PRODUCT: V-260	PROTOCOL/AMENDMENT VERSION NO.: V260-077/V5.0
REVOPS ID NO: NIS008322 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP008011.033	CORE DRC APPROVAL DATE: 28-APRIL-2023

PASS INFORMATION

Title	Post-marketing study to assess serotype-specific effectiveness of Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ®) in China
Protocol Version identifier	*Version 5.0*
Date of last version of protocol	*14-July-2022*
EU PAS Register No:	*EUPAS36666*
Active substance	*G1：2.2×10^6* ***infectious units*** *；G2：2.8×10^6* ***infectious units*** *；G3：2.2×10^6* ***infectious units*** *；G4：2.0×10^6* ***infectious units*** *；P1A[8]：2.3×10^6* ***infectious units***
Medicinal product(s):	*Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell)*
Joint PASS	*No*
Research question and objectives	*The objective of this non-interventional study is to assess the serotype-specific effectiveness of ROTATEQ® after large scale use in China*
Country(-ies) of study	*China*
Author	PPD Associate Principal Scientist, Biostatistical and Research Decision Sciences (BARDS) Epidemiology, Merck Sharp & Dohme LLC., PPD
Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc. 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065 USA.
Merck Final Repository (REDS) Date	12-May-2023
Date of Health Authority Approval of Protocol	

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
AE	Adverse Event
AGE	Acute gastroenteritis
CDE	Center for Drug Evaluation
DSUR	Development Safety Update Report
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
IRB	Institutional Review Board
LLR	Lanzhou Lamb Rotavirus Vaccine
OR	Odds ratio
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase Chain Reaction
PSUR	Periodic Safety Update Report
RV	Rotavirus
RVGE	Rotavirus acute gastroenteritis
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
VE	Vaccine effectiveness
WHO	World Health Organization

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1 RESPONSIBLE PARTIES

Principal investigator	PPD
Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD
Other contacts	Not applicable
Supplier/Collaborator	Hangzhou Tigermed Consulting Co.,Ltd
Investigators	Not applicable
Shared responsibilities	Not applicable

2 ABSTRACT

Title	Post-marketing study to assess serotype-specific effectiveness of the Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ®) in China
Protocol Number / Version	Version 5.0
Date	28-April-2023
Author	PPD MSD R&D (China) Co., Ltd

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Rationale & Background	In clinical trials and post-marketing studies abroad, ROTATEQ® demonstrated consistently high efficacy and effectiveness against severe rotavirus gastroenteritis (RVGE) of >90%. Serotype-specific efficacy and effectiveness against genotypes G2P[4], G3P[8] and G4P[8] was > 80% in those studies. However, in the China Phase 3 trial, serotype-specific efficacy was only demonstrated for RV serotypes G1 and G9, and not for G2, G3 and G4 because those serotypes were not circulating in the study region during the period when the study was performed. ROTATEQ® received marketing authorization in China in April 2018, CCI [redacted]
Research Question(s) & Objective(s)	**Primary objective** • To assess the effectiveness of ROTATEQ ® in children treated in the hospital for RVGE due to at least one of the RV serotypes G2/G3/G4. • To assess the effectiveness of ROTATEQ ® in children treated in the hospital for RVGE due to at least one of the RV serotypes G1/G2/G3/G4/G9.
Study Design	Test-negative case-control design
Population	Children age-eligible to be fully vaccinated with 3 doses of ROTATEQ® and receiving treatment for acute gastroenteritis (AGE) in hospitals.
Variables	Exposure: vaccination with ROTATEQ®. Outcome: RV positive AGE (serotype-specific) receiving treatments in hospitals.
Data Sources	A primary data collection study to prospectively identify serotype-specific RVGE cases and RV negative AGE controls receiving treatments in hospitals and vaccination cards, providing information about ROTATEQ® vaccination status of cases and controls.

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Study Size	Based on current enrollment rate, approximately 7,393 (maximum 7,600) age-eligible AGE cases are estimated to be included by end of the fourth season. Assuming RVGE representing 33% of all cause of AGE in the peak season (October to April of the following year), 4.5% of RVGE are due to serotypes G2/G3/G4, 97% of enrolled AGE cases with complete rotavirus vaccination information, and 20% of them having been vaccinated with other rotavirus vaccines, 85 cases of RVGE due to serotypes G2/G3/G4 are expected to be included in the final analysis after four seasons. Assuming 25% ROTATEQ® coverage according to the recommended schedule in selected hospital catchment areas during the study period, a VE of 60%, and 30 controls available by case, there will be around 80% probability to observe a lower bound of the 95% CI of VE >0%, 85% probability to observe a point estimate of VE >45%, or 76% probability to observe a point estimate of VE >50%. For the second primary objective, assuming 50% of RVGE are due to serotypes G1/G2/G3/G4/G9, 946 cases due to G1/G2/G3/G4/G9 are expected to be included in the final analysis after four seasons. Assuming a VE of 60% and 3 controls available by case, the sample size provides >99% probability to observe a lower bound of 95% CI of VE >0%, >99% probability to observe a point estimate of VE >45%, or 99% probability to observe a point estimate of VE>50%. Final VE will be estimated based on data from four seasons, among children eligible to be vaccinated with ROTATEQ®. One interim analysis will be conducted by a third party after the 3rd season. By then, it is expected that 5, 200 AGE cases, 59 cases due to G2/G3/G4 and 665 cases due to G1/G2/G3/G4/G9 will be accumulated. For the first primary objective of VE against RVGE due to serotypes G2/G3/G4, there will be a probability of 65%, 81%, or 73% to observe a lower bound of the 95% CI of VE >0%, a point estimate of VE > 45%, or a point estimate of VE >50%, respectively. For the second primary objective of VE against RVGE due to serotypes G1/G2/G3/G4/G9, there will be a probability of >95% is to observe a lower bound of the 95% CI of VE >0%, >99% probability to observe a point estimate of VE > 45%, or 99%

	probability to observe a point estimate of VE >50%, respectively. The interim analysis will be submitted to DMC for review. Based on pre-specified criteria in the DMC charter, the DMC might provide a recommendation to anticipate the end of enrollment in the study. CCI [redacted] A final study report including data from the whole study period will be prepared at the end of the study CCI [redacted]
Data Analysis	The following indicators will be computed (by selected hospitals and year if relevant): - Number of AGE cases in children age-eligible to be vaccinated with ROTATEQ®; - Number of RVGE in children age-eligible to be vaccinated with ROTATEQ®; - Number of G1, G2, G3, G4, G9 RVGE cases in children age-eligible to be vaccinated with ROTATEQ®. VE will be computed as: 1- odds ratio (OR), where OR is the ratio of the likelihood of ROTATEQ® vaccination among RVGE to the likelihood of vaccination among RV negative AGE.

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Milestones	
Start of data collection:	Q4/2020
End of data collection:	Q2/2024
Interim report(s) of study results:	Q3/2023
Study progress report(s):	Q2/2022
Final report of study results:	Q1/2025

3 AMENDMENTS AND UPDATES

Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<1>	18-DEC-2019	Template	Template was changed from secondary data collection to primary data collection.	Update to retain only the primary data collection	18-DEC-2019	V1.0
<2>	18-DEC-2019	ABSTRACT: Start of data collection:	The wording referring to secondary data source study was removed.	Update to retain only the primary data collection	18-DEC-2019	V1.0
<3>	18-DEC-2019	ABSTRACT: Final report of study results:	Changed from “March, 2022” to “Before applying licensure renewal”	Updated to reflect timeline	18-DEC-2019	V1.0
<4>	18-DEC-2019	7.2 Exclusion criteria	Exclusion criteria specific for secondary data source study were removed;	Update to retain only the primary data collection	18-DEC-2019	V1.0

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Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<5>	18-DEC-2019	7.4 Data sources	Secondary data sources. i.e., China CDC AGE surveillance network introduction and its feasibility assessment was removed. Information about the primary data collection were copied from previous section 7.10 to current section 7.4.	Update to retain only the primary data collection	18-DEC-2019	V1.0
<6>	18-DEC-2019	7.4.1 Study procedures	The follow chart and the description were updated to reflect the primary data collection procedures	Updated flowchart to make it clear.	18-DEC-2019	V1.0
<7>	18-DEC-2019	7.5 Study size	Due to the fact that a primary data collection study would include children who have AGE symptoms whereas a secondary data collection study would directly include RV genotype data, the sample size needed some adjustments, the following assumptions were added to calculate the sample size of age-eligible AGE cases that need to be screened to demonstrate 60% VE with 80% statistical power using 1:3 ratio case control design: - RVGE representing 30% of all cause AGE in China - 90% of RVGE are due to G1/G2/G3/G4/G9 serotypes The sample size might be re-calculated once the hospitals are selected and the assumptions are better known (coverage, etc.).	Update to make it clear	18-DEC-2019	V1.0
<8>	18-DEC-2019	7.6 Data Management	Activities referring to the China CDC surveillance network were removed.	Update to retain only the primary data collection	18-DEC-2019	V1.0

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Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<9>	18-DEC-2019	7.9 Limitations of the research methods	Limitations for secondary data source study were removed.	Update to retain only the primary data collection	18-DEC-2019	V1.0
<10>	18-DEC-2019	9.1 Adverse events reporting	Procedures for secondary data collection were removed	Update to retain only the primary data collection	18-DEC-2019	V1.0
<11>	May 26th, 2020	Section 6.1	Moved the "VE against G2/G3/G4" from secondary to the primary objective	CCI [redacted]	July 23rd, 2020	V2.0
<12>	May 26th, 2020	Section 7.5	Recalculated the sample size per updated primary objective	CCI [redacted]	July 23rd, 2020	V2.0
<13>	15-June-2021	CRF V2.1	Added the father's and mother's education level	CCI [redacted]	19-JULY-2021	
<14>	15-June-2021	CRF V2.1	Removed the vaccination information in the key consideration of enrollment	Address external experts' comment	19-JULY-2021	
<15>	15-June-2021	CRF V2.1	Removed Rotavirus detection and genotyping results	To combine the external lab data into EDC instead of entering	19-JULY-2021	
<16>	September 23rd, 2021	Section 5	Updated epidemic season from October-March to October to April.	Extend the enrollment period according to recent epidemiological data of RV.	November 10th, 2021	V3.0
<17>	September 23rd, 2021	Section 7.2	Revised "at least two" to "at least three" RV peak seasons.	Extend the study duration according to actual enrollment speed.	November 10th, 2021	V3.0
<18>	September 23rd, 2021	Section 7.4	Revised ~200 stool samples per hospital per year to ~100 stool samples per hospital per year.	Adjust the site selection criteria according to actual number of enrolled cases.	November 10th, 2021	V3.0
<19>	September 23rd, 2021	Section 7.4.1	Revised the flow.	Revised the flow to make it clear.	November 10th, 2021	V3.0

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Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<20>	September 23rd, 2021	Section 9.1.2	Removed '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. '	Removed the paragraph from template according to CORE DRC confirmation.	November 10th, 2021	V3.0
<21>	September 23rd, 2021	Section 9.5.1	Added section of Data monitoring committee.	CCI [redacted]	November 10th, 2021	V3.0
<22>	September 23rd, 2021	Throughout protocol	Used the 12-Jul-2021 PASS PDC 12 template	Updated the template to use the template from July 2021	November 10th, 2021	V3.0
<23>	May 25th, 2022	Section 7.2	Added specifications regarding gastroenteritis onset and treatment length (consecutive calendar days)"	Added to make it clear	14-July-2022	V4.0
<24>	May 25th, 2022	Section 7.4	Increase from 10 to 30 hospitals planned to participate in the study	Updated according to 2nd season	14-July-2022	V4.0
<25>	May 25th, 2022	Section 7.4	Updated the case control ratio	Updated according to the available data of 1st and 2nd seasons	14-July-2022	V4.0
<26>	May 25th, 2022	Section 7.5	Updated the sample size	Updated according the available data of 1st and 2nd seasons	14-July-2022	V4.0

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Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<27>	May 25th, 2022	Section 7.5	Added the sample size when considering the confounders	CCI	14-July-2022	V4.0
<28>	May 25th, 2022	Section 7.7	Added matched analyses (by age, gender and calendar time) as sensitivity analyses for the first and second primary objectives	CCI	14-July-2022	V4.0
<29>	May 25th, 2022	Section 9.5.1	Updated the DMC description	CCI	14-July-2022	V4.0
<30>	Mar 23th, 2023	Section 1	Update Principal investigator information	Update Principal investigator information	28-April-2023	V5.0
<31>	Mar 23th, 2023	Section 7.1	Updated the sample size case control ratio in study design	Updated according to the available data of 1-3rd seasons	28-April-2023	V5.0
<32>	Mar 23th, 2023	Section 7.2	Updated study duration	Updated according to the available data of 1-3rd seasons	28-April-2023	V5.0
<33>	Mar 23th, 2023	Section 7.4.1	Changed case:control ratio to 1:30 for the first primary objective; changed case:control ratio to 1:3 for the second primary objective	Updated according to the available data of 1-3rd seasons	28-April-2023	V5.0
<34>	Mar 23th, 2023	Section 7.5	Changed vaccine coverage rate to 25%	Updated according to the available data of 1-3rd seasons	28-April-2023	V5.0
<35>	Mar 23th, 2023	Section 7.5	Changed content of Table 2 (sample size calculation for a case control design for the first and second primary objective)	Updated according to the available data of 1-3rd seasons	28-April-2023	V5.0

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Amend-ment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
<36>	Mar 23th, 2023	Section 7.5	Removed Table 3 (sample size estimation considering confounders) and related wordings	To increase the statistical power, sample size was calculated without considering the confounders	28-April-2023	V5.0
<37>	Mar 23th, 2023	Section 7.5	Added Table 3 of Probability of observing a point estimate of VE for the first primary objective and second primary objective in final analysis and interim analysis	Added probability based on different scenarios	28-April-2023	V5.0
<38>	Mar 23th, 2023	Section 7.7	Added interim analysis and DMC review	Team aligned to add an interim analysis and DMC review	28-April-2023	V5.0
<39>	Mar 23th, 2023	Section 7.7	Added matched analyses (parents' education level) as sensitivity analyses for the first and second primary objectives	CCI [redacted]	28-April-2023	V5.0
<40>	Mar 23th, 2023	Section 7.9	Change case control ratio	Changed case control ratio to 1:30	28-April-2023	V5.0
<41>	Mar 23th, 2023	Section 9.5.1	The composition and responsibility of DMC was updated, with one vaccinologist/virologist/pediatrician and DMC will review the available data from the study including the interim analysis data.	To reflect the update of DMC role on interim analysis	28-April-2023	V5.0

4 MILESTONES

Milestone	Planned Date
<Registration in the EU PAS register>	September 3rd, 2020
Start of data collection	Q4/2020
End of data collection	Q2/2024
<Study progress report 1>	Q2/2022
Interim report(s) of study results	Q3/2023
Final report of study results	Q1/2025

5 RATIONALE AND BACKGROUND

Rotavirus (RV) is the leading cause of severe diarrhea 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, World Health Organization (WHO) recommended RV vaccination for all children worldwide, especially in countries with high number of diarrhea-associated deaths.[2] In China, RV caused over 40% of diarrhea hospitalizations and about 30% of diarrhea related outpatients visits in children aged < 5 years. Over 50% of RV-related hospitalizations in China occurred by age 1 year and about 90% occurred by age 2 years; [3] this indicates that a vaccination program with doses given early in infancy has the potential to prevent the majority of the burden of severe RV disease in China.[4] The peak seasonality of RV activity in China is typically from October to April of the following year, although this may vary regionally to include additional months.[5]

There are 2 RV vaccines currently approved for marketing in China: Lanzhou Lamb Rotavirus (LLR, Lanzhou Institute of Biological Products) vaccine and ROTATEQ® (Merck & Co., Inc., Kenilworth, NJ, USA).

LLR vaccine has been in use in China since 2000,[6] and includes the genotype G10P[15].[7] It has been widely distributed in China with a coverage up to 28.6% in some regions.[8] To our knowledge, no clinical trials to estimate the efficacy of LLR have been published. Results from a few post-marketing effectiveness studies for LLR performed in China, using different study designs, are not consistent ranging from 35.0% to 77%.[8-13]. The serotype-specific effectiveness of LLR against G3 and G9 has been reported to be respectively 52.0% and 40.8%. No VE results against the serotypes G1, G2, and G4 have been published so far.

ROTATEQ® was approved for marketing in China on April 12th, 2018. 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.[14] 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.[14]

The serotype-specific efficacy and effectiveness of ROTATEQ® has been widely assessed in clinical trials[15] and in several post-marketing studies worldwide[16-18]. ROTATEQ® demonstrated high overall and serotype-specific efficacy/effectiveness against both severe (hospitalized and/or Vesikari Score ≥11) RV gastroenteritis (RVGE) and RVGE of any severity. The results from these studies are summarized in Table 1. Statistically significant vaccine effectiveness (VE) results could only be obtained for serotypes that circulated in a sufficient amount in the areas where the studies were conducted.

Table 1 Serotype-Specific Efficacy and Effectiveness of ROTATEQ® in Clinical Trials and Post-Marketing Studies Conducted out of China

RVGE Severity	Serotype-Specific Efficacy/Effectiveness (%, 95%CI)					Study Type	Country	Ref
	G1	G2	G3	G4	G9			
Any severity	75(67,81) †	63(3,88) †	83(<0,100)	48(<0,92)	65(<0,99)	RCT	Multi-country	Vesikari, NEJM, 2006
Hosp and ED visits	95(92,97) †	88(<0,99)	93(49,99) †	89(52,98) †	100(70,100) †	RCT	Multi-country	Vesikari, NEJM, 2006
Hosp and ED visits	89(55,97) †	87(65,95) †	80(64,89) †	ND	ND	PMS	US	Payne, CID, 2015
Severe (VS≥11)	66(28,84) †	77(55,89) †	100(<0,100)	93(29,99) †	83(<0,99)	PMS	Nicaragua	Mast, PIDJ, 2011
Hosp and ED visits	96(79,99) †	72(7,92) †	86(60,95) †	ND	83(17,97) †	PMS	US	Staat, Pediatrics, 2011

RCT: randomized clinical trial; PMS: post marketing study: VS: Vesikari Score is the results of the Vesikari Scoring System, which was developed to evaluate the effectiveness and efficacy of rotavirus vaccines based on the intensity of different AGE symptoms ; ND: no data.

† Statistically significant

In the Phase 3 trial that was conducted in China,[19] overall efficacy against RVGE of any severity and severe RVGE caused by any serotype were 69.3% (95%CI: 54.5%-79.7%) and 78.9% (95%CI: 59.1%-90.1%), respectively. Serotype-specific efficacy was also demonstrated against the serotypes G1 (74.4%, 95%CI: 47.8%-88.6%) and G9 (67.4%, 95%CI: 45.2%-81.4%). It could not be demonstrated against the serotypes G2, G3 or G4 because of the very small number of cases caused by any of those three serotypes among

vaccinated (3 cases) and unvaccinated infants (8 cases) given the low circulation of these three RV serotypes in China during the study period.

5.1 Rationale

CCI [redacted]

The circulation of RV G2, G3, and G4 serotypes has been described to be decreasing and unpredictable in China since 2009. A sentinel-based surveillance of acute diarrhea indicated that among 2,533 genotyped RV serotypes, G2, G3 and G4 represented an average of 4.5%, 21.1% and <1%, respectively.[20] The previously dominant serotype G3 decreased rapidly from ~60% in 2009/2010 to ~10% in the more recent years.[20] Moreover, some published local studies that assessed the RV serotype distributions among AGE cases in children under 5 years of age in China also indicated unpredictable circulation of G2, G3, G4, ranging from respectively 7.8% to 14.0%, 0.9% to 18.7% and <1% to 1.5 of RVGE cases with the combined circulation of G2/G3/G4 as 12.0% to 27%.[13,21-23] In a recent publication, G2, G3, and G4 strains were identified in 12.3% of Chinese children with severe RVGE during the peak season (September 2012 to June 2013).[24]

The Sponsor proposes to use a test-negative study design to assess the serotype-specific effectiveness of ROTATEQ. The test-negative studies are expected to reduce confounding bias because cases and controls have similar symptoms and therefore are likely to have similar care-seeking behaviors and may also be similar with respect to other characteristics, such as age, comorbidities or access to health care. By collecting vaccination data prior to knowledge of the test results, bias in ascertainment of vaccination among cases and controls can be avoided through the test-negative studies.[25-29] This design had been widely used to evaluate VE of RV vaccines in China,[11] US,[26] Finland,[30] Israel,[31] Japan[27,32], Philippines,[33] Portugal,[34] Spain,[35] and Zimbabwe.[36]

6 RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to estimate the serotype-specific effectiveness of ROTATEQ® in a large population using a test-negative design.

6.1 Primary Objectives

- To assess the effectiveness of ROTATEQ® in children treated in the hospital for RVGE due to at least one of the RV serotypes G2/G3/G4.
- To assess the effectiveness of ROTATEQ® in children treated in the hospital for RVGE due to at least one of the RV serotypes G1/G2/G3/G4/G9.

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7 RESEARCH METHODS

7.1 Study Design

This study does not involve active administration of ROTATEQ®. Under this protocol, all recipients of ROTATEQ® received ROTATEQ® previously, in the course of ordinary public health practice.

The design is a test-negative case-control. All RVGE cases identified during the study period in the study population, age-eligible to be fully vaccinated with 3 doses of ROTATEQ® and receiving treatment for AGE in hospitals with any of RV serotypes G2/G3/G4 (first primary objective) and G1/G2/G3/G4/G9 (second primary objective) identified will be "cases". All RV negative AGE cases receiving treatments in hospitals identified from the same data source over the same study period in children, age-eligible for vaccination with ROTATEQ® will be "controls".

The study will enroll eligible children during four RV peak seasons. One interim analysis by a third party is planned after the third season with all available data. The interim analysis results will be submitted to an external DMC for review. The DMC will make recommendations to stop or continue the enrollment, based on prespecified criteria that will be outlined in the DMC charter. CCI [redacted] A final study report including data from the whole study period will be prepared CCI [redacted]

7.2 Setting

The study population is the children age-eligible to be fully vaccinated with 3 doses of ROTATEQ® and receiving treatment for AGE in hospitals.

Age-eligible: to be fully vaccinated with 3 doses of ROTATEQ® denotes children who could have received 3 doses of ROTATEQ® + 14 days to develop immunity based on following criteria:

- Minimum age of 16 weeks at the time of AGE onset; and
- Maximum age of 12 weeks (upper age limit for dose 1) when ROTATEQ® was launched in the respective hospital catchment area.

AGE is defined as 3 or more watery or looser than normal stools within 24 hr period and/or forceful vomiting. The onset of gastroenteritis should be ≤ 14 days prior to admission.

Receiving treatment for AGE in hospitals denotes:

- Admission to the inpatient ward due to AGE; or
- Received intravenous (IV) rehydration treatment for at least 2 consecutive calendar days due to AGE in the outpatient hospital setting.

Study Duration

The study will start at the date of study initiation in the selected hospitals where ROTATEQ® has been launched and conducted for four or less RV peak seasons.

Inclusion Criteria

All children, age-eligible to be vaccinated with ROTATEQ® (infants not older than 12 weeks when ROTATEQ® was introduced in the catchment areas of the selected hospitals), presenting with symptoms of severe AGE to one of the selected hospitals and whose parents signed an informed consent.

Exclusion Criteria

None

7.3 Variables

7.3.1 Exposure

The study exposure of interest is ROTATEQ® vaccination status. However, this study does not involve active administration of ROTATEQ®. The study will include children who received ROTATEQ® in routine immunization practice.

Children are considered “vaccinated” if they have received all 3 doses of ROTATEQ® at least 14 days before the onset of AGE. Children are considered “not vaccinated” if they haven’t received any dose of ROTATEQ®. Those who received an incomplete ROTATEQ® schedule or a mixed schedule with ROTATEQ® and other RV vaccines will be excluded from the main analysis..

7.3.2 Outcomes

The study outcome is AGE receiving treatments in hospitals.

For the first primary objective, a child with RVGE receiving treatment in hospitals and positive for at least one of the serotypes G2/G3/G4 is considered a “case”.

For the second primary objective, a child with RVGE receiving treatments in hospitals positive for at least one of the serotypes G1/G2/G3/G4/G9 is considered a “case”.

Children are considered a "control" both for the first and second primary objectives if they have RV negative AGE receiving treatments in hospitals.

Health outcomes: Clinical events or outcomes which may be represented as diagnoses, treatment or procedures (examples include syncope, disease progression or hypoglycemia collected as study endpoints). Any herein described health outcomes, collected per the protocol, will be summarized as part of any interim analysis (if required) and in the final study report in addition to being reported in real-time as individual AE/s if the criteria in section 9 are met. Refer to section 9 for AE reporting requirements and procedures.

7.3.3 Covariates

- Child's gender;
- Child's age (in weeks);
- Location (urban vs rural);
- Calendar time

Analyses will be carried out using the 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 datasets on all variables.

7.4 Data Sources

AGE cases receiving treatments in hospitals will be prospectively identified from selected hospitals. Stool samples of AGE cases will be collected for RV antigen testing and samples of RVGE cases will undergo serotype characterization. Demographics and clinical information will be collected through interviews and/or medical charts, and the vaccination status will be collected from vaccination cards or from immunization registers/ application programs (APPs) if vaccination cards are not available. Vaccination status will be collected from vaccination cards or from immunization registers if vaccination cards are not available.

Hospital Selection Criteria:

Hospitals are eligible to be selected if they meet the following criteria:

- Expected to have at least 15% ROTATEQ® coverage in the catchment area;
- Able to collect ~100 stool samples per year from children with AGE receiving treatment in hospitals;
- Able to collect demographic and clinical information relevant to the study;
- Able to determine RV vaccination status of children with AGE either from vaccination cards or by linking to regional immunization registers.

The number of selected hospitals needs to be sufficient to ensure that the estimated sample size can be reached and depends also on the expected ROTATEQ® coverage in the hospital catchment areas. At least 30 hospitals are planned to participate to the study.

Regional Immunization Register and Vaccination Cards

For each vaccine recipient, vaccination is required to be recorded in both the regional immunization register and the vaccination cards, including recipient's name, gender, personal ID, birth date, resident address, date of vaccination, vaccine name, injection site, vaccine lot number, dose number, manufacturer, and name of the vaccination clinic. The immunization register is maintained by the Center for Disease Control and Prevention (CDC) at national, provincial and city level according to their jurisdictions, while parents of children hold the vaccination cards as the proof of vaccination.

There are also officially authorized mobile APPs available for parents in some regions/cities of China to get access to the vaccination information of child without direct visit to regional immunization register or carrying the vaccination card all the time.

7.4.1 Study Procedures

General Procedure

This study does not involve active administration of ROTATEQ®. The study protocol will be submitted for approval by the institutional review board.

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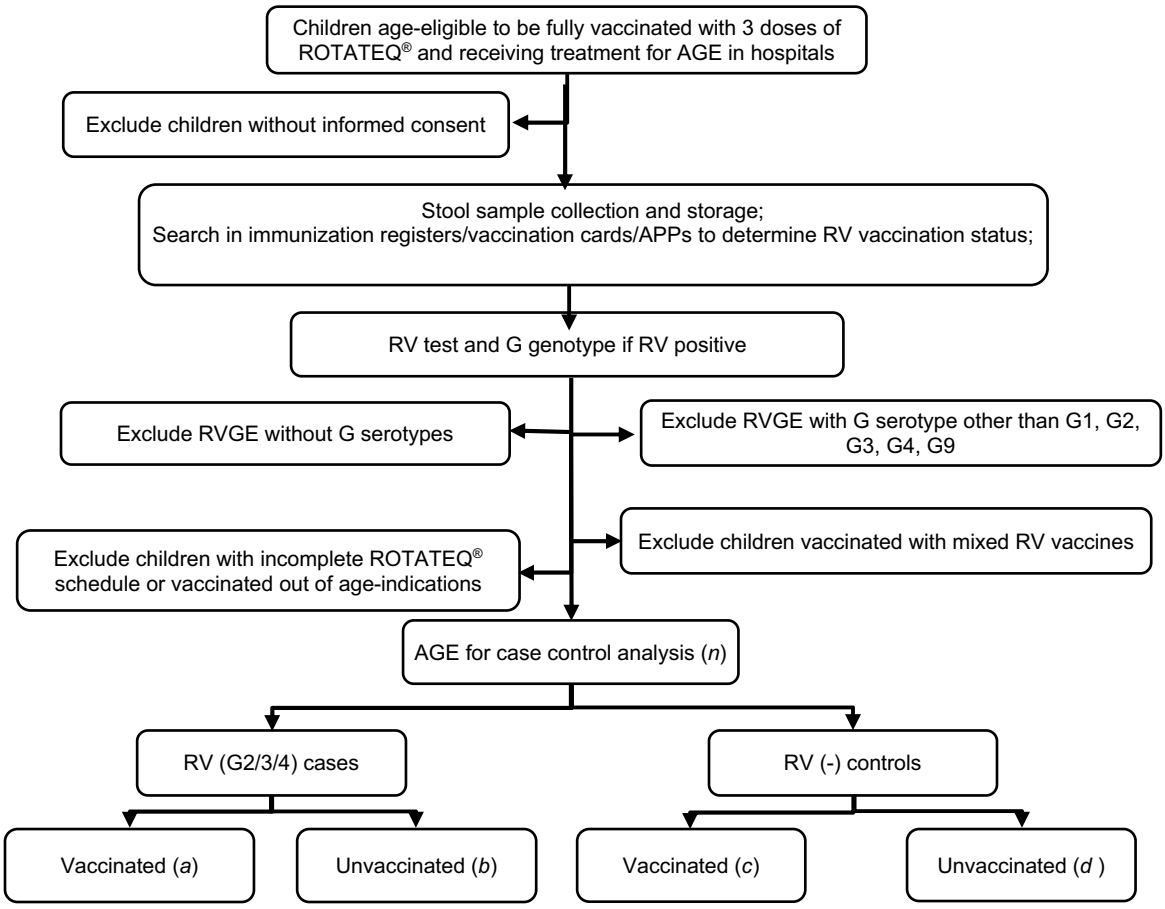
Figure 1 Flow Chart for Post-Marketing Study to Assess Serotype-Specific Effectiveness of ROTATEQ® Against RVGE Receiving Treatments in Hospitals And Tested Positive for at Least one of the RV Serotypes G2/G3/G4



	RV(G2/3/4) case	RV(-) control	Total
Vaccinated	*a*	*c*	*a* + *c*
Unvaccinated	*b*	*d*	*b* + *d*
Total	*a* + *b*	*c* + *d*	*n*

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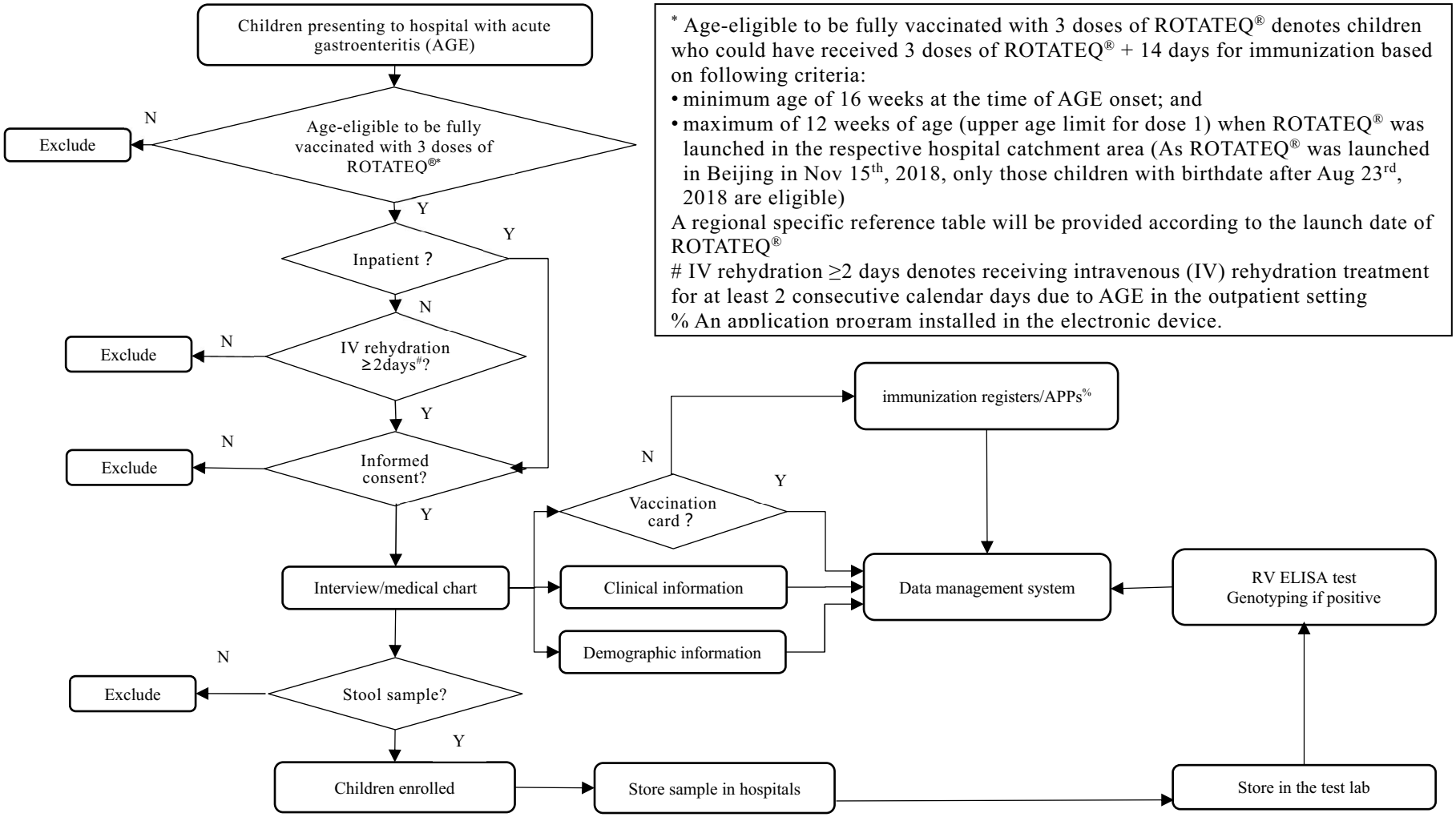
Figure 2 Procedures of Eligible Patients Enrollment and Data Generation in the Present Study



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The Primary Data Collection Procedure

Children age-eligible to be fully vaccinated with 3 doses of ROTATEQ® and receiving treatment for AGE in hospitals will be eligible for enrollment in the study and recorded in a enrollment log.

After informing the parents about the study, the participating practitioner will check the eligibility of the child to participate in the study and will request the parent to sign an informed consent form.

Once the informed consent has been signed, parents of the enrolled children will be interviewed with the use of a standardized case report form. Additional medical information will be abstracted from medical charts by trained staff if needed. The collected information includes demographics (e.g., gender, date of birth, educational status of the parents) and clinical characteristics (e.g., signs/symptoms, date of symptom onset, date of diagnosis). RV vaccination (ROTATEQ®, LLR and other RV vaccines) status will be collected from vaccination cards/immunization registers/APPs. After enrollment, fresh, whole stool samples will be collected.

All stool samples will be stored at the appropriate temperature until testing is performed and transported to the laboratory according to the samples management guidelines. These guidelines will be developed by the laboratory in collaboration with MSD China.

A standardized method and operation procedure will be adopted by a central laboratory for RV testing and characterization of serotypes and will be validated before initiating the primary data collection. Group A RV antigens will be detected directly in stool samples by using ELISA assay. For ELISA-positive samples, multiplex reverse-transcription polymerase chain reaction assays will be used for further genotyping of the strains.

AGE cases without RV test results and RVGE cases that do not contain any of the serotypes G1/G2/G3/G4/G9 or that are untypable will be excluded from the data analysis.

Vaccination Status

Vaccination information will be extracted from vaccination cards, and if not available, it will be extracted from the immunization registers or eligible APPs. For children whose vaccination information will be collected from vaccination cards, parents of the included child will be asked to provide the photograph/copy of the vaccination card cover page and the RV vaccination entry of their child.

Vaccination information can also be extracted from the immunization registers based on child's name, gender, birth date, parents' name and residence address. Regional practitioner or trained staff from regional CDC will take this responsibility. If there is more than one entry with the same name, gender, and birth date, parents' name and resident's address will be added stepwise to remove the duplication due to individuals with the same name, gender and birth date.

Test-Negative Case Control Analysis

For the first primary objective, the numbers of vaccinated RVGE (G2/3/4) cases (*a*), unvaccinated RVGE (G2/3/4) cases (*b*), vaccinated RV (-) AGE cases (*c*) and unvaccinated RV (-) AGE cases (*d*) will be summed up based on RV testing, G/P genotyping results and ROTATEQ® vaccination histories for each eligible AGE case. The numbers of *a*, *b*, *c*, and *d* will be entered into the table listed in Figure 1. The ratio of RVGE (G2/3/4) cases (cases) to RV (-) AGE cases (controls) is expected to be around 1:30, depending on the available number of controls.

For the second primary objective, the RVGE (G1/2/3/4/9) cases will be considered as cases and the ratio to RV (-) AGE cases (controls) is expected to be around 1:3, depending on the available number of controls.

7.5 Study Size

Only children (cases and controls) who are age-eligible to be fully vaccinated with 3 doses of ROTATEQ® and receiving treatment for AGE in hospitals are eligible to be included in the study. That means, only children aged at least 16 weeks (minimum age for full completion of 3-dose schedule + 2 weeks for immunity to develop) will be included.

The test-negative case-control study is designed to estimate the ROTATEQ® vaccine effectiveness (VE) against RVGE due to RV serotypes G2/G3/G4 (first primary objective) and the ROTATEQ® VE against RVGE due to RV serotypes G1/G2/G3/G4/G9 (second primary objective). Based on current enrollment rate, approximately 7,393 (maximum 7,600) age-eligible AGE cases are estimated to be included by the end of the fourth season.

For the first primary objective, assuming RVGE representing 33% of all cause AGE in the peak season (October to April of the following year),[37] 4.5% of RVGE being due to serotypes G2/G3/G4, 97% of enrolled AGE cases having complete rotavirus vaccination information, 20% of them having been vaccinated with other rotavirus vaccines, 85 cases of RVGE due to serotypes G2/G3/G4 are expected to be accumulated for inclusion in the analysis. Assuming a 25% ROTATEQ® coverage according to the recommended schedule in selected hospital catchment areas during the study period, a VE of 60% and 30 controls available by case, the estimated study sample size (7,393) is expected to provide around 80% probability to observe a lower bound of the 95% CI of VE >0%, 85% probability to observe a point estimate of VE >45%, or 76% probability to observe a point estimate of VE >50%.

For the second primary objective, assuming 50% of RVGE are due to serotypes G1/G2/G3/G4/G9, 946 cases due to G1/G2/G3/G4/G9 are expected for inclusion in the final analysis. Assuming a VE of 60% and 3 controls available by case, the estimated sample size (7,393) will provide >99% probability to observe a lower bound of 95% CI of VE >0%, >99% probability to observe a point estimate of VE >45%, or 99% probability to observe a point estimate of VE>50%.

By the time of interim analysis at the end of the third season, based on the assumptions described above, 5,200 AGE cases are expected to be included in the study, 59 of which are due to G2/G3/G4 and 665 are due to G1/G2/G3/G4/G9. For the first primary objective of VE against RVGE due to serotypes G2/G3/G4, there will be a probability of 65%, 81%, or 73% to observe a lower bound of the 95% CI of VE >0%, a point estimate of VE > 45%, or a point estimate of VE >50%, respectively. For the second primary objective of VE against RVGE due to serotypes G1/G2/G3/G4/G9, there will be a probability of >95% to observe a lower bound of the 95% CI of VE >0%, >99% probability to observe a point estimate of VE > 45%, or 99% probability to observe a point estimate of VE >50%, respectively.

The current assumptions used for sample size estimations are based on previously collected samples, which may change depending on the proportion of RV positive samples among all cause AGE as well as on the proportion of RV G2/G3/G4 specific cases. Table 2 presents the total number of cases needed to provide 80% probability to observe a lower bound of the 95% CI of VE >0% for each primary objective, under varying assumptions of ROTATEQ® coverage and expected VE. For the first primary objective, the calculations assume that 30 controls will be available for each G2/G3/G4 case and for the second primary objective, the calculations assume 1, 2, or 3 controls available per G1/G2/G3/G4/G9 case.

Table 2 Total Number of Cases Needed to Provide 80% Probability to Observe a Lower 95% Confidence Bound of VE Greater Than Zero for the First Primary Objective and Second Primary Objective

ROTATEQ® coverage (%)	**Expected vaccine effectiveness (%)**	**Number of G2/G3/G4 cases (combined, case: control ratio 1:30)**	**Number of G1/G2/G3/G4/G9 cases (combined, case: control ratio 1:1/1:2/1:3)**
20	50	156	270/214/194
20	60	100	172/138/125
20	70	67	115/93/84
25	50	131	226/180/164
25	60	84	144/116/105
25	70	56	97/78/70
30	50	116	198/159/144
30	60	74	126/102/92
30	70	49	84/68/62

Table 3 presents the probability of observing a point estimate of VE >45% and >50% for the first primary objective and second primary objective respectively in the final and interim analysis, under varying assumptions of number of cases in interim/final analysis and expected VE. For the first primary objective, the calculations assume 30 controls available by G2/G3/G4 case and for the second primary objective, the calculations assume 3 controls available by G1/G2/G3/G4/G9 case.

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Table 3 Probability of Observing a Point Estimate of VE for the First Primary Objective and Second Primary Objective in Final Analysis and Interim Analysis

	ROTATEQ® Coverage (%)	**Expected Vaccine Effectiveness (%)**	**Probability of Observing a Point Estimate of VE > 45%**	**Probability of Observing a Point Estimate of VE > 50%**
Based on 85 G2/G3/G4 cases (combined, case: control ratio 1:30)	25	50	63	52
	25	60	85	76
	25	70	97	94
Based on 946 G1/G2/G3/G4/G9 cases (combined, case: control ratio 1:3)	25	50	83	52
	25	60	>99	99
	25	70	>99	>99
Based on 59 G2/G3/G4 cases (combined, case: control ratio 1:30)	25	50	63	53
	25	60	81	73
	25	70	95	91
Based on 665 G1/G2/G3/G4/G9 cases (combined, case: control ratio 1:3)	25	50	78	50
	25	60	>99	99
	25	70	>99	>99

7.6 Data Management

All data management activities including data capture, data storage, data cleaning, data security, and system backup processes will be undertaken by qualified personnel and will follow all procedures detailed in a separate “Data Management Plan”.

The Study will comply with Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and regional laws, rules and regulations relating to the conduct of the study.

7.7 Data Analysis

The study includes one interim analysis (planned after the third season) and a final analysis at the end of the study with data from the entire study period over four seasons CCI [redacted]

Descriptive Analysis

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 (by each serotype and in aggregate) 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)

The VE will be estimated among children eligible to be vaccinated with ROTATEQ®. In order to estimate the VE against RVGE receiving treatments in hospitals, logistic regression will be fitted for each primary objective to estimate the odds ratio of RVGE associated with ROTATEQ® vaccination (defined as three doses of ROTATEQ® according to the recommended schedule plus 14 days), adjusted for potential confounders such as age, gender, calendar time of onset, location (urban/rural) and hospital (more details will be provided in the Staitsitcal Analysis Plan). The VE will be calculated as 1 minus the odds ratio.

VE will be stratified and adjusted if numbers allow according to age, gender, calendar time of onset, location (urban/rural) and hospital.

CCI [redacted], a matched analysis will be done as sensitivity analysis. For the first primary objective, if the number of controls allows, up to 30 controls will be matched by age, gender, calendar time and parents' education level to each case. For the second primary objective, if the number of controls allows, up to 3 controls will be matched by age, gender , calendar time and parents' education level to each case. The matching criteria and case control ratio will be further described in the Statistical Analysis Plan. For sensitivity analysis, VE will be estimated among children eligible to be vaccinated with ROTATEQ®.

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.

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 30 ratio impossible and resulting in decreased statistical power. Beyond 4 controls per case, gain in statistical power is marginal; however, is needed in this study due to limited number of cases.

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

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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.

All demographic and clinical information for each eligible AGE case, as well as RV testing and genotyping results from their stool samples are generated during the conduct of the prospective AGE study. The RV vaccination information both from regional immunization registers and vaccination cards will be tracked, collected, stored and used by the study staff of the prospective study and will not be provided to entities outside the study.

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

8.1 Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

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.

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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 primary data collection non-interventional 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.

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 Sponsor product, then the AE* and/or PQC must be reported according to Table 4. If any health outcomes are described in section 7.3.2, they must be assessed for AE reportability according to Table 4 (refer to section 7.3.2 for more information).

* 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

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 4.

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

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Table 4 AE and PQC Reporting Timeframes and Process for Investigators and Suppliers

AEs AND PQCs	INVESTIGATOR TIMEFRAMES Investigator to Supplier[1,2]	SUPPLIER TIMEFRAMES Supplier to Sponsor[3]
SAE regardless of causality Serious Special Situation, regardless of causality	24 hours from receipt	24 hours from time of receipt from investigator
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 from investigator
Follow-up to any AE/PQC-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
Non-Sponsor Products: If the investigator elects to submit AEs/PQCs for **non-Sponsor 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 Sponsor study product and other Sponsor products are submitted to Supplier via fax or secure email. [2] Supplier enters AEs for Sponsor study product into study database (or equivalent repository) for tabulation in study report [3] **Supplier to Sponsor:** Supplier submits AEs and PQCs for Sponsor study product and *other* Sponsor products to Sponsor for reporting to worldwide regulatory agencies as appropriate		
Submitting AEs and PQCs to MSD Local China PV: All AEs and PQCs must be submitted to CCI [redacted] **in English/Chinese using the AE/PQC reporting form.**		

9.1.2 Study Report

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

9.1.3 Periodic Safety Update Reports:

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

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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 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.

9.2.7 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.

9.2.8 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.

9.2.9 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 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.

9.4 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.

9.5 Study Governance and Oversight

9.5.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will monitor safety and effectivenss data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (e.g., they cannot be study Investigators) and must have no competing interests that could affect their roles with respect to the study. The DMC will consist of 3 members including one pharmacoepidemiologist, one vaccinologist/virologist/pediatrician and one statistician. The DMC will review the available data from the study including the interim analysis data. The pre-specified criteria for the interim analysis will be defined in the DMC charter.

Specific details regarding the DMC will be described in a separate Data Monitoring Committee Charter.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will produce a final report to be submitted CCI [redacted]. The Sponsor also intends to publish the results after the final report has been accepted CCI [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/).

Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally.

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12 ANNEXES

Annex 1 List of Stand-Alone Documents

No.	Document Reference No	Date	Title
1.	ER212-PV001, v3.0	1-May-2022	External Adverse Event and Product Quality Complaint Form
2.	<No>	<Date>	<Text>
N	<No>	<Date>	<text>

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Annex 2 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 if applicable such information will be divulged to 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 (if applicable), 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. By signing

this protocol, the investigator expressly consents to these uses and disclosures. 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. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

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.

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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.

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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 Sharp & Dohme LLC, 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 Sharp & Dohme LLC, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck Sharp & Dohme LLC 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.

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13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	PPD
TITLE	Study lead, Biostatistical and Research Decision Sciences (BARDS) Epidemiology, Merck Sharp & Dohme LLC.
SIGNATURE	
DATE SIGNED	

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13.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	PPD
TITLE	Professor, MD Department of Gastroenterology, Beijing Children's Hospital
SIGNATURE	
DATE SIGNED	

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13.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	PPD
TITLE	Project Manager Hangzhou Tigermed Consulting Co.,Ltd
SIGNATURE	
DATE SIGNED	