A COHORT STUDY TO EVALUATE IMMUNOGENICITY FOR CHILDREN AGED 5 MONTHS TO ≤60 MONTHS AT THE TIME OF CLINICAL PNEUMONIA DIAGNOSIS

Therapeutic Area (TA):	Vaccines
Protocol Number:	B1851196

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	25 Jul 2018	Not applicable (N/A)

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APPENDICES

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Procedure/ Assessment	Visit 0[c]	Visit 1
Review inclusion/exclusion criteria, including initial assessment of 13vPnC vaccination history	x	
Informed consent	x	
Assign subject number	x	
Confirmation of 13vPnC vaccination history	x	
Enroll subject, assign cohort		x
Demography, medical history, and antibiotic usage		x
Record dates of 13vPnC vaccination		x
Obtain blood sample[d]		x
Record deep upper respiratory aspirate specimen information[a] or collect aspirate as a study procedure[e]		x
Adverse event reporting[b]		x

a. Obtained as per local standard of care or performed as a study procedure.

b. See Section 7.1 for adverse event report requirements.

c. Visit 0 and Visit 1 will occur on the same day.

d. ELISA and MOPA will be conducted on all 13vPnC cohort patients and a subset of non 13vPnC patients.

e. Culture will be performed on these samples. If *S. pneumoniae* positive, serotyping, will be performed.

1. INTRODUCTION AND RATIONALE

Streptococcus pneumoniae (*S. pneumoniae*) causes invasive pneumococcal disease (IPD), including bacteremia, sepsis, and meningitis) in infants and young children throughout the world. Non-invasive pneumococcal diseases, including otitis media, sinusitis, and bronchitis, are less severe but much more common than invasive disease, thus also pose a significant disease burden. *S. pneumoniae* also causes bacteremic and non-bacteremic pneumonia.

According to the World Health Organization (WHO), there is a high burden of pneumococcal disease and it is estimated that 1.6 million people die each year from the disease, 0.7 to 1 million of whom are children aged less than 5 years.[1] Pneumonia was the leading cause of death from 1996 to 2000 in children under 5[2] and data reported by WHO/United Nations Children's Fund (UNICEF) indicate that 72,000 children less than 5 years of age died of all cause pneumonia in China in 2004.[3] Pneumococcal meningitis is a severe disease with high mortality and high incidence of neurological sequelae.

In an epidemiological study conducted in 18 provinces and cities in China from 1982 to 1985, 482 out of 10,446 cases of bacterial pneumonia, meningitis, and otitis media were caused by culture-confirmed *S. pneumoniae*.[4] The percentages of bacterial pneumonia, meningitis, and otitis media caused by *S. pneumoniae* were 1.4%, 7.9%, and 6.8%, respectively. Between 40% and 73% of the infections caused by *S. pneumoniae* were in infants and children less than 3 years old. The overall mortality of pneumonia and meningitis caused by culture-confirmed *S. pneumoniae* was 16% for both conditions, but in infants less than 1 year old it was as high as 29% and 17%, respectively. Major pathogens causing lower respiratory tract infections in young children are *S. pneumoniae* and *Haemophilus influenzae* and the proportion of lower respiratory tract infections caused by *S. pneumoniae* is 13% to 53% depending on the age group.[5,6,7] In a systematic review of *S. pneumoniae* cases in reported studies from 1980 to 2010; 48% of bacteremic pneumonia was caused by *S. pneumoniae* and the average percentages of cases of meningitis due to *S. pneumoniae* were 5% (95% confidence interval [CI]: 2%-12%) among 0 – 4 years old and 28% (95%CI: 17%-45%) in older children and adults.[8]

Prevenar 13, the 13-valent pneumococcal conjugate vaccine (13vPnC) was approved in China in October 2016 for the prevention of invasive pneumococcal disease in infants 6 weeks to 15 months of age. The approved regimen only allows vaccination with Prevenar 13 at 2, 4, 6 months for the primary series and the toddler or booster dose at 12 to 15 months of age. Local serotype coverage in China of 13vPnC can range from 80.5% to as high as 87.2%. There is also some regional difference where Northern China appears to have serotype coverage of 75% as compared to Southern China that has serotype coverage of 92%.[9-13]

The introduction initially of 7-valent pneumococcal conjugate vaccine (7vPnC) and then of 13vPnC in the national immunization program of various countries reduced dramatically the incidence of invasive and mucosal pneumococcal infections in children.[14,15] Quantitative serotype-specific anti-capsular polysaccharide immunoglobulin G (IgG) antibody levels of ≥0.35 μg/ml after the primary series are considered to correlate with protection for invasive pneumococcal disease (IPD) and have been used for licensure of 13vPnC.[16] In addition, the amount of antibodies after vaccination and the quality of these antibodies is also important.

The avidity of antibodies is a quality measurement which defines the affinity of antibodies for a particular antigen. An increased avidity is related to a more effective antibody function. Another functional measurement of pneumococcal specific antibodies is its multiplex opsonophagocytic activity (MOPA titers). The primary mechanism for anti-capsular immunity in the host is phagocytosis, through opsonisation by anticapsular antibodies and activation of complement. Functional antibody levels, measured as opsonophagocytic activity, provide valuable additional information for serotype-specific differences in protection.[17] It is generally accepted that higher antibodies are required for the prevention of colonization and mucosal disease caused by vaccine-type *S. pneumoniae*.

Studies have shown that following primary vaccination with 13vPnC, circulating antibodies decline but are boosted following the booster dose after vaccination with the 12 – 15 month vaccination. This decline in circulating antibodies is not associated with increase in mucosal or invasive pneumococcal disease as antibodies are boosted in case of new colonization or infection with a vaccine-type *S. pneumoniae* after vaccinated with 13vPnC.[18,19] Studies have also shown that one month after the booster dose, vaccinated children present an increase in B-memory-cells that return to baseline levels at the age of 24 months. The meaning of the boost effect on B-memory cells needs to be further elucidated but may be correlated with long term memory protection.[20,21] As a part of Post Approval Commitments, the Center for Drug Evaluation (CDE) requested Pfizer to conduct an effectiveness study in a large scale population measuring herd protection in order to assess the clinical benefit; validate the correlation between surrogate endpoints (enzyme-linked immunosorbent assay [ELISA], MOPA) and protection, and the rationale of the criteria; investigate the immune persistence. This study is designed to assess the blood levels of circulating antibodies (IgG and MOPA) at the time of the diagnosis of clinical pneumonia.

Pfizer is currently conducting an observational study in Suzhou Children's Hospital (SCH) to evaluate 13vPnC vaccine effectiveness (VE) in preventing clinical pneumonia associated with 13vPnC vaccine type *S. pneumoniae* (study number WI232403). Pfizer will utilize the VE estimate from study WI232403 in combination with the post-approval commitment 3 (PAC3) immunogenicity study (study number B1851178) among infant cohort to estimate the correlation of protection (CoP). Additionally, based on recommendation from CDE, a descriptive immunogenicity study to measure the antibody levels at the time of disease onset was required. Therefore, this study will be conducted in parallel with the VE study in SCH to fulfill CDE request. Both the VE study (WI232403) and this immunogenicity sub-study, along with the analysis of CoP and the immune persistency portion included in study B1851178, will address these post licensure commitments from the CDE.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
To describe the antibody levels as measured by IgG and MOPA by 13vPnC vaccination status and vaccine-type (VT) carriage status, among children 5 months to ≤60 months of age with diagnosis of clinical pneumonia per local standard.	The serotype-specific IgG geometric mean concentration (GMC) and MOPA geometric mean titers (GMT) for each of the pneumococcal serotypes measured at the time of diagnosis of clinical pneumonia.

3. STUDY DESIGN

This is a cohort study designed to describe serotype-specific antibody levels by 13vPnC vaccination status (in children who completed at least 2 doses of 13vPnC, versus children that did not receive any 13vPnC) and vaccine type (VT) carriage status, among children 5 months to ≤60 months of age with clinical pneumonia. Thus, there will be four subgroups in this study: the 13vPnC cohort with VT carrier; the 13vPnC cohort without VT carrier; the unvaccinated cohort with VT carrier; and the unvaccinated cohort without VT carrier.

Children hospitalized with a diagnosis of clinical pneumonia will be considered for the study. Upon identification of a potential subject, all Inclusion and Exclusion criteria will be reviewed. The vaccination history of 13vPnC will initially be obtained either from the patient's parent/caregiver; confirmation of 13vPnC receipt from vaccine book or image of vaccine book is required. If 13vPnc vaccination is confirmed as received, and all other inclusion/exclusion criteria are met, this child will be enrolled and assigned to the vaccinated group. If 13vPnC vaccination is confirmed as not received, and all other inclusion / exclusion criteria are met, this child may be enrolled and assigned to the unvaccinated group. After the subject is enrolled, the 13vPnC receipt date and history of other vaccination status will be recorded, as well as other medical and demographic information. The blood draw of approximately 5 mL will be performed at this time.

Based on SCH local standard practice, deep upper respiratory aspirates are obtained and cultured for children hospitalized with clinical pneumonia. This may occur before the consent or enrollment. If the aspirate was not obtained as part of standard practice, the aspirate will be collected as a study procedure. Once the subject is enrolled, the sample identification (ID) and culture results for this procedure will be recorded into the case report form (CRF). In SCH all *S. pneumoniae* isolates recovered from hospitalized children regardless of patient age will be serotyped by FuDan University as part of study WI232403. Therefore, any additional ID used to label those *S. pneumoniae* isolates will be entered into the CRF so that the serotype information can be imported into this study database.

3.1. Approximate Duration of Subject Participation

Subjects will participate in the study for one day. Subjects will followed for 12 hours after blood draw and deep respiratory aspirate if collected as a study procedure.

3.2. Approximate Duration of Study

The study is anticipated to last approximately 24 months. The study duration may differ depending on the start-up of the study. It is expected that the study will complete enrollment by the end of year 2020, so that the serological assay testing and serotype data can be available for the final report.

3.3. Approximate Number of Subjects

Study sample size is based on feasibility; not for hypothesis testing.

It is anticipated that approximately 3,800 clinical pneumonia patients aged 5 to ≤60 months are admitted to SCH per year. Assuming 5% of admitted children have received at least 2-dose 13vPnC, with a 2-year enrollment period, it is expected that 380 cases would be

eligible for the 13vPnC cohort. Assuming 30% will be consented, about 100 children will be enrolled in the 13vPnC cohort. With a 1:2 ratio between the 13vPnC cohort and the unvaccinated cohort, a total of about 300 children will be enrolled.

The study will stop enrollment at the end of year 2020 regardless of the number of children enrolled.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Evidence of a personally signed and dated informed consent document indicating that the parent(s)/legal guardian has been informed of all pertinent aspects of the study.

2. Subjects whose caregiver is willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

3. Residents of Suzhou municipal districts (Gusu, New and high-tech, Wuzhong, Xiangcheng, Industrial Park).

4. A diagnosis of clinical pneumonia per SCH standard of care.

5. 5 months to ≤60 months of age at the time of consent.

6. Vaccination history (ie, vaccine book or picture of vaccine book) is available for confirmation.

    a. For the 13vPnC cohort: Participants should have received at least 2 doses of 13vPnC prior to hospitalization. There must be a minimum of 2 weeks between the second 13vPnC dose and enrollment.

    b. For the unvaccinated cohort: Children did not receive any dose of 13vPnC in the past.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Infant or child who is a family member of:

    - Investigator site staff members directly involved in the conduct of the study;

- Site staff members otherwise supervised by the investigator;
- Pfizer employees directly involved in the conduct of the study.

2. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
3. Blood draw is counter indicated.
4. Previous participation in this study within 30 days.
5. Previous vaccination with licensed or investigational pneumococcal vaccine. This excludes previous vaccination with 13vPnC as per the approved recommendations in China.
6. Received blood, blood fractions, plasma, or immunoglobulins within 3 months of the study blood draw.
7. Hospital acquired pneumonia (ie, onset >48 hours after hospitalization).

4.3. Diagnosis of Community-acquired Pneumonia

The standard guidance for the diagnosis of pneumonia at Suzhou Children's Hospital will be followed for entry into the study. Pneumonia diagnosis is made by the clinical judgment of treating doctors based on the Clinical Diagnosis and Treatment Guidelines for Pediatric Internal Medicine, issued by the Chinese Medical Association.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study reference manual.

5. STUDY PROCEDURES

The study will be conducted at SCH in Suzhou, Jiangsu province. SCH is located in the central area of Gusu district and is the only tier III children's hospital serving most of the young children in Suzhou.

Children who are residents from Suzhou municipal districts (Gusu, New and high-tech, Wuzhong, Xiangcheng, Industrial Park) admitted to the SCH with diagnosis of clinical pneumonia per SCH local standard will be evaluated by investigator.

Inclusion and exclusion criteria will be evaluated and those that fulfill all inclusion criteria and none of the exclusion criteria will be offered to participate in the study. Once Informed Consent has been obtained from parents or legal guardians of participants (vaccinated patient and control), study procedures may start.

If a patient is eligible for this study, all study-related procedures will be conducted by study personnel within one day. For every study subject enrolled in the 13vPnC cohort, two study subjects that did not receive 13vPnC will be enrolled on the same day (or ± 7 days) into the unvaccinated cohort. These control subjects will be matched by age (5 to ≤12 months, >12 to ≤24 months, >24 months to ≤60 months). In other words, for every subject enrolled in the 13vPnC cohort, two subjects within the same age group who did not receive 13vPnC will be enrolled if the non-13vPnC subjects hospital admission dates are within 7 days (±) of the vaccinated subjects.

Treatment and non-study procedures will be provided by the patient's physician as per local standard of care.

5.1. Visit 0 (Screening)

For subjects enrolled into this study, procedures for both screening and enrollment are conducted on the same day. For subjects not eligible for this study, only screening procedures are performed.

1. Evaluate patient eligibility, including review of 13vPnC vaccination. This may be obtained through the vaccination booklet, or an image of the vaccination booklet.

2. For subjects who meet all inclusion/exclusion criteria, obtain informed consent from the subject's parent(s)/legal guardian(s) prior to performing any protocol-required procedures.

3. Assign a subject number to all participants after signing informed consent.

5.2. Visit 1 (Enrollment)

1. Enroll the subject to this study, if eligible, and assign the participant to a study cohort.

2. Obtain and record the subject demography (including date of birth, sex, residence, and number/age of siblings, if any).

3. Obtain and record the subject's significant medical history (see Section 6.1).

4. For 13vPnC subjects, record date(s) of 13vPnC vaccination based on the patient's vaccine book.

5. Record antibiotic usage for the current pneumonia episode, to include antibiotic name, dosage, and start/stop date.

6. Collect a blood sample (approximately 5 mL) within 24 hours of enrollment. Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

7. Enter deep upper respiratory aspirate specimen information if this standard procedure was performed for this episode of pneumonia. The sample can be from before or after the enrollment. If an aspirate was not collected as a standard practice, this should be collected as a study procedure. The aspirate should be collected within 24 hours of enrollment.

8. Adverse events (AEs) that occur within 12 hours after the blood draw or aspirate collection (if collected as a study procedure) should be recorded in the source documents and in the AE section of the CRF.

9. The investigator or an authorized designee completes the CRF.

5.3. Subject Withdrawal

Subjects may withdraw from the study at any time at the request of their parent(s)/legal guardian, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

6. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

6.1. Significant Medical History Collection

Significant medical malformation, any immunocomprised condition, spleen anomaly, bone marrow anomaly, and any other significant medical history at the discretion of the Investigator will be collected.

6.2. Biological Samples

Collected samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. All serologic testing will be conducted by the National Institutes for Food and Drug Control (NIFDC). After completion of the study, all remaining serum samples will be under the custody of NIFDC.

The subject's parent/legal guardian may request that his or her child's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research.

Further details with regard to collection, processing and storage of biological samples will be maintained in the study specific laboratory manual.

6.2.1. Blood Samples

Approximately 5mL of blood will be collected from all participating subjects with a signed Informed Consent. Blood should be collected within 24 hours of enrollment.

The blood samples will be sent to an in-country central laboratory for processing before being sent to the NIFDC for testing.

6.2.2. Deep Respiratory Aspirate

Based on SCH local standard practice, deep upper respiratory aspirates are obtained and cultured for children hospitalized with clinical pneumonia. This may occur before enrollment. If a deep respiratory aspirate was not collected as a standard practice, an aspirate sample will be collected as a study procedure.

The aspirates will first be cultured at SCH laboratory, in appropriate culture medium that supports the growth of *S. pneumoniae*. If *S. pneumoniae* is isolated, serotyping will be performed at Fudan University as part of study WI232403.

6.2.2.1. Immunogenicity Evaluation

Immunologic assays will be performed at NIFDC.

6.2.2.1.1. ELISA Assessments

Serum concentrations of anticapsular IgG will be determined by ELISA for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in all subjects with a collected blood sample.

6.2.2.1.2. MOPA Assessments

Serum levels of MOPA for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all 13vPnC cohort subjects with adequate blood volume. In the non 13vPnC cohort, a sample of subjects with adequate blood volume will be selected, to be equal to the number of the 13vPnC cohort included for MOPA testing. Further details regarding the selection of this sub-cohort to be identified for MOPA testing will be outlined in the Statistical Analysis Plan (SAP).

7. SAFETY

7.1. Adverse Events

An AE is defined as any untoward medical occurrence and can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the subject's participation in the study.

Any AE that occurs from the time of the blood draw or aspirate collection through and including 12 hours must be recorded. The investigator is required to assess whether the AE may be related to the subject's participation in the study.

The investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a research related injury requiring immediate notification to Pfizer as described below.

7.1.1. Research Related Injury

Should a subject, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) and will be maintained by the sponsor.

The number and proportion of subjects with *S. pneumoniae* isolates detected will be summarized for both cohorts: the 13vPnC cohort and unvaccinated cohort. Additionally, the number and proportion of each serotype, serotype included in 13vPnC (VT), and serotypes not included in 13vPnC (non-VT) will be summarized for both cohorts.

For each cohort, children will be assigned to 2 groups: Participant in whom a 13vPnC vaccine type (VT) strain has been isolated from the respiratory tract, and participant from whom a 13vPnC VT strain has not been isolated from the respiratory tract (VT carrier versus without VT carrier). Therefore, a total of 4 subgroups are available: 13vPnC cohort with VT carrier; 13vPnC cohort without VT carrier; unvaccinated cohort with VT carrier; unvaccinated cohort without VT carrier.

For each of the 13 serotypes contained in 13vPnC, the IgG concentration and MOPA titers will be transformed in logarithm scale. Crude geometric mean concentrations (GMCs) and geometric mean titers (GMTs) and 95% confidence interval (CI) will be calculated for the 4 cohort/carriage subgroups.

A multiple regression model will be used with the log concentration or log titers as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, residence location, season of enrollment). Adjusted GMCs (or GMTs) and adjusted geometric mean ratios (GMRs) along with 95% CI will be estimated based on this model. The (GMRs) will compare antibody levels between any 2 of the 4 subgroups, as well as between the 2 cohorts, and between the carriage status.

Additionally, serotype-specific GMC/GMT (or adjusted GMC/GMT) and 95% CI may be provided for each 13vPnC serotype carriage status (Yes/No), for both 13vPnC cohort and unvaccinated cohort. Similar to any 13vPnC VT carriage status, the descriptive comparisons will be presented as GMR (or adjusted GMR) and 95% CI.

All of the analyses are considered as descriptive and no multiplicity adjustment will be made.

8.1. Analysis Timing

As this is a descriptive study, data may be summarized on an ongoing basis.

9. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the Institutional Review Board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10. DATA HANDLING AND RECORD KEEPING

10.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

10.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the International Conference on Harmonisation (ICH) guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

11. ETHICS

11.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

11.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject[, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent/assent from each subject or subject's parent(s) or legal guardian before any study-specific activity is performed. The investigator will retain the original of each subject's parent(s) or legal guardian-signed consent/assent document.

12. PUBLICATIONS BY INVESTIGATORS

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
AE	adverse event
CDE	center for drug evaluation
CI	confidence interval
CoP	correlate of protection
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
DCT	data collection tool
EC	ethics committee
ELISA	enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMR	Geometric mean ratio
GMT	geometric mean titer
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IRB	institutional review board
MOPA	multiplex opsonophagocytic activity
N/A	not applicable
NIFDC	National Institutes for Food and Drug Control
PI	principal investigator
SAP	statistical analysis plan
SCH	Suzhou Children's Hospital
UNICEF	United Nations Children's Fund
VE	vaccine effectiveness
VT	vaccine type
WHO	World health organization