU QPPV)
Merck Sharp & Dohme (Europe), Inc.
Siège d'exploitation : 5, Clos du Lynx 1200 Bruxelles
Exploitatiezetel : Lynx Binnenhof, 5 1200 Brussel
Tel: PPD ; GSM: PPD Fax: PPD
Email: PPD

Emergency/Out of Hours: GSM numbers above or via PPD

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN:

Product: Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ®)

Protocol No.: V260-075/version 3.0

Epidemiology No.: EP08011.031

Protocol Date: October 13th, 2020

MAH: Merck Sharp & Dohme Corp

In line with the Guideline on Good PharmacoVigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

PPD

Associate Vice President,
EU Qualified Person for Pharmacovigilance

ADDITIONAL ANNEXES SHOULD BE ADDED AS NECESSARY

Example of an Adjudication Charter

TABLE OF CONTENTS

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.
- 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.
- 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