

**BLA Real World Evidence Consultant Review Memorandum for the submitted draft Phase 4 Post-licensure effectiveness study protocol**

Application Type	Biologics License Application
STN	125731/0
CBER Received Date for Phase 4 (draft) protocol	January 14, 2021
PDUFA Goal Date	June 8, 2021
Division / Office	Division of Vaccines and Related Product Applications (DVRPA)/Office of Vaccines Research and Review (OVRR)
Priority Review	Yes
Reviewer Name	Hector S. Izurieta, MD, MPH, PhD Associate Director for Novel Clinical Investigations, OVRR
Review Completion/ Stamped Date	05/30/2021
Applicant	Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc
Established Name	Pneumococcal 20-valent Conjugate Vaccine (Diphtheria CRM <sub>197</sub> Protein)
(Proposed) Trade Name	Prevnar 20
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	<ul style="list-style-type: none"> <li>• 2.2 µg of each of <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F saccharides and 4.4 µg of <i>S. pneumoniae</i> serotype 6B saccharides</li> <li>• ~51 µg diphtheria cross reactive material (CRM<sub>197</sub>) carrier protein*</li> <li>• 125 µg aluminum as aluminum phosphate adjuvant</li> </ul> <p>* CRM protein is approximate and dependent on the saccharide-to-protein ratio of the saccharides used in the formulation</p>
Dosage Form and Route of Administration	Suspension for intramuscular injection
Dosing Regimen	Single dose
Indications and Intended Population(s)	Active immunization for the prevention of pneumonia and invasive disease caused by <i>S. pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults ≥18 years of age
Orphan Designated	No

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## GLOSSARY

ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CAP	community-acquired pneumonia
CAPiTA	Community Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CSR	clinical study report
DMC	Data Monitoring Committee
DVRPA	Division of Vaccines and Related Products Applications
ECG	electrocardiogram
FDA	Food and Drug Administration
GERD	gastrointestinal esophageal reflux disease
GMFR	geometric mean fold rise
GMT	geometric mean titer
IND	Investigational New Drug (application to the FDA)
IPD	invasive pneumococcal disease
IR	Information Request
ISS	Integrated Summary of Safety
LL	lower limit
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
OVRR	Office of Vaccines Research and Review
PCRU	Pfizer Clinical Research Unit
PCV7	Prevnar 7-valent pneumococcal conjugate vaccine
PCV13	Prevnar 13-valent pneumococcal conjugate vaccine
PCV20	Prevnar 20-valent pneumococcal conjugate vaccine
PeRC	Pediatric Review Committee
PPSV23	Pneumovax 23-valent pneumococcal polysaccharide vaccine
PREA	Pediatric Research Equity Act
PS	polysaccharide
PT	Preferred Term
SAE	serious adverse event
sBLA	Supplemental Biologics License Application
SD	standard deviation
SOC	System Organ Class
STN	Submission Tracking Number
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed
U.S.	United States
VT	vaccine type

## Executive Summary

### Background:

In the United States, *S. pneumoniae* is a leading cause of disease, including pneumonia, invasive disease and death, among older adults in the United States. Wyeth Pharmaceuticals LLC (the Applicant), a subsidiary of Pfizer Inc, submitted a (draft) protocol for a post-licensure PHASE 4 study required as part of its Biologics License Application (BLA) for their Pneumococcal 20-valent Conjugate Vaccine, a successor to Prevnar 13.

Prevnar 20 is composed of capsular polysaccharides derived from the 13 pneumococcal serotypes contained in Prevnar 13 (1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and from 7 additional pneumococcal serotypes that are also contained in Pneumovax 23 (8, 10A, 11A, 12F, 15B, 22F, and 33F), each individually conjugated to non-toxic diphtheria CRM<sub>197</sub> protein.

The proposed indications are for the active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1,3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F. The proposed regimen consists of a single intramuscular injection.

According to CDC's Active Bacterial Core surveillance (ABCs), serotypes 22F, 11A, 33F, 8 and 15B were the 5 most prevalent causes of IPD in the United States; also, the 7 new serotypes were isolated from approximately 30% of IPD cases in adults ≥19 years of age from 2017-2018.

Because, at the time of PCV20 development, its precursor, PCV13, was recommended routinely for adults ≥65 years of age and for adults <65 years of age with certain underlying conditions, a randomized placebo-controlled efficacy trial of PCV20 was not considered ethical. Also, an active control randomized study was not considered feasible due to the sample size it would require.

The accelerated approval of Prevnar 20 is based on an established immunologic surrogate endpoint (OPA titer), as defined in the Accelerated Approval regulations (21 CFR 601.41), that is reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes in PCV20, which applies to biologics intended to treat serious or life-threatening illnesses that provide meaningful therapeutic benefit to patients over existing treatments (21 CFR 601.40). Pneumococcal pneumonia is a serious condition, and PCV20 is intended to provide meaningful therapeutic benefit to patients over existing treatments. Therefore, the proposed indication meets the qualifying criteria for accelerated approval.

As a condition of the accelerated approval, Wyeth has proposed to conduct a post-approval real-world observational test-negative case control effectiveness study as a confirmatory study to verify and describe clinical benefit for the prevention of pneumonia in adults caused by the 7 new serotypes in PCV20.

### Overview of Phase 4 study protocol:

The sponsor's Phase 4 post-approval study is a multicenter real-world evidence (RWE) investigation of the effectiveness of the 20-valent pneumococcal conjugate vaccine (20vPnC) against vaccine-type (VT) radiologically-confirmed community-acquired pneumonia (RAD+CAP) using a test-negative case control design to be conducted at investigator hospital sites in the United States.

The proposed study is contingent upon licensure of 20vPnC by the FDA and upon a recommendation by CC's ACIP for use of 20vPnC in adults ≥65 years of age.

Its primary objective is to determine vaccine effectiveness (VE) of 20vPnC against RAD+CAP caused by the 7 additional serotypes contained in 20vPnC beyond the licensed 13-valent pneumococcal conjugate vaccine (13vPnC; serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F) plus 15C among adults ≥65 years of age. Approximately 12,500 adults ≥65 years of age are expected to be enrolled at approximately 10–20 sites.

### **Reviewer's comments:**

The sponsor's Phase 4 post-approval study is a multicenter (RWE) investigation of the effectiveness of the 20-valent pneumococcal conjugate vaccine (20vPnC) against VT RAD+CAP using a test-negative case control design to be conducted at investigator hospital sites in the United States. The study is contingent upon licensure of 20vPnC by the FDA and upon a recommendation by CDC's ACIP for use of 20vPnC in adults  $\geq 65$  years of age. Therefore, because PCV20 may be licensed and recommended for adults ages  $\geq 65$  years, the Applicant considers that a randomized study would be unethical. Also, a randomized, active comparator study would require a too large sample size.

Given the constraints for implementation of a randomized study, a TND, if properly designed and implemented, provides a robust design with some advantages in regard to the control for bias and confounding, particularly for infectious diseases studies.

The selection of test negative controls decreases unmeasured health seeking behavior bias, which is a major concern very difficult (and sometimes impossible) to measure accurately, in which individuals more likely to seek care when ill may also be more likely to receive the recommended vaccines and, also, to avoid unnecessary exposure to disease, thus potentially reducing the risk of a given vaccine-preventable disease.

The use of a highly specific diagnostic test to discriminate between cases and controls, which is the case in this study, should minimize outcome misclassification, another frequent problem with observational studies. Moreover, because the case definition is the same for the selection of potential cases and controls (they differ only on the specific etiologic agent), controls would be likely to seek care at a similar hospital facility if sick with the disease being investigated.

The study has some constraints that could threaten success, specified by CBER in information requests sent to the Applicant. In responses to the IRs, the applicant agreed to make changes in the protocol to satisfy CBER's main requests.

### **Conclusions and Recommendations:**

As a condition of accelerated approval of PCV20 for the prevention of pneumonia in adults  $\geq 18$  years of age caused by the 7 new vaccine serotypes (8, 10A, 11A 12F, 15B, 22F, and 33F), the Applicant has agreed to conduct a required well-controlled postmarketing study (B7471015) to verify the clinical benefit of PCV20 in preventing pneumococcal pneumonia caused by the 7 new vaccine serotypes in adults  $\geq 65$  years of age.

A draft protocol for study B7471015, a Phase 4 study using a test-negative design, was submitted to STN 125731/0.8. In responses to CBER's information requests, the Applicant has agreed to follow CBER's recommended changes to the protocol.

According to this reviewer, once the modifications recommended by CBER are incorporated as agreed, the Phase 4 protocol will satisfy CBER's concerns regarding study quality.

This reviewer recommends that the Phase 4 protocol submission should be approved, with the following contingencies: (1) submission of the final study protocol, including the modifications accepted by the Applicant in its responses to CBER's information requests, by August 31, 2021; (2) For the study to be operationally feasible, an additional contingency would be a recommendation by the CDC ACIP for PCV20 vaccination for adults ages  $\geq 65$  years.

## BACKGROUND

In the United States, *S. pneumoniae* is a leading cause of disease, including pneumonia, invasive disease and death, among older adults in the United States. It colonizes the nasopharynx, can cause invasive and non-invasive (IPD) disease. IPD is defined by isolation of *S. pneumoniae* from a normally sterile site. Among patients hospitalized with community-acquired pneumonia, approximately 5%-10% will have pneumococcal bacteremia. Non-bacteremic pneumococcal pneumonia accounts for approximately 13%-34% of pneumonia hospitalizations among adults (see also clinical review).

Conditions making adults to be at highest risk for include various immunosuppressive conditions, functional/anatomic asplenia, and renal disease. Other conditions that increase the risk include chronic heart disease, lung disease (including asthma), liver disease, smoking cigarettes, alcoholism, a CSF leak, and having a cochlear implant.

Although 100 serotypes have been identified, most invasive disease is caused by a relatively limited number of serotypes. Antibiotic resistance can lead to treatment failure.

The vaccine, PCV20, is intended to prevent both pneumococcal pneumonia and IPD caused by the 20 serotypes contained in the vaccine. The 7 non-PCV13 serotypes included in PCV20 (8, 10A, 11A, 12F, 15B, 22F and 33F) were selected based on their relative prevalence as a cause of IPD, their general geographic distribution and other factors such as presence of antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and greater disease severity such as meningitis or with relatively high mortality (10A, 11A, 22F).

According to CDC's Active Bacterial Core surveillance (ABCs), serotypes 22F, 11A, 33F, 8 and 15B were the 5 most prevalent causes of IPD in the United States. Also according to CDC, the 7 new serotypes were isolated from approximately 30% of IPD cases in adults  $\geq 19$  years of age from 2017-2018. Altogether, the 20 serotypes in PCV20 were isolated from approximately 55%-64% of all IPD cases among adults. Serotype 15B, which is closely related to 15C<sup>1</sup>, has been shown to contribute 1.5% of IPD in adults  $\geq 65$  years of age. The proportion of all-cause CAP caused by serotypes contained in PCV20 has been estimated to be 7.1% in 2014-2016 and 6.3% in 2019-2020 based on preliminary data from Wyeth presented by the CDC (Gierke 2021a).

The applicant, Wyeth Pharmaceuticals LLC (a Pfizer Inc, subsidiary), submitted a Biologics License Application (BLA) for their Pneumococcal 20-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) (proposed proprietary name, Prevnar 20), that includes capsular polysaccharides derived from the 13 pneumococcal serotypes contained in Prevnar 13 (1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and from 7 additional pneumococcal serotypes also contained in Pneumovax 23 (8, 10A, 11A, 12F, 15B, 22F, and 33F), each individually conjugated to non-toxic diphtheria CRM<sub>197</sub> protein. The proposed indications for Prevnar 20 are for the active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1,3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F. The proposed regimen consists of a single intramuscular injection.

Among pneumococcal vaccines, none other has shown to be effective in the prevention of vaccine serotype non-bacteremic pneumococcal pneumonia caused by the seven new serotypes in PCV20. These seven serotypes are responsible for a substantial proportion of the invasive and noninvasive

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pneumococcal disease burden in adults globally. Non-bacteremic pneumococcal pneumonia is a more common pneumococcal disease manifestation than IPD in adults. Therefore, CBER, considers protection of adults  $\geq 18$  years of age from non-bacteremic pneumococcal pneumonia to be a meaningful therapeutic benefit over existing treatments.

The approval of Prevnar 20 for the prevention of pneumonia in adults caused by the 7 new serotypes is based on an established immunologic surrogate endpoint (OPA titer), as defined in the Accelerated Approval regulations (21 CFR 601.41), that is reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes in PCV20. This regulation applies to biologics intended to treat serious or life-threatening illnesses that provide meaningful therapeutic benefit to patients over existing treatments (21 CFR 601.40).

Because pneumococcal pneumonia is a serious condition and PCV20 will provide meaningful therapeutic benefit to patients over existing treatments, the proposed indication meets the qualifying criteria for accelerated approval. A randomized, active-controlled efficacy trial of PCV20 was not considered feasible due to the sample size that would be required. A placebo-controlled trial was also not ethically feasible in the United States where, at the time of PCV20 development, PCV13 was recommended routinely for adults  $\geq 65$  years of age as well as for adults  $< 65$  years of age with certain underlying conditions that increase the risk of serious pneumococcal disease.

Because antibody levels have not been found as being indicative of prevention of non-invasive pneumococcal disease, CBER did not accept that immunogenicity data alone could be sufficient to support a non-invasive disease (i.e., pneumonia or otitis media) indication for non-PCV13 serotypes.

As a post-licensure requirement for accelerated approval, the sponsor has agreed to conduct a post-approval real-world observational effectiveness (Phase 4) study as a confirmatory study to evaluate the clinical benefit for the prevention of pneumonia in adults caused by the 7 new serotypes in PCV20.

## DESCRIPTION OF THE PHASE 4 DRAFT STUDY PROPOSAL

### Overview:

The sponsor's Phase 4 post-approval study is a multicenter real-world evidence (RWE) investigation of the effectiveness of the 20-valent pneumococcal conjugate vaccine (20vPnC) against vaccine-type (VT) radiologically-confirmed community-acquired pneumonia (RAD+CAP) using a test-negative case control design to be conducted at investigator hospital sites in the United States.

### Contingencies:

The proposed study is contingent upon licensure of 20vPnC by the FDA and upon a recommendation by CC's ACIP for use of 20vPnC in adults  $\geq 65$  years of age.

### Objectives and endpoints:

Primary objective: To determine vaccine effectiveness (VE) of 20vPnC against RAD+CAP caused by the 7 additional serotypes contained in 20vPnC beyond the licensed 13-valent pneumococcal conjugate vaccine (13vPnC; serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F) plus 15C among adults  $\geq 65$  years of age.

Effectiveness of 20vPnC will be evaluated for RAD+CAP due to the 20vPnC serotypes including the original serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), the 7 additional serotypes in 20vPnC beyond 13vPnC (8, 10A, 11A, 12F, 15B, 22F, or 33F), and highly-related, cross-reacting non-20vPnC serotypes 6C and 15C.

Objectives	Endpoints
<b>Primary</b>	<b>Primary</b>
To determine the effectiveness of 20vPnC against all (invasive + non-invasive) RAD+CAP due to the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C.	VE calculated as 1 minus the odds ratio for 20vPnC vaccination among cases versus controls multiplied by 100 adjusted for potentially confounding variables.
<b>Secondary</b>	<b>Secondary</b>
1. To determine the effectiveness of 20vPnC against non-invasive RAD+CAP due to the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C (i.e., restricted to participants where <i>S. pneumoniae</i> is not isolated from a	1. VE calculated as 1 minus the odds ratio for 20vPnC vaccination among cases and controls multiplied by 100 adjusted for potentially confounding variables.
2. To determine the effectiveness of 20vPnC against all RAD+CAP due to any 20vPnC serotype plus 6C and 15C.	2. VE calculated as 1 minus the odds ratio for 20vPnC vaccination among cases and controls multiplied by 100 adjusted for potentially confounding
3. To determine the effectiveness of 20vPnC against non-invasive RAD+CAP due to any 20vPnC serotype plus 6C and 15C.	3. VE calculated as 1 minus the odds ratio for 20vPnC vaccination among cases and controls multiplied by 100 adjusted for potentially confounding



4. To determine the proportion of participants with RAD+CAP due to the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C, individually and aggregately.	4. The proportion of participants with RAD+CAP who are positive for any of the 7 additional serotypes contained in 20vPnC beyond 13vPnC plus 15C as detected by UAD <sup>(b) (4)</sup> or culture.
5. To determine the proportion of all RAD+CAP due to any 20vPnC serotype plus 6C and 15C, individually and aggregately.	5. The proportion of participants with RAD+CAP who are positive for any of the serotypes contained in 20vPnC plus 6C and 15C as detected by UAD <sup>(b) (4)</sup>

Objectives	Endpoints
6. To determine the proportion of all RAD+CAP due to any 13vPnC serotype plus 6C, individually and aggregately.	6. The proportion of participants with RAD+CAP who are positive for any of the serotypes contained in 13vPnC plus 6C as detected by either UAD- <sup>(b) (4)</sup>
7. Among those positive for a serotype detected by serotype-specific UAD, to determine the proportion of participants with any RAD+CAP due to each UAD serotype individually and aggregately.	7. Among those positive for a serotype detected by serotype-specific UAD, the proportion of participants with RAD+CAP who are positive for any of the UAD serotypes as detected by UAD- <sup>(b) (4)</sup> or culture
8. To determine the proportion of participants with any RAD+CAP due to <i>S. pneumoniae</i> .	8. The proportion of participants with RAD+CAP who have <i>S. pneumoniae</i> identified by culture, <sup>(b) (4)</sup> or serotype specific UADs
9. To describe the clinical characteristics of disease and hospitalization among those with any RAD+CAP due to all 13vPnC and/or 20vPnC serotypes plus 6C and 15C individually and aggregately.	9. In participants with RAD+CAP, the following metrics overall, and among those positive for any of the serotypes contained in 13vPnC and/or 20vPnC plus 6C and 15C, or positive for individual serotypes contained in 13vPnC and/or 20vPnC plus 6C and 15C: <ul style="list-style-type: none"> <li>• Proportion with Pneumonia Severity Index (PSI) Grade I-V</li> <li>• Mean, Median, Min, and Max PSI Grade</li> <li>• Proportion in ICU</li> <li>• Mean, Median, Min, and Max length (in days) of ICU stay</li> <li>• Proportion on ventilator and by type of ventilation used</li> <li>• Mean, Median, Min, and Max length (in days) of ventilator use</li> <li>• Mean, Median, Min, and Max length (in days) of hospital stay</li> <li>• Proportion with respiratory rate</li> </ul>
Exploratory	Exploratory
To determine the effectiveness of 20vPnC by various participant characteristics (e.g., age, sex, chronic medical conditions, immunocompromising conditions) among participants with RAD+CAP.	Among participants with RAD+CAP: <ul style="list-style-type: none"> <li>• VE by age group (i.e., 65–74 years, 75–84 years, and ≥85 years)</li> <li>• VE by sex (i.e., male vs female)</li> <li>• VE by ACIP-defined risk group and by age group</li> <li>• VE by prior influenza vaccination in</li> </ul>

### Design:

Observational test-negative case-control study (TND), similar the 13vPnC effectiveness in US adults published in 2018. The main procedures will be a non-invasive urine specimen collection for pneumococcal detection using (b) (4) *S. pneumoniae* and the serotype-specific urinary antigen detection (UAD) assays. Test positives (cases) and controls will be differentiated by presence of vaccine serotypes. The assays detect the (b) (4)

\_\_\_\_\_. Serotypes after the slash are cross-reacting serotypes also detected by the UAD assays; of these, serotypes 6C and 15C are the most common and most likely to receive cross-protection by 20vPnC.

### Cases and controls:

For the primary objective, cases will be defined as participants hospitalized for RAD+CAP in whom the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C are identified. All other participants for whom 20vPnC serotypes are not identified from any source and all other RAD+CAP of non-pneumococcal etiologies will serve as test-negative controls. This approach mimics the definition of test-negative controls that i) was used in the aforementioned TND of 13vPnC against RAD+CAP,<sup>2</sup> and ii) is commonly used in TND studies of influenza VE.

### **Vaccination history:**

History of 20vPnC vaccination documented in medical and claims records from primary care providers, health-insurance providers, pharmacies, and any local, state, or national adult immunization registries will be recorded. Participants will be considered vaccinated if 20vPnC is documented as being received >30 days before hospitalization for RAD+CAP. Participants will be asked to provide vaccination history information as well as contact information for primary care physician(s), pharmacies where vaccination was provided and health insurance providers so that site staff may obtain documented vaccination history data. State registries, if available, will also be explored as an additional source for documented vaccination history.

### **Outcomes:**

Adults ≥65 years of age admitted for hospitalization at a study hospital with signs, symptoms, and radiologic evidence of CAP will be screened for enrollment eligibility. All participants will have a non-invasive urine specimen collected for pneumococcal detection by (b) (4) *S. pneumoniae* and vaccine serotype determination by serotype-specific UAD assays. All other clinical and medical data collection will be done through direct participant interview and review of medical records. Determining VE for 20vPnC will require access to documented vaccination history on all participants.

### **Data collection:**

Participants are expected to actively participate for up to 2 days if the interview and urine collection cannot be completed at a single visit on Day 1. Additional data will be collected at Day 30 including hospitalization details, in-hospital death, final diagnosis at hospital discharge, and the accumulated vaccine history data. It is expected that the visit window for the Day 30 visit (i.e. up to Day 45) should be sufficient for sites to review the various sources providing vaccine history information. Approximately 12,500 adults ≥65 years of age will be enrolled at approximately 10–20 sites. Each site will be expected to enroll a minimum of approximately 500 participants per study year with no upper limit.

### **Chest imaging:**

Includes CXR, CT scan, MRI, performed per SOC will be used to determine eligibility and confirm the diagnosis of pneumonia on all enrolled participants. All images will be independently read and adjudicated by a third-party central reader(s) to confirm the diagnosis of pneumonia.

### **Inclusion criteria:**

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female participants ≥65 years of age.
2. Hospitalized participant with physician clinical suspicion of CAP with the presence of ≥2 of the following 10 clinical signs or symptoms:
  - fever (oral temperature >38.0°C/100.4°F or tympanic temperature >38.5°C/101.2°F),
  - hypothermia (<35.5°C/95.9°F measured by a healthcare provider)
  - chills or rigors,
  - pleuritic chest pain,

- new or worsening cough,
- sputum production,
- dyspnea (shortness of breath),
- tachypnea (respiratory rate >20/min),
- malaise, or
- abnormal auscultatory findings suggestive of pneumonia (rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, or egophony).

3. With a radiographic finding consistent with pneumonia (e.g., pleural effusion, increased pulmonary density due to infection, the presence of alveolar infiltrates [multi-lobar, lobar, or segmental] containing air bronchograms).
4. Capable of giving signed informed consent

**Exclusion criteria:**

Participants are excluded from the study if any of the following criteria apply:

1. Any participant who develops signs and symptoms of pneumonia after being hospitalized for  $\geq 48$  hours (either at the study site, another transferring hospital, or a combination of these).
2. Received any pneumococcal vaccine  $\leq 30$  days prior to enrollment.
3. Unable to provide urine specimen (e.g. anuric).
4. Previous enrollment in the study within the past 30 days.

The selection criteria and definition of CAP for this proposed study are similar to those applied in other prospective, active CAP surveillance studies and are consistent with the most-recent definition of CAP put forth by the Infectious Disease Society of American (IDSA) and the American Thoracic Society (ATS).

**Enrollment and sampling:**

Participants can be enrolled in the study more than once as long as the previous enrollment occurred  $>30$  days prior. Each enrollment will be considered a new episode of pneumonia and a new participant identifier will be assigned. Prior participant identifiers will be documented in the CRF for the current episode.

The required sample size depends on the accrual of cases, the estimated vaccine effectiveness, and the percentage of individuals vaccinated, as well as other factors. The base case assumptions used to estimate the sample size of the analysis population for evaluation of vaccine effectiveness are:

- 1:31 ratio of cases to controls (3% of participants will be defined as a case, and 93% of participants will be defined as a control)
- 20% of participants will have received 20vPnC (based on the assumption that ACIP will recommend 20vPnC for routine use among 13vPnC naïve adults  $\geq 65$  years of age and that 20% of these adults will have received 20vPnC by 26 months post-introduction)
- 70% true VE
- 1-sided test with significance level  $\alpha=0.025$

- 90% power

In addition to these assumptions, there are 3 factors that will impact the total number of enrolled participants who will be evaluable in the primary analysis population.

1. The proportion of participants with complete vaccination history available: estimated to be 70%
2. The proportion of participants with CAP and adjudicated radiology reading: estimated to be 65%
3. The proportion of participants excluded due to being positive for 13vPnC serotypes: estimated to be 4%

Consequently, approximately 44% of the total number of enrolled participants will meet the criteria for inclusion in the primary analysis population for evaluation of vaccine effectiveness. Therefore, the sample size of the total enrolled population has been increased accordingly. In total, 170 cases are needed in the primary VE analysis along with the associated 5,285 controls according to the expected case-control ratio. After applying the adjustment factor to estimate the total number of participants that need to be enrolled such that the primary analysis sample size will be achieved, a total of approximately 12,500 participants will need to be enrolled in the study to identify the needed 170 cases.

However, because the sample size is dependent upon the proportion of CAP participants who have vaccine-type pneumococcal CAP (i.e., case accrual) and the proportion of the population vaccinated, the required sample size may be adjusted based on ongoing information from UAD testing results and vaccine exposure data. These parameters will be monitored separately and no less frequently than semi-annually to inform the end of enrollment. Performing these periodic checks will allow for assessment of the base case assumptions and recalculation of the sample size if any update is needed over the course of the study.

### **Data analysis:**

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

### **Primary analysis population (RAD+CAP):**

The RAD+CAP Population will include all participants who:

1. Meet all inclusion and exclusion criteria,
2. Have radiologic imaging confirmed to be consistent with pneumonia by adjudication process,

3. Have 5 years of documented pneumococcal vaccination history ascertained from participant's primary care physician records, the participant's electronic medical record, pharmacy records, insurance claims data, or state registries,
4. Did not receive a pneumococcal vaccine  $\leq 30$  days prior to enrollment,
5. Did not receive the (b) (4) [REDACTED] which is under development by (b) (4) [REDACTED] or an investigational pneumococcal vaccine.

This population will serve as the primary analysis population for identifying cases and controls for estimation of VE. These criteria are stricter than those used in a previous observational study of 13vPnC VE against vaccine-type RAD+CAP.

#### **Non-invasive RAD+CAP population:**

Subset of the RAD+CAP Population where *S. pneumoniae* is not isolated from a normally sterile site specimen (e.g., blood and pleural fluid) of participants with RAD+CAP. The secondary endpoints evaluating VE against non-invasive (only) RAD+CAP will be performed in this population.

#### **Five-year PPSV23-naïve Population:**

Subset of the RAD+CAP Population that includes participants who have not received PPSV23 within the last 5 years. To better understand the impact of PPSV23 use on VE of 20vPnC, all VE endpoints will be analyzed in this population as a sensitivity analysis.

#### **Concordant and discordant participants:**

For the primary analysis, exposure is defined as receipt of 20vPnC  $>30$  days prior to hospital admission for CAP. In separate secondary analyses, exposure will be defined as concordant or discordant receipt of 20vPnC according to the ACIP recommendation for adult pneumococcal vaccination. Based on the current ACIP recommendations for 13vPnC and PPSV23, participants who were administered 20vPnC and PPSV23 concordant to the current ACIP recommendation would be defined as any: (a) participants lacking an ACIP-defined risk group condition who received PPSV23  $\geq 1$  year after 20vPnC, immunocompetent participants who received PPSV23  $\geq 1$  year after 20vPnC, and, (b) immunocompromised participants who received PPSV23  $\geq 8$  weeks after 20vPnC. Discordant use will be defined as receipt of 20vPnC and PPSV23 contrary to these recommendations.

Any changes to the current recommendations regarding the timing between pneumococcal conjugate and pneumococcal polysaccharide vaccines that occur prior to study start will be reflected in the final study protocol and/or SAP.

Participants will be excluded from analyses if vaccinated with 15vPnC or any other newly-licensed or investigational pneumococcal conjugate vaccine prior to hospital admission for CAP or if PPSV23 was administered prior to 20vPnC.

#### **Vaccine effectiveness estimation:**

The primary analysis is to calculate vaccine effectiveness of 20vPnC against RAD+CAP due to the 7 serotypes in 20vPnC beyond 13vPnC plus 15C. Vaccine exposure for the primary analysis will be 20vPnC receipt. Secondary analyses of ACIP recommended concordant or discordant 20vPnC



receipt will also be performed. Vaccine effectiveness will be estimated using the generalized estimating equation with logit link function and take account of correlation in the data within the site. To adjust the effect of the confounding variables, we will select the variables that were independently associated with the outcome at  $p < 0.10$  in a bivariate analysis and include those variables in the multivariable model. The estimates will be exponentiated to get the odds ratios. The crude OR of prior 20vPnC receipt for cases and controls will be calculated as well. Crude and adjusted VE will be calculated as  $1 - \text{OR} \times 100$ . The lower bound of two-sided 95% CI for the adjusted VE estimate will be calculated and compared to the success criteria of 20%. For the primary analysis, the adjusted VE with its corresponding 95% CI will be the final VE estimates reported. Additionally, we will do the subgroup analyses of VE according to prior influenza vaccine receipt in the past 12 months (yes vs. no), age group (65–74 years, 75–84 years, and  $\geq 85$  years), sex (male vs. female), and ACIP-defined risk group (low-risk, at-risk, and high-risk) overall and by age groups. For the subgroups, we will present the values of VE with its corresponding 95% CI. The ACIP-defined risk groups of high-risk, at-risk, and low-risk will be constructed according to the presence of chronic medical conditions known to modify pneumococcal disease risk. Any changes made by ACIP to the risk group definitions will be reflected in the SAP. Risk groups are mutually exclusive and hierarchical. If a participant had both a high-risk and at-risk medical condition, the participant would be classified as high-risk only. Risk groups are defined as follows:

High-risk (immunocompromised): Chronic kidney disease, including chronic renal failure and nephrotic syndrome; cochlear implant; cerebrospinal fluid leak; functional or anatomic asplenia, including sickle cell disease or other hemoglobinopathy, and congenital or acquired asplenia; congenital or acquired immunodeficiency; human immunodeficiency virus infection; hematologic cancer or malignancy; cancer or malignancy manifesting as solid tumor; organ transplantation; immunosuppressant drug therapy.

At-risk (immunocompetent, but chronic disease present): Chronic lung disease, including chronic obstructive pulmonary disease, asthma, and emphysema; chronic heart disease, including congestive heart failure and cardiomyopathies; diabetes mellitus (with or without complications); chronic liver disease, including cirrhosis.

Low-risk: Absence of a high-risk or at-risk chronic medical condition.

Other details for secondary/exploratory analysis and sensitivity analyses will be specified in the SAP.

### **Descriptive analyses:**

Additional descriptive analyses will be performed to compare characteristics of cases and test negative controls. Comparisons between proportions will be performed using  $\chi^2$  test, the Fisher's exact test, or the Likelihood Ratio test, as appropriate. For quantitative variables, the Student's t-test or the Analysis of Variance (ANOVA) test will be used, and when data did not show normality in the Kolmogorov-Smirnov test, the Kruskal-Wallis and Mann-Whitney tests will be used.

There is no formal interim analysis planned in this study. However, in order to evaluate if the assumptions used to calculate the sample size are accurate, periodic review of serotype-specific UAD data may be done by a Clinician, Statistician, or Scientific/Medical Affairs representative who is not directly involved in the study and who does not have access to the clinical database. The Pfizer team will also monitor vaccine uptake in the US throughout the course of the study.

### **Statistical methods:**

Because the primary objective is to determine VE of 20vPnC against the 7 additional serotypes contained in 20vPnC beyond 13vPnC plus 15C among individuals  $\geq 65$  years, the primary hypothesis test is to assess VE of 20vPnC in preventing CAP due to the 7 additional vaccine serotypes in 20vPnC beyond 13vPnC: 8, 10A, 11A, 12F, 15B, 22F, or 33F, plus highly-related serotype 15C. The null hypothesis ( $H_0$ ) versus the alternative hypothesis ( $H_1$ ) is  $H_0$ : VE  $< 20\%$  versus  $H_1$ : VE  $\geq 20\%$ , where VE is 1-Odds Ratio, and the Odds Ratio is the odds of having received 20vPnC by the cases (i.e., CAP cases with any of the following serotypes 8, 10A, 11A, 12F, 15B, 22F, 33F plus 15C is identified) relative to the odds of having received 20vPnC by the test-negative controls (i.e., CAP cases for whom 20vPnC serotypes are not identified). To estimate VE, the generalized estimating equation with logit link function will be employed to account of correlation in the data within sites.

To adjust for the effects of confounding variables, variables that are independently associated with the outcome at  $p < 0.10$  in a bivariate analysis will be selected and included in the multivariable model. Assuming 70% VE, 20% vaccine exposure in the control group, 1:31 case-control ratio, one-sided test with significance level 0.025 and 90% power, a total of 170 cases will be required for the primary analysis of VE in this study (along with the associated 5,285 controls according to the expected case-control ratio).

**Sample size:**

Approximately 12,500 adults  $\geq 65$  years of age will be enrolled at approximately 10–20 sites geographically dispersed across the US. The geographic distribution of sites will ensure representation of study participants across a spectrum of socioeconomic and demographic characteristics. Each site will be expected to enroll a minimum of approximately 500 participants per study year with no upper limit.

**Study duration:**

The start of enrollment is expected to occur after 20vPnC licensure and an ACIP recommendation for 20vPnC use in older adults. Duration of enrollment will be impacted by the type of ACIP recommendation and vaccine uptake in the target population. The type of ACIP recommendation could include one of the following 4 scenarios:

- Routine recommendation of  $\geq 65$  years for 20vPnC use among 13vPnC naïve (category 1) or including those previously vaccinated with 13vPnC (category 2).
- Shared-clinical decision-making recommendation (SCDM) of  $\geq 65$  years for 20vPnC use among 13vPnC naïve (category 3) or including those previously vaccinated with 13vPnC (category 4).

Based on these 4 recommendation categories and observed uptake of 13vPnC in adults  $\geq 65$  years of age following the 2014 ACIP recommendation, it is expected that approximately 26, 18, 37, or 24 months will be needed to achieve the base case 20vPnC uptake of 20% over the entire study period according to recommendation categories 1, 2, 3, or 4, respectively.

The duration and sample size calculations for this study are based on the assumption that ACIP will recommend routine use of 20vPnC for 13vPnC naïve adults  $\geq 65$  years of age (category 1).

Accordingly, the Sponsor assumed that 20% of 13vPnC naïve adults  $\geq 65$  years of age will receive 20vPnC by 26 months post-licensure with a linear increase in uptake over this time. Based on possible variation in this assumption and prior study experience enrolling older adults with CAP, the Sponsor estimates that 36 months will be needed to enroll the target number of cases for the primary endpoint at 10-20 sites.

If the ACIP recommends 20vPnC for all persons aged  $\geq 65$  years regardless of previous 13vPnC receipt, the study will occur over approximately 36 months such that at least 3 respiratory viral seasons will be included. However, if the ACIP recommends 20vPnC only for persons who did not receive 13vPnC, our target population will be persons ageing into the group aged  $\geq 65$  years and the small proportion of this population who did not receive 13vPnC (and who may be less likely to receive 20vPnC). In this circumstance, a study limited to the US will take substantially longer, so that we would look for sites in other countries with a true age-based recommendation.

## **REFERENCED DOCUMENTS**

Reference is made to the following documents:

1. CBER's information request (IR) from November 8, 2019, and the Applicant's response received on May 1, 2020
2. CBER's IR from July 20, 2020, and the Applicant's response received on October 13, 2020
3. Phase 4 protocol (draft) submitted by the Applicant on January 14, 2021
4. CBER's IR from March 12, 2021, and the Applicant's response received on March 19
5. CBER's IR from April 13, 2021, and the Applicant's response received on April 20
6. CBER's IR from April 28, 2021, and the Applicant's response received on May 4.
7. CBER Clinical review
8. CBER Statistics review

## REVIEWER'S COMMENTS

(please also refer to the clinical and statistical reviews)

The sponsor's Phase 4 post-approval study is a multicenter (RWE) investigation of the effectiveness of the 20-valent pneumococcal conjugate vaccine (20vPnC) against VT RAD+CAP using a test-negative case control design to be conducted at investigator hospital sites in the United States. The study is contingent upon licensure of 20vPnC by the FDA and upon a recommendation by CDC's ACIP for use of 20vPnC in adults  $\geq 65$  years of age. Therefore, because PCV20 may be licensed and recommended for adults ages  $\geq 65$  years, the Applicant considers that a randomized study would be unethical. Also, a randomized, active comparator study would require a too large sample size.

Given the constraints for implementation of a randomized study, a TND, if properly designed and implemented, provides a robust design with some advantages in regard to control for bias and confounding, particularly for infectious diseases studies.

The selection of test negative controls decreases unmeasured health seeking behavior bias, which is a major concern very difficult (and sometimes impossible) to measure accurately, in which individuals more likely to seek care when ill may also be more likely to receive the recommended vaccines and, also, to avoid unnecessary exposure to disease, thus potentially reducing the risk of a given vaccine-preventable disease.

The use of a highly specific diagnostic test to discriminate between cases and controls, which is the case in this study, should minimize outcome misclassification, another frequent problem with observational studies. Moreover, because the case definition is the same for the selection of potential cases and controls (they differ only on the specific etiologic agent), controls would be likely to seek care at a similar hospital facility if sick with the disease being investigated.

The study has some constraints that could threaten success:

1. Unlike randomized studies, observational studies require the assessment of bias and confounding. The applicant could consider using negative endpoints (negative exposure and/or outcomes) to help determine the existence of residual bias.
2. It is unknown if the ACIP will recommend the use of 20vPnC vaccine in the US in adults  $\geq 65$  years of age, and if the use of the vaccine will be sufficient for the study to obtain the necessary power. If vaccine use is insufficient, the study recruitment would have to be extended, maybe significantly, and/or include data from other countries. In both scenarios, the timely completion and maybe even the quality of the study could be threatened.
3. The investigators must accurately obtain vaccination histories for all cases and controls. Although failure to accurately confirm vaccination status could bias results in either direction, it is most often towards the null. However, the Applicant has stated that significant efforts will be made to select Sites based on their experience and/or ability to obtain vaccination history data from additional sources, which have been well described by the Applicant in their submission. The Applicant has also explained that enrolled participants without a documented vaccination history will be excluded from the analysis. However, inclusion of individuals who appear to be unvaccinated in the analysis could still underestimate VE.
4. Because only a relatively small proportion of the eligible population is likely to receive the vaccine, vaccinees could represent individuals at higher risk of disease, thus biasing the study towards the null. Proper adjustment for confounding factors would be needed to

overcome this limitation, this would require a thorough ascertainment of all likely confounders. The Applicant's submission has included consideration of this limitation.

5. Differences in compliance with COVID-19 recommendations for social distancing and facial covering between vaccinated and unvaccinated study participants could threaten study validity if not accounted for. Although the Applicant's use of a well-designed test negative approach would decrease health seeking behavior differences, residual bias may still occur. For that purpose, negative endpoints could be considered for the estimation of residual bias.
6. Recommendations for social distancing and facial covering can dramatically decrease disease incidence, thus decreasing the number of eligible study participants. The Applicant will monitor case accrual over time to determine when the target number of cases has been reached, this will permit the identification of delays.
7. CBER expressed concerns regarding sample size estimates for the Phase 4 study, and overreliance on foreign data. However, CBER considers that the VE estimate may be supported by the points raised by the sponsor in their IR response. Given the possibility that individuals with "other RAD+CAP of non-pneumococcal etiology" may have different risk profiles than the cases, CBER requested a sensitivity analysis that restricts the controls to those with "non-vaccine type pneumococcal etiologies except 15C and 6C" to minimize potential confounding. In their response from March 19, 2021, the Applicant agreed to perform sensitivity analyses for each objective evaluating vaccine effectiveness with controls restricted to participants with RAD+CAP due to non-vaccine-type pneumococcal etiologies except serotypes 6C and 15C.
8. Because of the possibility of effect modification by immunosuppressive status, CBER requested that the Applicant includes in the analysis a subgroup analysis stratified by immunosuppressive status. In its response, the applicant agreed to conduct subgroup analyses to evaluate vaccine effectiveness for immunosuppressed persons using the ACIP-defined risk groups of low-risk, at-risk, and high-risk. Also, because the ACIP-defined high-risk group includes people with immunocompromising conditions but also includes other conditions not considered to be immunocompromising, the Applicant agreed to perform an additional subgroup analysis that includes immunocompromised conditions only.
9. CBER observed that, in Section 9.5.3 of the protocol regarding the primary efficacy analysis of 20vPnC, the Applicant proposed "to adjust the effect of the confounding variables and select the variables that were independently associated with the outcome at  $p < 0.10$  in a bivariate analysis and include those variables in the multivariable model." Compared to other variable selection methods, this proposed strategy might be more susceptible to selecting non-confounders or excluding important confounders and therefore introducing bias. Due to the ambiguity in the variable selection process, CBER suggested that the Applicant pre-specify a set of prognostic covariates that are anticipated to be strongly associated with the outcome in the statistical model as the primary efficacy analysis, and suggested that inclusion of additional covariates in the model may be considered in the sensitivity analyses. In its response, Pfizer agreed to have as the primary effectiveness analysis a multivariable model that includes a priori identified prognostic covariates based on relationship with the outcome of CAP and the exposure of 20vPnC. As recommended, Pfizer also agreed to develop additional models for sensitivity analysis that will include additional covariates according to the original covariate selection strategy described in protocol Section 9.5.3. In their response, Pfizer also submitted a summary of changes document summarizing the critical content changes by protocol section.

10. CBER noted that the Applicant revised the case definition for the primary and secondary objectives to include cross-reactive serotypes 6C and 15C. Although serotypes 6C and 15C may not be analyzed separately due to an inability to distinguish these serotypes from serotypes 6B and 15B. Pfizer, in its response, acknowledged that data associated with these study objectives would not be sufficient to support an indication for cross-reactive serotypes 6C and 15C.
11. CBER requested that the Applicant revise the protocol to include the specific selection criteria and definition of CAP that apply for this protocol (rather than refer to this information in the scientific literature), and asked that the definition includes criteria that will exclude healthcare associated pneumonia (HCAP). In their response, Pfizer clarified the specific selection criteria, and also explained its rationale for including HCAP, providing appropriate references.
12. CBER asked that, for the culture diagnostics, the Applicant should provide evidence showing that the serotyping method is specific enough to distinguish related serotypes 6B from 6C and 15B from 15C. In its response, Pfizer argued, with references, that the expected contribution of bacteremic vaccine serotype cases as identified by culture should be very low, and anticipated that the majority of RAD+CAP cases in the proposed vaccine effectiveness study will also be non-bacteremic and most vaccine serotype cases will be identified by the UAD assays. Nevertheless, Pfizer confirmed the ability to differentiate serotype 6A from 6C and serotype 15B from 15C, which would facilitate the conduct of sensitivity analysis removing 6C and 15C invasive cases.
13. CBER recommended that, for the subgroup analysis that includes immunocompromised conditions, the Applicant excludes other conditions not considered immunocompromising (i.e., persons with functional or anatomic asplenia, and chronic kidney disease not consisting of chronic renal failure and nephrotic syndrome), to which Pfizer agreed.
14. CBER recommended that, in order to restrict the CAP definition to exclude nosocomial pneumonia (usually not pneumococcal), the case definition exclude subjects who meet strong risk factors for non-pneumococcal pneumonia, to which Pfizer agreed.
15. CBER noted that subjects vaccinated with PPSV23 after 20vPnC will be included in the primary analysis population and observed that, since PPSV23 is expected to provide protection against invasive pneumococcal pneumonia caused by the 7 additional serotypes, inclusion of subjects vaccinated with PPSV23 may confound the evaluation of the effectiveness of 20vPnC. Therefore, CBER recommended that the Applicant use the five-year PPSV23-naïve population as the primary analysis population for the primary endpoint and key secondary endpoint. In its response, Pfizer explained that the protocol will exclude from the primary analysis population any participants with PPSV23 at any time prior to receipt of PCV20 (to eliminate the effects of any potential hyporesponsiveness that might occur from vaccine administration in this sequence) In contrast, Pfizer did not propose to exclude participants from the primary analytic population who received PPSV23 after PCV20 given that it is the likely recommended schedule per ACIP guidelines. Also, Pfizer argues that PPSV23 is not considered to have impact on non-bacteremic pneumonia, and that the proportion of all CAP due to the 7 additional serotypes in PCV20 beyond PCV13 due to bacteremic CAP is expected to be small. As example, Pfizer indicated that, in study B1851147, among persons  $\geq 65$  years of age with radiologically-confirmed CAP due to the additional 7 serotypes (n=181), only 15 (8.3%) came from a sterile site. Consequently, Pfizer considers that the potential incremental impact of PPSV23 on prevention of



bacteremic CAP due to these serotypes would be negligible and too small to affect interpretation of vaccine effectiveness estimates in a meaningful way. The review team considers that a possible solution would be to use PPSV23 as a covariate, also including an interaction term for PSV23. That should permit the identification of interaction by PPSV23.

## CONCLUSIONS AND RECOMMENDATIONS

As a condition of accelerated approval of PCV20 for the prevention of pneumonia in adults  $\geq 18$  years of age caused by the 7 new vaccine serotypes (8, 10A, 11A 12F, 15B, 22F, and 33F), the Applicant has agreed to conduct a required well-controlled postmarketing study (B7471015) to verify the clinical benefit of PCV20 in preventing pneumococcal pneumonia caused by the 7 new vaccine serotypes in adults  $\geq 65$  years of age. Approximately 12,500 adults  $\geq 65$  years of age will be enrolled at approximately 10–20 sites, with each site expected to enroll a minimum of approximately 500 participants per study year.

A draft protocol for study B7471015, a Phase 4 study using a test-negative design, was submitted to STN 125731/0.8. In responses to CBER's information requests, the Applicant has agreed to follow CBER's recommended changes to the protocol. The applicant has also indicated that, for the study to be feasible, a recommendation by the CDC ACIP for PCV20 vaccination for adults ages  $\geq 65$  years would be needed.

According to this reviewer, once the modifications recommended by CBER are incorporated as agreed, the Phase 4 protocol will satisfy CBER's concerns regarding study quality.

This reviewer recommends that the Phase 4 protocol submission should be approved, with the following contingencies: (1) submission of the final study protocol, including the modifications accepted by the Applicant in its responses to CBER's information requests, by August 31, 2021; (2) Study completion by May 31, 2027, (3) Final report submitted by November 30, 2027.

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