Study Information

Title	A Low Intervention Study of the Effectiveness Of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Against Vaccine Type Pneumococcal Hospitalised Community Acquired Pneumonia (CAP) in Adults 60 Years and Older Using A Test Negative Design Study in A Well-Defined Area of the South of Madrid Region
Study Phase	Not applicable
Protocol number	B1851202
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Date	03 February 2022
Research question and objectives	To determine the effectiveness of PCV13 to prevent hospitalised vaccine-type (VT)-pneumococcal CAP among adults aged ≥60 years in Madrid using a test-negative design study, overall and among immunocompetent persons only
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CAP	Community Acquired Pneumonia
CAPA	Acronym for an epidemiological study assessing the burden of hospitalised community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae* in adults in Spain using urinary antigen detection (UAD) testing
CAPITA	Community-acquired Pneumonia Immunisation Trial in Adults
CDC	United States Centres for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRB-65	Confusion Urea Respiratory Rate Blood Pressure
CST	Clinical Study Report
CT	Computed Tomography
CXR	Chest X-ray
eCRF	Electronic Case Report Form
FiO2	Fraction of inspired Oxygen
FSFV	First Subject First Visit
ICD	International Disease Classification
ICU	Intensive Care Unit
IEC	Independent Ethic Committee
ID	Identification
IPD	Invasive Pneumococcal Disease

Abbreviation	Definition
IRB	Institutional Review Board
ISCIII	Instituto de Salud Carlos III
LSLV	Last Subject Last Visit
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PCL	Pfizer Central Laboratory
PCV13	13-valent Pneumococcal Conjugate Vaccine
PCV20	20-valent Pneumococcal Conjugate Vaccine
PI	Principal Investigator
PPV23	23-valent Pneumococcal Polysaccharide Vaccine
PSI	Pneumonia Severity Index
RIP	Regional Immunisation Program
RL	Reference Laboratory
RRI	Research Related Injury
RSV	Respiratory Syncytial Virus
SISPAL	"Sistema de Información en Salud Pública y Alimentación" (in Spanish)
SP	Streptococcus pneumoniae, *S. pneumoniae*
SpO2	Oxygen saturation level
SOC	Standard Of Care
TND	Test Negative Design
UAD	Urinary Antigen Detection
US	United States
VE	Vaccine Effectiveness
VT	Vaccine Type

2. RESPONSIBLE PARTIES COUNTRY COORDINATING INVESTIGATORS

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3. SUMMARY

A Low Intervention Study of the Effectiveness Of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Against Vaccine Type (VT) Pneumococcal Hospitalised Community Acquired Pneumonia (CAP) in Adults 60 Years and Older Using A Test Negative Design Study (TND) in A Well-Defined Area of the South of Madrid Region.

Version 3.0, dated 03 February 2022.

Main author: PPD , Pfizer S.L.U, Spain.

Rationale and background

The approval of the 13-valent pneumococcal conjugate vaccine (PCV13) for both adults and children offers the opportunity to prevent pneumococcal disease in the two groups of population with highest incidence rates, namely children <5 years of age and the elderly. In the Community of Madrid, PCV13 is recommended and reimbursed for all adults over

60 years of age not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPV23) nor PCV13 since January 2018. For this age group a single dose of PCV13 is recommended. In addition, it is recommended that individuals ≥18 years with a chronic disease such as Chronic Obstructive Pulmonary Disease (COPD), diabetes, heart failure, regardless of previous vaccination status, will receive one dose of PCV13. Sequential immunisation with both vaccines (PCV13+PPV23) is recommended for high-risk immunocompromised patients ≥18 years of age. This recommendation is supported by results of the CAPA study (Epidemiological study assessing the burden of hospitalised community-acquired pneumonia [CAP] due to *Streptococcus* pneumoniae (SP) in adults in Spain using urinary antigen detection [UAD] testing) that showed a significant proportion (9%) of hospitalised all-cause CAP cases were caused by PCV13 serotypes in adults 18 years and older.[1]

The paediatric heptavalent pneumococcal conjugate vaccine (PCV7) was first available in Spain in June 2001 and incorporated in the Madrid regional immunisation programme (RIP) in 2006, remaining in the private market for other regions. From mid-2010 through 2016, Spanish regions introduced the 13-valent conjugate vaccine (PCV13) in their RIPs.

Adult vaccination with the 23-valent polysaccharide (PPV23) officially started in 2004, and with PCV13 in 2016 for some cohorts. Most adult pneumococcal vaccination occurs during annual influenza vaccination campaigns. Pneumococcal vaccination for adults in the Madrid region changed as of January 2018. An overview of pneumococcal adult vaccination is described in Table 1.

Note that for persons ≥60 years with past PPV23 administration, only those with underlying disease or at high risk will be given PCV13, and others without risk factors will not receive another pneumococcal vaccination (Table 1). Thus, in the ≥60 years age group, the population with PCV13 will be enriched for those with risk factors, and this will need to be accounted for in the analysis as a source of confounding (ie, confounding by indication).

Current PCV13 and PPV23 average uptake in Madrid Region as of March 2019 is described in Table 2, with a peak for PCV13 in people of 63 years old (see Table 2). People of over 60 years in the whole of Madrid region are 1,511,750 as of January 2018 (Instituto Nacional de Estadística, INE, www.ine.es).

The Regional Health System operates a database known as “Sistema de Información en Salud Pública y Alimentación” (SISPAL) [in English “Information System for Public Health and Food”] which includes information on previous vaccination history, including influenza, PPV23 and PCV13 vaccination, with lot number and date of administration per person.

Pneumococcal vaccination status will be based on whether receipt of ≥1 dose of PCV13 or PPV23 could be confirmed by electronic registries. All available vaccination data will be collected from the registry on subjects and time from vaccination will be incorporated in the analysis phase. Patients will be included regardless of the timing of their vaccination relative to their qualifying pneumonia admission but will be excluded from vaccine effectiveness

(VE) and serotype distribution analysis if they received pneumococcal vaccination ≤30 days before hospitalisation for CAP because of risk of false positive UAD test. We will obtain previous influenza vaccination status (within the last year) via electronic registries as well.

Respiratory syncytial virus (RSV) has long been recognized as a problematic respiratory pathogen causing illness in children, but the scope and impact of RSV in adults is less well-defined. Severe disease occurs especially among those with compromised cardiac, pulmonary, or immune systems and in the elderly but estimates of the RSV disease burden requiring hospitalization in adults are limited. Previous studies have suggested that up to 10% of adults presenting with acute respiratory illness during the winter have RSV. Further, Pfizer is CCI [redacted].

Research question and objectives

Primary Objective

- To determine the effectiveness of PCV13 to prevent hospitalised VT-pneumococcal CAP among adults aged ≥60 years in Madrid using a TND, overall and among immunocompetent persons only.

Secondary Objective(s)

- To describe the distribution of SP serotypes using blood, high-quality respiratory cultures, and a serotype-specific UAD assay among adults 60 years of age and older with CAP.

- To determine the proportion of persons with respiratory pneumococcal carriage among adults 60 years of age and older presenting with CAP by testing saliva specimens using both conventional culture and the sensitive molecular method of polymerase chain reaction (PCR) for the detection of two target genes (lytA and ply).

- To describe the proportion of participants with CAP and with *S. pneumoniae* (SP+CAP) who present with underlying at-risk and high-risk medical conditions.

- To describe the frequency and type of antibiotic resistance among SP isolates, overall and by specimen type.

Exploratory Objectives

- To estimate incidence rates for hospitalised CAP and SP+CAP (both overall and radiologically confirmed) in the surveillance region within the limitations of the expected under ascertainment of hospital-based screening process and current diagnostic testing.

- To compare the effectiveness of PPV23 to that of PCV13 in preventing cases of hospitalised VT-pneumococcal CAP among adults aged ≥60 years using a test-negative study design, overall and among immunocompetent persons only.

- To compare pneumococcal serotype results from high-quality respiratory specimens (standard –of care), UAD1/2 (study procedure), and saliva specimens taken for carriage testing (study procedure).

- To estimate incidence rates for hospitalised CAP among adults aged ≥60 years with underlying at-risk and high-risk medical conditions, in aggregate and for individual risk conditions within the limitations of the expected under ascertainment of hospital-based screening process and current diagnostic testing.

Additional 2019 Novel Coronavirus Disease 2019 (COVID-19)-related Exploratory Objectives

- To determine if the frequency of pneumococcal infection differs between hospitalised CAP patients with COVID-19 infection compared to those without COVID-19 infection, overall and stratified by age, sex, and pneumococcal risk status.

- Among the subset of hospitalised CAP patients with COVID-19 identified, to determine if the proportion who experience severe clinical outcomes (eg, intensive care unit [ICU] stay, mechanical ventilation, prolonged hospitalisation, and sequelae) differs between those with pneumococcal co-infection compared to those without pneumococcal co-infection, overall and stratified by age, sex, and pneumococcal risk status.

- Using a test-negative design to determine the VE of PCV13 against severe COVID-19 clinical outcomes among COVID-19 positive hospitalised CAP patients, overall and among immunocompetent persons only.

- To assess if pneumococcal carriage differs for those with current or past COVID-19 infection, overall and stratified by age, sex, and pneumococcal risk status.

Additional 2022 Respiratory Syncytial Virus (RSV) Exploratory Objective

- To determine the proportion of persons with RSV infection among adults 60 years of age and older presenting with CAP by testing saliva specimens using the PCR method.

Study design

This study is a low interventional, prospective, multicentre, hospital-based study involving adults 60 years of age and older hospitalised with CAP at participating sites. Hospital surveillance data will be used for incidence rates calculations. Vaccine effectiveness will be calculated using a TND. The approximate study duration will be 4 years.

Population

This study will prospectively enroll adults, aged 60 years and over, who are hospitalised with CAP in one of the study hospitals: Hospital Universitario de Móstoles, Hospital Universitario Fundación de Alcorcón, and Hospital Rey Juan Carlos de Móstoles (as of February 2022, additional sites may be included at a later date).

Variables

Please see Section 10 for full listing. In summary, the screening step will collect demographic information, eligibility for the study, whether consented, any standard of care

(SOC) test results. If consent is given, then further data collection and enrolment would include: medical and vaccination history, smoking and alcohol use, details of current illness including all symptoms, treatment, severity score, vital signs and test results.
At follow up, confirmation of CAP or alternative diagnosis, event disposition and vital status would be recorded at two visits: 30 and 180 days after hospital admission.

Data sources

Data will be collected from the hospital, including radiology and laboratory results, as well as primary care medical records.

Study size

The required sample size depends on the accrual of immunocompetent VT-CAP cases, the VE point estimate, percentage of individuals vaccinated, as well as other factors. Based on current estimates, the overall number of subjects to be enrolled is expected to be between 2,000 and 5,500 and required time for enrolment will be between 1.7 and 4 years, depending on the values for the parameters mentioned above and enrolment rates. See Section 12.1.2 for full information on these calculations. As the required number of enrolled subjects is highly dependent on the proportion of CAP subjects that have VT pneumococcal CAP 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 if needed. An interim analysis will be conducted after accrual of 170 VT-cases but, given additional subjects may be needed to allow for adequate statistical power, at least 4 years of enrolment is planned.

Data analysis

Vaccine Effectiveness will be calculated as follows. Odds of having received PCV13 for cases and controls will be constructed and compared using odds ratios (OR) and 95% Confidence interval (CIs). We will calculate VE as 1-OR x 100. In addition to constructing crude OR and VE estimates, we will also perform propensity score matching cases and controls using potentially confounding factors for VE, and then construct a conditional logistic regression to assess PCV13 and PPV23 VE. For the other study objectives, descriptive analysis will be carried out, presenting the absolute and relative frequencies of the qualitative variables and the main measures of centralization and dispersion in case of quantitative variables. CAP incidence rates per 100,000 inhabitants of the study age group will be assessed based on CAP events captured on screening log during the recruitment period in the participating sites. Methodologies for the statistical analyses of the data collected in this study are outlined here and will be provided in detailed in the full study protocol and statistical analysis plan (SAP).

Milestones

Milestone	Planned date
Completion of feasibility assessment	Q2 2020
Start of data collection, First Subject First Visit (FSFV)	March 2021
End of data collection, Last Subject Last Visit (LSLV)	Q1 2025
Interim analysis	After approximately 170 immunocompetent VT-CAP cases available for analysis [~Q2 2022]
Study results	Q2 2025
Final study report	Q3 2025

4. AMENDMENTS AND UPDATES

Document History

Document	Version Date	Substantial or Administrative Amendment	Protocol section(s) changed	Rationale
Original protocol	26 May 2020			Not applicable (N/A)

Amendment 1	13 April 2021	Substantial amendment	Protocol authors: Information about the authors is updated -Section 2: the name of the principal investigators and sites participating in the study is updated. - Section 3: Update of version and authors and *errata* correction. - Section 5: Update of study milestones dates. - Section 6, 7, 8: *errata* correction.	Changes in personnel responsible for the study Change of participating site: Hospital de Fuenlabrada is replaced by a new site, Hospital de Móstoles Updated timelines, taking into account the actual start date of the study.

			- Section 9: Update of data for the new participating site and update of population data for both sites. -Section 9.1.1 Inclusion criteria wording, modified to refer to "the designated surveillance area of participating hospitals." - Section 10.2 Vaccination history. - Section 10.3 and 10.4 Visit 2 and 3. -Section 12.1.2. *Erratum* correction. -References: Update reference 12.	Inclusion of new site with updated population data. Data are also updated with the available figures as of 2021 for the previous site, to homogenize the sources of information in the two participating sites. Replacement of Hospital de Fuenlabrada with a new site, Hospital de Móstoles. Update to include COVID vaccination. Detail cause of death. Updated reference for latest population figures.
Amendment 2	03 Feb 2022	Substantial amendment	Protocol authors: Information about the authors' contact details is updated. -Section 2: the name of the principal investigators and sites participating in the study is updated. - Section 3: Update of study version.	Changes in personnel responsible for the study. Addition of one new participating site: Hospital Universitario Rey Juan Carlos de Móstoles in order to increase recruitment.

			-Section 7. Rationale for the addition of Respiratory Syncytial Virus (RSV) testing.	Addition of RSV testing.
			- Section 8: Update of exploratory objectives.	Inclusion of new exploratory objective: RSV PCR testing in saliva samples collected for pneumococcal testing.
			- Section 9: Update of data for the new participating site.	Inclusion of new site.
			- Section 9.1.1: Deletion of inclusion criterion #4.	Residents and non-residents of hospitals' geographical catchment area will be included to increase enrolment.
			-Section 10. Study procedures first paragraph deleted.	It was repeated.
			-Section 10.2: Addition of RSV vaccination history.	Control of confounding.
			-Minor wording and grammatical changes.	

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	Q2 2020
Start of data collection (FSFV)	March 2021
End of data collection (LSLV)	Q1 2025
Interim Analysis	After approximately 170 immunocompetent VT-CAP
Study results	Q2 2025
Final study report	Q3 2025

6. SCHEDULE OF ACTIVITIES

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 (and record this information in repeating forms within Visit 1) in order to conduct evaluations or assessments required to protect the well-being of the subject.

Procedure/Assessment	**Visit 1 Day 1[h]**	**Visit 2 Day 30**	**Visit 3 Day 180**
Visit Window	**Within 48 hours of admission[a]**	**30 to 45 days after admission[b]**	**180 to 195 days after admission**
Setting	**In person**	**Telephone call[a] and/or medical record review**	**Telephone call and/or medical record review**
Verification of inclusion/exclusion criteria	X		
Informed Consent	X		
Demographics	X		
Behavioural factors considered potential risks for disease	X		
Antibiotic treatment within 14 days prior to admission	X		
Specific Medical History	X		
Details of current illness	X		
CRB-65 score Pneumonia Severity Index score	X		
Healthcare facility exposure in past 3 months	X		
Charlson Comorbidity Index data			X[g]
Record results of SOC tests	X		
Record results of SOC pneumococcal, Coronavirus disease 2019 (COVID-19) and RSV testing	X	X[d]	
Record hospitalisation-related data including vital signs	X	X[e]	
Urine sample[c]	X		
Saliva sample (selected sites)	X		
Pneumococcal Conjugate Vaccine vaccination record	X		
23-valent Pneumococcal Polysaccharide Vaccine (PPV23) vaccination record	X		

Procedure/Assessment	Visit 1 Day 1	Visit 2 Day 30	Visit 3 Day 180
Visit Window	**Within 48 hours of admission[a]**	**30 to 45 days after admission[b]**	**180 to 195 days after admission**
Setting	**In person**	**Telephone call[a] and/or medical record review**	**Telephone call and/or medical record review**
Influenza and RSV vaccination record	X		
Final diagnosis for event		X	
Selected adverse event monitoring[f]	X	X	X
Vital Status		X	X

a. Participants should ideally be enrolled as soon as feasible (ie, within 24 hours of admission on normal weekdays) but may be enrolled later if admitted on the weekend and/or if person cannot consent during that time period (eg, if intubated).

b. Visit 2 may be performed in person in lieu of a telephone call if patient being seen at study hospital for standard of care visit.

c. If subject readmitted within 14 days of the qualifying hospitalisation, that follow up hospitalisation will be considered part of the same event as the initial hospitalisation. An additional urine sample will be taken upon readmission.

d. Any additional results from standard of care pneumococcal and viral respiratory testing, including COVID-19 and RSV, not captured during Visit 1 Day 1 could be recorded at Visit 2 Day 30 (and data can be entered on Visit 1 eCRF).

e. Any additional information on hospitalisation data electronic case report form (eCRF) items not captured during Visit 1 Day 1 could be recorded at Visit 2 Day 30.

f. Please see full details of which adverse events to record in Section 16 Table 8.

g. Information to calculate Charlson Comorbidity Index (CCI) will be collected. Diagnosis codes such as International Classification of Diseases (ICD) discharge codes may be provided as a separate file linked by participant number to calculate CCI or data will be collected via eCRF at Day180 or prior visit.

h. SOC assessments (for example, details of current illness, vital signs, radiology exams, microbiological testing and others) could be performed before hospital admission or enrolment (Date of Visit) and captured in eCRF.

7. RATIONALE AND BACKGROUND

The Madrid health authority has recommended the administration of 13-valent pneumococcal conjugate vaccine (PCV13) in the adult population. This has provided the opportunity to maximize the benefit of pneumococcal vaccination in preventing pneumococcal disease in the population groups with highest incidence rates, children <5 years of age and the elderly.[2] The effectiveness of PCV13 in preventing both invasive and non-invasive pneumococcal disease (IPD) has been demonstrated in children in different countries.[3,5] PCV13 efficacy for the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and IPD was established in the Community-acquired Pneumonia Immunisation Trial in Adults (CAPITA) aged 65 and older.[6] However, there are still few available real-life effectiveness estimates in adults.

As a result of the CAPITA trial and the evidence that despite herd protection induced by the PCV13 infant vaccination program in the United States (US) roughly 10% of all adult CAP was still caused by PCV13 serotypes, in September 2014 the US Centres for Disease Control and Prevention (CDC) Advisory Committee on Immunisation Practices revised their 17-year-old pneumococcal vaccination recommendation for older adults to include PCV13 use for all adults aged ≥65 years. A recent study in the US evaluating the real-life effectiveness of PCV13 in adults over 65 to prevent CAP has shown a 72.8% effectiveness to prevent VT-CAP in this population. This study was done using a test-negative design.[7]

The paediatric heptavalent pneumococcal conjugate vaccine (PCV7) was first available in Spain in June 2001 and incorporated in the Madrid RIP in 2006, remaining in the private market for other regions. From mid-2010 through 2016, Spanish regions introduced the 13-valent conjugate vaccine (PCV13) in their RIPs.

PCV13 was introduced in Spain in June 2010 for immunisation of healthy children but, in contrast to most European countries, it was not included into the national immunisation programmes and was given only when funded by parents until 2015–2016, except in two Regions, Madrid and Galicia (into the national immunisation programsince June 2010 and January 2011, respectively).

In the Community of Madrid, PCV13 replaced the 7-valent (PCV7) in the fully government-funded RIP in May 2010 (2+1 schedule), but was later on excluded in May 2012 and reintroduced into the RIP in March 2015 for infants born after January 2015 (including catch-up doses for children following vaccination programmes that had already started).[8] Vaccine uptake reached 95% in periods with public-funded pneumococcal vaccination but fell to 67% in the only private funding period.[8] Overall, incidence rates (IR) of IPD in children less than 15 years of age decreased by 70% ($p<0.001$) in 2016 compared to the PCV7 period (2007-2010), due to 91% reduction in the IR of PCV13-type IPD ($p<0.001$).[8] Following universal vaccination with PCV7/PCV13 in infants in the Community of Madrid, the IR of PCV7-type IPD in adults 60 years and older significantly decreased by 61% in 2013-2015 (IR: 1,25 per 10^5) compared to the PCV7 period (2008-2010, IR: 2.07 per 10^5) and also PCV13-non PCV7 type IPD by 47% ($p<0.05$; 2013-2015

IR: 3.45 per 10^5 vs 7.33 per 10^5 in 2008-2010).[9] IPD caused by serotype 3 was the second most prevalent serotype among all IPD cases (2013-2015 IR: 1.61 per 100,000 population).[9] No significant changes in the overall IPD in 60 years and older were observed (2013–2015 IR: 17.09 per 10^5 vs 17.97 per 10^5 in 2008-2010). The incidence of IPD due to serotypes 8, 9N, 10A, 23B and 24F significantly increased in the 2013-2015 period. Serotypes 8 and 9N accounted for 51% in the population aged 5 to 59 years and serotypes 8 and 22F for 25% in the population aged 60 years and older.[9] Similar trends were observed in 2017 with an overall IPD incidence rate in adults 65 years and older of 26.45 cases per 10^5 inhabitants.[10]

Adult vaccination with the 23-valent polysaccharide (PPV23) officially started in 2004, and with PCV13 in 2016 for some cohorts. Most adult pneumococcal vaccination occurs during annual influenza vaccination campaigns.

In January 2018, the new recommendations and funding for PCV13 that were approved in the Community of Madrid, confirmed that all adults over 60 years of age not previously vaccinated either with PPV23 or PCV13, should receive one dose of PCV13 and those over 18 years with a chronic disease such as Chronic Obstructive Pulmonary Disease (COPD), diabetes, heart failure, regardless of previous vaccination status, should receive one dose of PCV13. Sequential immunisation with both vaccines (PCV13+PPV23) was recommended for adults with high risk immunocompromising conditions.[11] This recommendation was based on the burden of non- bacteraemic CAP in adults and the assumption based on the CAPA study (*Epidemiological study assessing the burden of hospitalised CAP due to Streptococcus pneumoniae in adults in Spain using UAD testing*) that there is still a significant burden due to PCV13 serotypes among all hospitalised CAP in adults 18 years and older (9%).[1] As of September 2019,
around 8% of adults 60 years and older have been vaccinated with PCV13 (Table 3),
this proportion is expected to increase in the following months/years.

The Regional Health System operates a database known as SISPAL which includes information on previous vaccination history, including influenza, PPV23 and PCV13 vaccination with lot number and date of administration per person. Pneumococcal vaccination status will be based on whether receipt of ≥1 dose of PCV13 or PPV23 could be confirmed by electronic registries. We will obtain previous influenza vaccination status (within the last year) via electronic registries as well.

The aim of this study is to evaluate the PCV13 VE against hospitalised VT-pneumococcal CAP among adults aged ≥60 years in the Community of Madrid (total population as of January 2018) of 6,578,079 inhabitants, of which 1,511,750 were aged 60 years and older).[12]

Rationale for the addition of Respiratory Syncytial Virus (RSV) testing

Respiratory syncytial virus has long been recognized as a problematic respiratory pathogen causing illness in children[13, 14, 15] but the scope and impact of RSV in adults is less well-

defined. Severe disease occurs especially among those with compromised cardiac, pulmonary, or immune systems and in the elderly[16,17,18,19,20] but estimates of the RSV disease burden requiring hospitalisation in adults are limited. Previous studies have suggested that up to 10% of adults presenting with acute respiratory illness during the winter have RSV.[21,22,23,24,25] Further, Pfizer is CCI [redacted].

[1] Data stemming from the SISPAL system, directly communicated by the Regional Health Authority.

Table 1. Pneumococcal Adult Vaccination in Madrid as of January 2018

Age group	New schedule		What was administered before 2018?
	Without previous vaccination	With previous vaccination (at least 1 dose of PPV23)	
≥60 years without risk factors	PCV13		PPV23 (except birth cohorts 1956–57: PCV13+PPV23)
Adults (≥15 years) with underlying disease	PCV13	PCV13 (at least 1 year apart)	PPV23 + Revaccination at 60 years
Persons of any age and high risk	PCV13+PPV23 (8 weeks apart) + Revaccination in 5 years with PPV23	PCV13 (at least 1 year apart) + Revaccination in 5 years with PPV23	PCV13+PPV23 + Revaccination in 5 years with PPV23

Table 2. PCV13 and PPV23 Uptake in Madrid Region Per Age (September 2019)

Age	*PCV13*	*PPV23*	*Cohort size*
60	7.43%	6.18%	73,865
61	15.40%	8.67%	71,294
62	23.58%	19.17%	67,364
63	25.72%	27.39%	67,235
64	11.34%	36.99%	66,110
65	11.71%	43.03%	62,288
66	12.16%	45.89%	61,535
67	11.17%	47.46%	63,514
68	10.56%	47.66%	66,411
69	11.50%	60.02%	59,676
70	12.97%	71.83%	55,635
71	13.09%	63.87%	57,778
72	11.61%	67.09%	55,496
73	11.89%	75.37%	53,122
74	14.31%	88.89%	44,381
75	15.70%	94.90%	39,960

8. RESEARCH QUESTION AND OBJECTIVES

Primary Objective(s):	**Primary Endpoint(s):**
• To determine the effectiveness of PCV13 to prevent hospitalised vaccine-type (VT)-pneumococcal CAP among adults aged ≥60 years in Madrid using a test- negative design study, overall and among immunocompetent persons only.	• VE calculated as 1 minus the OR comparing the odds of having received PCV13 for cases and controls, multiplied by 100%, overall and restricted to immunocompetent subjects only.
Secondary Objective(s):	**Secondary Endpoint(s):**
To describe the distribution of *S. pneumoniae* serotypes using blood, high-quality respiratory cultures, and a serotype-specific urinary antigen detection (UAD) assay among adults 60 years of age and older with CAP.	• Proportion of CAP events for each pneumococcal serotype, PCV-13, and 20-valent pneumococcal conjugate vaccine (PCV20) serotypes among all CAP subjects with UAD1/2 testing (overall) and among all CAP subjects with a pneumococcus identified.
• To determine the proportion of persons with respiratory pneumococcal carriage among adults 60 years of age and older presenting with CAP by testing saliva specimens using both conventional culture and the sensitive molecular method of PCR for the detection of two target genes (lytA and piaB).	• Proportion of CAP events where the pneumococcus was identified from saliva by culture or PCR divided by all CAP events where the subject had a valid saliva specimen test result.
• To describe the proportion of participants with CAP and with SP+CAP who present with underlying at-risk and high-risk medical conditions.	• Proportion of CAP subjects with underlying at-risk and high-risk medical conditions, overall and restricted to those with pneumococcus isolated from blood, high-quality respiratory cultures, and a serotype-specific UAD assay.
• To describe the frequency and type of antibiotic resistance among *S. pneumoniae* isolates, overall and by specimen type.	• Proportion of *S. pneumoniae* isolates with antibiotic resistance identified by SOC testing, overall and by resistance type.

Exploratory Objectives	Exploratory Endpoints
• To estimate incidence rates for hospitalised CAP and SP+CAP (both overall and radiologically confirmed) in the surveillance region within the limitations of the expected under ascertainment of hospital-based screening process and current diagnostic testing.	• Number of CAP events identified by screening log divided by number of persons ≥60 years in surveillance region.
• To compare the effectiveness of PPV23 to that of PCV13 in preventing cases of hospitalised VT- pneumococcal CAP among adults aged ≥60 years using a test-negative study design, overall and among immunocompetent persons only.	• Final adjusted VE point estimate for PPV23 subtracted from final adjusted VE subtracted for PCV13, overall and among immunocompetent persons only.
• To compare pneumococcal serotype results from high-quality respiratory specimens (standard –of care), UAD1/2 (study procedure), and saliva specimens taken for carriage testing (study procedure).	• Percent agreement in serotype results between specimen types for events that have both types available. (Three comparisons: 1. high-quality respiratory culture [standard –of care specimen] versus UAD1/2; 2. UAD1/2 versus saliva carriage sample; 3. High-quality respiratory culture versus saliva carriage sample).
• To estimate incidence rates for hospitalised CAP among adults aged ≥60 years with underlying at-risk and high-risk medical conditions, in aggregate and for individual risk conditions within the limitations of the expected under ascertainment of hospital-based screening process and current diagnostic testing.	• Number of CAP events identified by screening log multiplied by the proportion of CAP subjects with specific risk condition(s) divided by the estimated number of persons ≥60 ears in surveillance region with the same specific risk condition(s), in aggregate for at-risk and high-risk conditions and for individual risk groups if the size of risk group is adequate for a stable estimate.

Additional COVID-19 Exploratory Objectives	Additional COVID-19 Exploratory Endpoints
• To determine if the frequency of pneumococcal infection differs between hospitalised CAP patients with COVID-19 infection compared to those without COVID-19 infection, overall and stratified by age, sex, and pneumococcal risk status.	• Percentage of CAP events with pneumococcal infection identified by any means (eg, UAD, *BinaxNOW®*, bacterial culture) among CAP events associated with a positive COVID-19 test compared to percentage of CAP events with pneumococcal infection identified by any means (eg, UAD, *BinaxNOW®*, bacterial culture) among CAP events associated with a negative COVID-19 test, overall and stratified by age, sex, and pneumococcal risk status.
• Among the subset of hospitalised CAP patients with COVID-19 identified, to determine if the proportion who experience severe clinical outcomes (eg, ICU stay, mechanical ventilation, prolonged hospitalisation, and sequelae) differs between those with pneumococcal co-infection compared to those without pneumococcal co-infection, overall and stratified by age, sex, and pneumococcal risk status.	• Among CAP subjects with COVID-19 infection, percentage of CAP subjects with severe clinical outcomes (overall and by individual outcome) among those with pneumococcal co-infection identified by any means (eg, UAD, *BinaxNOW®*, bacterial culture) compared to percentage of CAP subjects with serious clinical outcomes among those without pneumococcal co-infection identified by any means (eg, UAD, *BinaxNOW®*, bacterial culture), overall and stratified by age, sex, and pneumococcal risk status.
• Using a test-negative design to determine the VE of PCV13 against severe COVID-19 clinical outcomes among COVID-19 positive hospitalised CAP patients, overall and among immunocompetent persons only.	• VE calculated as 1 minus the OR comparing the odds of having received PCV13 for cases and controls, multiplied by 100%, overall and among immunocompetent persons only, adjusted for confounders. (Cases = COVID-19-positive CAP subjects with severe clinical outcomes; Controls = COVID-19-positive CAP subjects without severe clinical outcomes).

• To assess if pneumococcal carriage differs for those with current or past COVID-19 infection, overall and stratified by age, sex, and pneumococcal risk status.	• Percentage of CAP events with pneumococcal carriage among CAP events associated with a positive COVID-19 test compared to percentage of CAP events with pneumococcal carriage among CAP events associated with a negative COVID-19 test, overall and stratified by age, sex, and pneumococcal risk status.

Additional RSV Exploratory Objective	**Additional RSV Exploratory Endpoints**
• To determine the proportion of persons with RSV infection among adults 60 years of age and older presenting with CAP by testing saliva specimens using the PCR method).	• Proportion of CAP events where RSV was identified from saliva by PCR divided by all CAP events where the subject had a valid saliva specimen test result.

Note: Saliva samples will be taken only in selected sites.

9. RESEARCH METHODS

9.1. Study Design

This is a low interventional, prospective, multicentre, hospital- based study in adults aged 60 years of age and older hospitalised with CAP at participating sites. Hospital surveillance data will be used for incidence calculations and a TND for VE calculations. Vaccine effectiveness will be calculated using a TND. The approximate study duration will be 4 years.

In the South of Madrid there are two municipalities that belong to the network of King Juan Carlos I University (Figure 1):

Móstoles is a city located in the southwest of the Madrid region. Its total population is 210,309 people,[12] 57,042 of them are people aged 60 years or older. For secondary care, the population that receives medical care at the Hospital Universitario de Móstoles includes 137,552

inhabitants which represents 65.4% of the total population of the town. There is another hospital, Hospital Universitario Rey Juan Carlos included in the study in February 2022, that covers the remaining population. The Hospital Universitario de Móstoles has 332 beds, while the Hospital Universitario Rey Juan Carlos has 358 beds.

Alcorcón is a city located in the Southwest of Madrid region. Its total population is 172,384 people,[12] 45,535 of them are people of 60 years or older. The population receives medical care at its only hospital, called Hospital Universitario Fundación Alcorcón, which is the only public hospital in Alcorcón. The hospital has 400 beds.

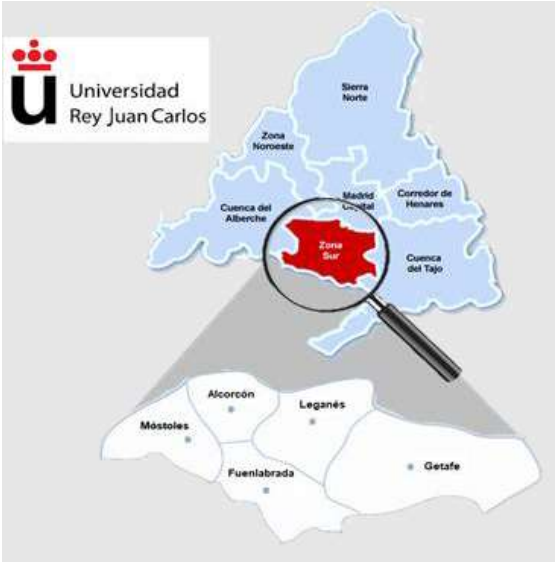
As of 1st January 2020, the total population of these two municipalities (Alcorcón and Móstoles) was 382,693 people, 103,844 of them were of 60 years and older that represents 6.5% of the total population of Madrid Region (in total: 1,593,526 inhabitants in this age group) (Table 3). In Spain, every town or village is obliged by law to maintain and update the census ("padrón municipal de habitantes"). An automated and electronic population registry is continuously updated (eg, with new people registering, leaving the village, or dying). Thus, these population denominators are not intercensus extrapolations but actual counts. An internal audit of the population by Dr. PPD has shown the populations are comparable to the averages across Spain.

Table 3. Population of Adults 60 Years and Older Living in Participating Hospitals' Geographic Catchment Area (January 2020)

	Population of 60 years and older	*Percentage of people of 60 years and older*
Hospital Universitario de Móstoles, Móstoles	35,106	25.5%
Hospital Universitario Rey Juan Carlos, Móstoles		
Hospital Universitario Fundación Alcorcón, Alcorcón	46,802	27,1%

Note: Hospital Universitario de Móstoles and Hospital Universitario Rey Juan Carlos have the same geographic catchment area.

Figure 1. Map of Study Locality



PCV13 effectiveness against hospitalised VT-Pneumococcal CAP will be assessed using a TND, which is a modified case-control study. In the TND, researchers are not aware of participants' case/control status at recruitment, but later classify the participants into cases or controls according to the test results. Cases are participants testing positive for PCV13 serotypes by any method, including routine culture from blood, high-quality respiratory culture, or serotype-specific UAD1. For the analysis, PCV13 serotypes will be defined as all serotypes contained in PCV13 (ie, 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).

Controls are hospitalised patients with pneumonia meeting the inclusion and exclusion criteria but testing negative for PCV13-type infection or related serotypes. Vaccine effectiveness is calculated as follows:
VE = (1 − vaccination odds ratio) × 100%.
TND validity is predicated on the core assumption that the intervention (vaccine) has no effect on other non-targeted aetiologies resulting in similar illness/disease incidence in the vaccinated and unvaccinated. Compared with conventional case-control or cohort designs, the TND is less susceptible to bias caused by differences in health-care- seeking behaviour among cases and controls and the use of non-specific outcome measurements. However, TND is prone to selection bias, residual confounding due to healthy vaccinee effects and risk-based vaccination strategies, bias due to indirect effects of the vaccine, and misclassification of false-negative cases and controls, these concerns will be addressed, discussed and acknowledged as limitations of the study.
Further, statistical adjustments will be undertaken to control for confounding (eg, propensity score matching).

An interim analysis is planned after accrual of 170 VT-cases but depending on the VE point estimate, the proportion of CAP cases that are vaccine serotype, and the frequency of PCV-13 vaccination in the study population, additional subjects may be needed to allow for adequate statistical power. On this basis, approximately 4 years of enrolment is planned.

If the anticipated PCV20 is approved during the enrolment of cases for VE analysis as expected (projected to be in use no sooner than late 2022), subjects with PCV20 exposure will be excluded from the cases and the controls for the PCV13 VE analysis. Initial PVC20 use is expected to primarily involve those aging into the over 60 age group, and substantial number of persons with a history of PCV13 vaccination are expected to remain in that age group population.

Laboratory testing. The Central laboratory will conduct BinaxNOW® (Alere, Walthman, MA) and the serotype-specific UAD1 and 2 assays (Pfizer, Inc) to test urine samples from all enrolled participants as the study-related procedures. Results from SOC tests performed on enrolled subjects will be also collected, including respiratory, blood, and pleural fluid cultures and urine pneumococcal antigen testing. All pneumococcal isolates will undergo serotyping.

Pneumococcal Carriage and RSV infection assessments. In addition, patients at selected study sites will provide a saliva sample to test for pneumococcal carriage and RSV infection but, if they decline this procedure at the time of collection, they will not be excluded from the study. Samples will be processed for pneumococcal detection by the standard, conventional culture diagnostic approach and molecular methods. RSV will be detected by molecular methods only.

Incidence assessment. Population-based incidence of CAP will also be estimated in this study. Nearly all CAP hospitalisations in the surveillance regions are expected to involve the study hospitals. Every effort will be taken to identify all pneumonia patients admitted to

study hospitals. Patients with pneumonia who are not enrolled will be recorded on the screening log, which will be the basis of the count of CAP events for incidence estimates. Where appropriate population-based denominators are available, incidence rates for at-risk and high-risk conditions will be generated in aggregate and by condition for more frequent conditions. Nevertheless, incidence estimates will be conservative, given established multiple risks for under ascertainment of pneumonia events in studies in this setting (for example, due to misdiagnosis, chest X-ray [CXR] false negative, or hospitalisation on a different inpatient ward). Non-residents of the hospitals' geographic catchment area will be excluded from incidence estimations.

COVID-19 and pneumococcal infection. The World Health Organization declared COVID-19 a pandemic during the finalization of this protocol (March 11, 2020). On this basis, additional exploratory objectives related to the relationship between COVID-19 and pneumococcal infection were added. If COVID-19 continues to occur at a sufficient frequency in the surveillance region during enrolment to allow for a meaningful analysis, these objectives will be pursued using COVID-19 infection status based on standard –of care testing. Further, if a high incidence of COVID-19 infections is burdening the hospitals at the anticipated time of study start or at some point during study enrolment period, enrolment will be delayed or halted to allow involved staff to focus on COVID-19 clinical care.

This study will prospectively enroll adults, aged 60 years and over, who are hospitalised with CAP in one of the study hospitals: Hospital Universitario de Móstoles, Hospital Universitario Fundación de Alcorcón, and Hospital Rey Juan Carlos de Móstoles (as of February 2022, additional sites may be included at a later date).

9.1.1. Inclusion Criteria

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

1. Age ≥60 years.
2. Evidence of pneumonia within first 48 hours of hospital admission based on:
    a. Documented pneumonia diagnosis or clinical suspicion of pneumonia* at the time of enrollment **OR**;
    b. Radiologic findings consistent with pneumonia (eg, increased pulmonary density due to infection and/or alveolar infiltrates [multilobar, lobar, or segmental]) **AND** presence of ≥2 of following 10 clinical signs or symptoms:
        i. fever (oral temperature >38.0°C or tympanic temperature >38.5°C);
        ii. hypothermia (<35.5°C measured by a healthcare provider) within 24 hours before enrollment;

iii. chills or rigors;

iv. pleuritic chest pain;

v. new or worsening cough;

vi. sputum production;

vii. dyspnea (shortness of breath);

viii. tachypnea (respiratory rate >20/min);

ix. malaise; or

x. abnormal auscultatory findings suggestive of pneumonia (rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, or egophony).

3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

*Note: Pneumonia may be clinically suspected, based on any combination of radiologic and laboratory findings as well as signs, symptoms and other clinical findings, regardless of a formal admission diagnosis or other diagnoses assigned during hospitalization and other acute or chronic comorbidities, including other pulmonary diagnoses.

9.1.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

4. Any patient who develops signs and symptoms of pneumonia after being hospitalized for ≥48 hours (either at current hospital, another transferring hospital, or a combination of these).

5. Previously enrolled subjects readmitted ≤14 days after discharge for their study qualifying admission.

6. At the time of enrolment, pneumonia has been excluded as the diagnosis or another diagnosis confirmed.

9.1.3. Variables

Please see listing of data collection per visit, Section 10.

9.1.4. Data Sources

In the Madrid Region, the primary and secondary medical care records are formally linked for routine clinical use. The information related to vaccine administration will be extracted from a population-based computerized vaccination registry that belongs to the Regional Health System, namely SISPAL (http://www.sanidadmadrid.org/saludpublica/e-sispal, restricted access). SISPAL vaccination registry provides nominal records (name, sex, date of birth) of every vaccine administered (vaccine, lot, date of administration) in the public or private sector to the entire population living in the Madrid Region and provides access to the information for every health care practitioner working in the public sector after request. The electronic database was created in 2005 but contains information on vaccination prior to 2005, transferred from manual records. Self-reported vaccination history will not be used as it has been demonstrated that vaccine self-reported data could significantly overestimate the vaccine coverage when compared with SISPAL database.[28]

10. STUDY PROCEDURES

10.1. Surveillance Process

10.1.1. Surveillance Manual

The Surveillance Manual should describe and identify the following:

- Description of the informed consent process, including the staff roles responsible for informed consent.
- Description of the study-level Surveillance Officer role, which will be responsible for coordinating all enrolment activities at the participating sites. Additionally, site-level surveillance coordinators may be utilized.
- Identification of key personnel in each hospital that will assist with enrolment. This list should include the key posts at each ward who will serve as important sources of information for identification of inpatients with pneumonia. Ideally, numerous sub-investigators and site staff across various departments/wards will be involved to ensure constant and complete surveillance.
- Surveillance team structure, training and engagement should be addressed.
- Description of the process for sample collection.
- Establishment of communication and collaboration mechanisms between the surveillance staff and the local laboratory that will manage samples.

- Development of validated links with the testing laboratories for result reporting, if possible.

- Description of the laboratory testing procedures for SP, and methods for safe shipping and handling of the samples.

- A detailed step-by-step description of the screening process. This should include a description of how staff will be contacted to identify patients being admitted with pneumonia. This can also include how hospital admissions records, patient medical records, radiology reports and microbiology reports will be reviewed to identify patients being admitted with pneumonia.

- A step-by-step process of enrolment, including procedures used to identify patients being admitted with pneumonia, consent, enrolment, specimen collection, review of medical records of enrolled individuals, participant follow-up.

- The use of the screening and enrolment log, which will record all identified hospitalised patients admitted with pneumonia, whether or not they are eligible for the study, and whether or not the eligible individuals were enrolled.

- Enrolment will ideally be within 24 hours of admission to the hospital on weekdays but may be enrolled later if admitted on the weekend and/or if person cannot consent during that time period (eg, if intubated). When a potentially eligible patient has been identified for the study (see screening criteria), the pneumonia hospitalisation registry (screening log) will be completed by staff trained to work on the study and then later the patient will be offered participation in the study.

10.2. Screening/Enrolment Log

- The study screening log will be completed by site personnel and be forwarded to the sponsor or its representatives weekly for the required study monitoring and follow-up. The registry will include the following information as permitted by the Independent Ethics Committee (IEC) and may include:

  - Screening date;

  - Hospital site and ward;

  - Sex;

  - Nationality;

  - Surveillance area resident (yes/no);

  - Eligibility – if not eligible, why;

- Consented (yes/no);
- Date of consent (day/month/year);
- If declined, reason not consented;
- Study participant ID;
- Date of admission to hospital (day/month/year);
- Year of birth;
- Pneumonia confirmed by Chest radiology (yes/no);
- ICU admission (yes/no);
- Samples collected.

10.3. Visit 1 Day 1 (Screening/Enrolment)

All relevant patients who are eligible via inclusion in the screening process will be offered enrolment to the consented study. The study would be explained by a healthcare professional who will also answer any questions the patient has before taking written informed consent to participate in the study. Once consent has been given, data and samples will be collected per the SCHEDULE OF ACTIVITIES in Section 6.

- If the patient meets all the inclusion criteria and none of the exclusion criteria, they will be informed of this study and asked for written informed consent (see Section 15.1).
- Once informed consent is obtained, a participant number will be assigned to the patient. The participant number will contain no initials or any other personal data that may identify the patient. Hospitalised participants that are recruited more than once as new cases (see Inclusion Criteria, Section 9.1.1) will be assigned a new participant number. Multiple events for a single participant will be linked in the electronic Case Report Form (eCRF) (for example, capturing prior study number(s) in the eCRF for the new event(s)).
- Collect Adverse Events (AEs) and Research Related Injury (RRI) as outlined in Section 16.
- Collection of urine for pneumococcal testing per Section 11.2.3.
- Collection of saliva sample at selected study sites per Section 11.2.4.

Specifically, at this visit the following data will be recorded in the eCRF:

- Date informed consent is obtained.
- Eligibility of the subject. It will be confirmed that the participant meets all inclusion criteria and no exclusion criteria to be eligible for the study.
- Demographic data: date of birth; sex, nationality, country of birth.
- Surveillance area resident: Do you live in the study catchment area? (yes/no).
- Residence setting (eg, nursing home, long-term care facility for those with disability or dependency, private residence, or other).
- Weekly exposure to children <5 years of age.
- Body Mass Index (BMI) (height and weight).
- Smoking status (current/previous/never).
- Alcohol/drug use.
- Vaccination history.
    - Pneumococcal, last date of administration for PCV13 and PPV23. PCV20 immunisation will also be collected once available in the region.
    - Influenza vaccination in last year, date of administration.
    - COVID-19 vaccination, dates and vaccines types.
    - RSV vaccination, dates and vaccine types.
- Hospitalisation data:
    - Dates and time of admission/discharge for qualifying admission.
    - ICU stay (yes/no).
    - Number of days in ICU.
    - Mechanical ventilatory support (invasive and non-invasive), if used and type.
    - Number of days of mechanical ventilator use.
    - Acute respiratory distress syndrome (ARDS) diagnosis during illness.

- Readmission within 14 days of discharge (If yes, dates of admission/discharge).
- Symptoms of qualifying pneumonia illness mentioned in inclusion criteria.
- Date of illness onset.
- Vital signs (initial respiratory rate, pulse oximetry, blood pressure, heart rate).
- Level of oxygen supplementation during pulse oximetry measurement (FiO2).
- SOC chest radiography results (eg, CXR and computed tomography [CT] scan), including if consistent with pneumonia per standard outlined in Section 11.3.

- SOC microbiology test results including test and specimen type:
  - Blood cultures.
  - Respiratory microbiology testing, including bacterial (eg, PCR and culture), viral testing (eg, RSV, influenza, and COVID-19), and Gram stain results.
    - All standard –of care COVID-19 testing during the qualifying illness will be recorded with result.
  - Pneumococcal testing (eg, *BinaxNOW*® or another pneumococcal antigen urine test).
  - Other body fluid/tissue sterile under normal conditions.
- CAP severity/prognosis scale (Confusion Respiratory Rate Blood Pressure [CRB-65] and Pneumonia Severity Index [PSI]) on presentation to hospital if information available from SOC testing to calculate score:
  - CRB-65 score [Contributing data elements: age, blood pressure, presence of confusion, and respiratory rate].
  - PSI score. Contributing data elements are:
    - Altered mental status.
    - Nursing home residency.
    - pH and partial pressure of arterial O2 (PaO2) from atrial blood or arterialised venous blood OR oxygen saturation level (SpO2) measured by pulse oximetry

and FiO2 during that assessment.

- Blood urea nitrogen.
- Serum sodium concentration.
- Plasma glucose concentration.
- Hematocrit.
- Presence of pleural effusion.

- Relevant medical history:
  - COPD.
  - Asthma.
  - Congestive Heart Failure.
  - Coronary Artery Disease (CAD).
  - Chronic Kidney Disease.
  - Diabetes (with or without complications).
  - Liver Disease.
  - Immunosuppressant Drug Therapy.
  - Autoimmune Disorders.
  - Immunodeficiency.
  - Human Immunodeficiency Virus (HIV).
  - Acquired Immunodeficiency Syndrome (AIDS).
  - Cancer/Malignancy, Solid Tumor only.
  - Cancer/Malignancy, Hematologic only.
  - Organ Transplantation.
  - Cerebrovascular accident (Stroke).
- Number of previous pneumonia events in year prior to admission.

- Healthcare facility exposure in past 3 months, includes inpatients stays, dialysis centers or long-term care, skilled-nursing, assisted-living, rehabilitation, or other healthcare facilities.

- Antibiotic treatment within 14 days prior to admission.

10.4. Visit 2 Day 30 (Final Diagnosis and Event Outcome)

The participant will be followed-up by telephone at 30 to 45 days after hospital admission. The date of the visit, the patient's final diagnosis and outcome for study-qualifying suspected CAP event will be recorded in the eCRF. If patient returns to study hospital for a standard –of care clinic visit for another reason, the visit may occur in person. RRIs will be collected if encountered during the collection of visit-related information or if the patient is contact by phone.

- The following data will be recorded in the study eCRF:

  - Any additional results from standard –of care pneumococcal and viral respiratory testing, including COVID-19 and RSV, that was not captured during Visit 1.

  - Additional information on hospitalisation data eCRF items not captured during Visit 1.

- Principal investigator (PI) or designee should make an outcome assessment of final diagnosis based on any information available over the hospitalisation of the patient. This may include both study and SOC exams, procedures and tests. This data point can be recorded on Day 30 or sooner if available. Final diagnosis categories will include:

  - CAP-radiologically confirmed;

  - CAP-not radiologically confirmed (eg, clinical CAP);

  - CAP-no chest radiology done; or

  - Other diagnosis (not CAP).

    - Acute Bronchitis.

    - Exacerbation of COPD.

    - Empyema/lung abscess.

    - Other Acute Lower Respiratory Infection.

- Acute pulmonary exacerbation of congestive heart failure.
- Non-infectious process.

- Event disposition at 30 days after admission:
  - Fatal/deceased.
  - Not recovered/not resolved.
  - Recovered/resolved.
  - Recovered/resolved with sequelae.
  - Recovering/resolving.
  - Unknown.
- Vital Status (ie, deceased or living), including date and cause of death if deceased.
- RRIs per Section 16.2 and selected exposures and AEs related to Pfizer products per Section 16.3.

Case Definition for Radiologically Confirmed CAP

Patients in whom the treating physician clinically suspected pneumonia who meet the following 2 criteria will be considered to have radiologically confirmed CAP:

1. Has a radiologic finding that is consistent with pneumonia (eg, pleural effusion, increased pulmonary density due to infection, the presence of alveolar infiltrates [multilobar, lobar or segmental] containing air bronchograms); AND
2. Illness involves ≥2 of the following signs or symptoms:
   a. fever (oral temperature >38.0°C/100.4°F or tympanic temperature >38.5°C/101.2°F) within 24 hours before enrolment;
   b. hypothermia (<35.5°C measured by a healthcare provider) within 24 hours of enrolment;
   c. chills or rigors;
   d. pleuritic chest pain;
   e. new or worsening cough;

f. sputum production;

g. dyspnea (shortness of breath);

h. tachypnea (respiratory rate >20/min);

i. malaise;

j. abnormal auscultatory findings suggestive of pneumonia (rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, or egophony).

10.5. Visit 3 Day 180 (Vital Status Assessment)

The participant will be followed-up by telephone at 180 to 195 days after hospital admission to assess vital status at Day 180 (ie, alive or dead). If investigator is definitively aware of vital status through other means (eg, access to vital statistics records or patient visit in electronic record after Day 180), this source may be used to determine vital status in lieu of a phone call. RRIs will be collected if encountered during the collection of vital status or if the patient is contact by phone.

The following data will be recorded:

- Vital Status at 180 days after admission (ie, deceased or living), including date and cause of death if deceased.
- Information to calculate Charlson Comorbidity Index (diagnosis codes such as International Classifications of Diseases [ICD] discharge codes may be provided as a separate file linked by participant number to calculate CCI or data will be collected via eCRF at this or prior visit).
- Record RRIs per Section 16.2 and selected exposures and AEs related to Pfizer products per Section 16.3.

11 ASSESSMENTS

Collection of clinical data. The study staff will complete a eCRF for each participant at each visit, as detailed above. The eCRF will be completed reviewing the medical records of the patient, the results of the tests performed, and interviewing the participant. Once the eCRF is completed, it will be signed and dated by the investigator verifying the information contained therein.

11.1. Additional Research

Not applicable.

11.2. Biological Samples

11.2.1. Blood and Respiratory Samples

All blood and respiratory specimens collected as part of SOC for culture (eg, blood, pleural fluid, transtracheal aspirate, bronchoalveolar lavage or other respiratory tract specimen) will undergo bacterial culture at the local site laboratory for the identification of SP according to their standard methodology. Best practices for blood culture collection involved obtaining 2 sets of blood cultures before antibiotic administration if possible. The blood culture should be collected and timed according to the local institution's policy using different sampling sites. Anaerobic and aerobic samples should be collected.
Whenever possible, blood should be collected from peripheral veins. Results of blood cultures (including antibiotic susceptibility) from this SOC bacterial culture testing will be recorded in the eCRF.

For sputum specimens collected as part of standard –of care testing, specimen quality will be assessed using the specimen's standard –of care Gram stain results. Only bacterial culture results from high-quality sputum specimens will be use in case categorisation for the VE analysis, but all pneumococcal isolates will be serotyped regarding of specimen quality.

Serotyping, Antimicrobial Resistance and Molecular Biology Testing of the Isolates

Pneumococcal bacterial isolates from SOC specimens will be shipped and analyzed in the Pneumococcal Reference Laboratory from the Centro Nacional de Microbiología which belongs to the Instituto de Salud Carlos III (ISCIII). In no case will there be any interference with the autonomous regional pneumococci monitoring systems at the sites participating in the study.

The ISCIII reference laboratories provide data and information of sanitary interest on the microorganisms that cause infectious diseases, environmental pollutants situation and the development of new technologies and/or surveillance strategies and control in accordance with the priorities established by the Ministerio de Sanidad, Consumo y Bienestar Social (MSCBS) following the recommendations of the European Centre for Disease Prevention and Control (ECDC). The pneumococcal reference laboratory is located in Majadahonda which is a city in Madrid region, it carries out a passive surveillance and receive the isolates from hospitals of all the Spanish regions.

Identification and Serotyping

All isolated pneumococcal strains will be stored frozen in skimmed milk at a temperature of -40ºC or lower in the Department of Microbiology of each participating site until delivery to the reference laboratory (RL) at ISCIII. From a fresh culture (18-24h) in blood agar a dense suspension will be obtained (all plate growth will be recorded) in a vial with 0.5 ml of sterile skimmed milk (Skim Milk, Oxoid). The vial will be immediately frozen at -40ºC.

The pneumococcus strains should be frozen as soon as possible and with the minimum number of runs.

The strains will be thawed in the site where they are isolated before being sent at room temperature to the RL. The strains may be sent in the following ways:

- On blood agar plates or tubes, after abundant seeding (without incubation).

Incubation will be performed on reception at the RL. If plates are used, only one strain should be seeded per plate.

- Transport media tubes are preferable. The whole quantity of a fresh culture should be collected from a blood agar plate by dragging with a swap and sent at room temperature in the transport media.

To prevent the loss of strains for reasons of viability during transportation, or other reasons, the microbiology laboratory of each site will keep a frozen sample for up to 6 months for study purposes. The frozen vials, plates or the tubes with transport medium will be identified by the site personnel using a label containing a study code and the subject identifier (site no. and participant no.) from which the isolate comes. In addition, a copy of the label containing the same codes used to identify the isolate will be attached to the study form for submission of strains to the RL. When preparing the pack with the strains, the safety rules applicable in Spain will be followed and standardised packages will be used. Strains will be sent to the ISCIII at regular intervals (every 1-2 months, depending on the volume of strains) using a courier service. Once the samples/strains have been received at the ISCIII a subculture will be performed in the appropriate medium (blood agar or chocolate agar) in order to ensure the viability and purity of the organisms.

For pneumococcal serotyping at the ISCIII, it will be used the Capsular Sequence Typing (CST) methodology.[16] The CST is a well-established molecular method to genotype the capsular locus in order to assess the serotype. It has been accepted as a generic method for typing SP among the different European Pneumococcal Reference Laboratories that belong to ECDC through the Invasive Bacterial Disease network (IBD-labnet). The primers used in the CST are based on the publicly available sequences of the capsular genes of the more than 90 known pneumococcal serotypes.[17] Capsular Sequence Typing (CST) is based on a part of the sequence of the wzh gene of the capsular locus. The 3 forward and 4 reverse primers used in the CST are based on the publicly available sequences of the capsular genes of the 90 known pneumococcal serotypes described by Bentley et al.[17] The primers contain an M13-tail, which facilitates sequencing with universal M13-primers. After sequencing of 506 base pairs of the wzh gene, a capsular type can be assigned. The capsular type is a composite assignment; the first part of the assignment is based on the phenotype assessed by conventional serotyping and the second part of the assignment is the consecutive number of the capsular type belonging to the same serotype.

Antimicrobial Susceptibility Testing

The measurement of the minimum inhibitory concentration (MIC) of each isolate will be performed at the using a broth microdilution method (Sensititre,Trek Diagnostic Systems

LTD, East Grinstead, United Kingdom) according to the The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[2] guidelines. For pneumococci Cation-Adjusted Mueller-Hinton Broth (CAMHB) broth will be used, with 2.5-5% lacquer horse blood (LHB). The following antimicrobials will be evaluated: penicillin, amoxicillin, cefotaxime, erythromycin, clindamycin, tetracycline, and levofloxacin.

[2] http://www.eucast.org/clinical_breakpoints/.

The laboratory investigator of the ISCIII or designee will be responsible for completing a record with the results of serotyping and susceptibility to be submitted to the sponsor regularly. These records will not include any personal data of the participants from whom the isolates were obtained.

11.2.2. Detection of Serotype-specific Pneumococcal Urine Antigen and BinaxNOW®

UAD 1 and UAD 2. The Pfizer UAD is a multiplex immunoassay, based on the Luminex xMAP bead technology, with the ability to combine multiple spectrally distinct microspheres, each conjugated to a different serotype-specific monoclonal antibody in a single well to allow the detection of all antigens simultaneously using only a small volume of urine sample. The 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) covered in the validated UAD 1 assay are the 13 polysaccharide antigens used in Pfizer's 13vPnC vaccine. The UAD 2 assay, using the same Luminex xMAP bead technology detects 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F).

BinaxNOW® SP test is a commercially available, Food and Drug Administration (FDA) approved assay for the detection of SP in the urine and cerebrospinal fluid (CSF) from patients with pneumonia or meningitis. The *BinaxNOW*® SP test is an in vitro rapid immunochromatographic test intended to be used in conjunction with culture and other methods, to aid in the diagnosis of pneumococcal pneumonia.

Aliquots for urine samples for testing conducted by Pfizer Inc will be processed and kept frozen in an appropriate local laboratory and will be shipped in bulk for analysis at the Pfizer Vaccines Research and Development (VRD) laboratory, Pearl River, New York, USA. Details regarding sample processing and shipping are provided in a separate laboratory manual. Residual samples from urine aliquots sent for UAD/*BinaxNOW*® testing may be stored for future testing at Pfizer laboratories and may be kept for up to [redacted] after the study ends, at which time they will be destroyed. In addition to testing for this study, any residual urine from these aliquots left over after the study is complete may be used for additional research related to the development of products. Pfizer will not perform any testing of genetic material. Residual urine samples at Pfizer may be shared with other researchers as long as confidentiality is maintained, and no testing of the participant's genetic material is performed.

11.2.3. Pneumococcal Carriage and RSV Infection Testing

The saliva samples will be placed in individual bags for transport and will be kept at room temperature until delivery. Samples will be delivered once or twice a week (preferably at the beginning of the week; Mondays or Tuesdays) to improve the culture efficiency. The samples will be referred to the ISCIII for conventional culture and molecular biology study (for culture-negative samples). Briefly, swabs with the saliva samples will be streaked onto blood agar plates containing gentamicin to select SP and avoid the growth of bacteria from the microbiota. For culture-negative samples, characterization of SP will be performed through a real-time PCR assay for the detection of pneumococcus target genes *lytA* and *piaB*. Once pneumococcus is confirmed, a CST methodology will be used to identify the serotype.

Additional PCR testing for RSV will be performed on the same saliva sample.

The PI of the ISCIII or designee will be responsible for completing a record with the results of the microbiological tests on the nasopharynx to be submitted to the sponsor regularly. These records will not include any personal data of the participants from whom the isolates were obtained.

11.3. Imaging Assessments - Chest Radiography

Patients hospitalised with CAP who have chest imaging studies normally performed as standard care (eg, CXR, CT, magnetic resonance imaging [MRI)]). Results of all imaging performed for this episode of CAP will be recorded on the eCRF. Radiologist review and interpretation will be documented on the eCRF. Radiologically confirmed CAP will be those considered to have a radiologic finding that is consistent with pneumonia (eg, pleural effusion, increased pulmonary density due to infection, the presence of alveolar infiltrates [multilobar, lobar or segmental] containing air bronchograms).

12. DATA ANALYSIS/STATISTICAL METHODS

12.1. Study Size

12.1.1. Defining Cases and Test-negative Controls

For the analysis of the primary endpoint, we will define cases as events involving hospitalised for CAP in whom PCV13 serotypes are identified by any method including UAD1 or routine culture of blood, pleural fluid, or other high-quality respiratory tract specimen. PCV13 VT serotypes are as follows: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Only sputum isolates from high-quality specimens (see Section 11.1) will be considered in assigning case status. All other episodes of CAP that met the inclusion criteria for the study, but for whom PCV13 or related serotypes are not identified from any source (ie, non-vaccine type [NVT] only) will serve as test-negative controls. Subjects with vaccine-related serotypes (eg, 6C) will be excluded from controls for the primary analysis. Subjects with VT serotype who also have an NVT or vaccine-related serotypes will be classified as cases. Subjects may only contribute one CAP event to any given VE analysis.

For PPV23 VE, cases will be those with one of 23 serotypes in PPV23: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F (including those where a NVT or vaccine-related serotype is also identified). Events with vaccine-related serotypes (either alone or in combination with an NVT) will be excluded from the controls for the primary analysis. Controls will be those with only nonvaccine serotypes (ie,

all other serotypes). Subjects with VT serotype who also have an NVT or vaccine-related serotypes will be classified as cases.

In sensitivity analyses, we will estimate PCV13 and PPV23 VE using different control group. In this case, controls will be defined as non-VT pneumococcal CAP (Broome method).[13] That is, controls will be patients in whom pneumococcus is detected by blood/pleural/high-quality sputum culture, *BinaxNOW®*, or UAD1/2 positive; but VT or vaccine-related serotypes are not identified from culture or UAD1/2. (ie, serotypes identified are not VT or related serotypes). In the second sensitivity analysis, we will define controls as CAP patients in whom pneumococcus was not detected by any method (culture, UAD, or *BinaxNOW®*), similar to a recently published TND.[14]

If PCV20 use is initiated in the surveillance area during the study, PCV20 vaccinated persons would be excluded from both case and control groups for the PCV13 VE analysis.

12.1.2. Study Size Estimates

The required sample size depends on the accrual of immunocompetent VT-CAP cases, the VE point estimate, percentage of individuals vaccinated, as well as other factors. Based on calculations outlined below in detail, the overall number of subjects to be enrolled is expected to be between 2,000 and 5,500 and will require between 1.7 and 4 years of enrolment period.

Hospitalised pneumonia cases have been forecasted here based on the incidence of all-cause hospitalised CAP in the Madrid Region derived from the Spanish *Conjunto Mínimo Básico de Dato* (CMBD) (https://pestadistico.inteligenciadegestion.mscbs.es/publicoSNS/comun/ArbolNodos.aspx) for the year 2015. CMBD is the Spanish centralized hospital discharge database that covers nearly the entire Spanish population and includes more than 95% of admissions to hospitals of the National Health System, thus providing a complete record of all hospitalisations at National level and by Region. To estimate the incidence of hospitalised pneumonia cases in adults 60 years and older, we use the seven ICD-9 codes for pneumonia (480, 481, 482, 483, 484, 485 and 486) that resulted in 22,487 hospitalisations per year with an incidence rate of 1.5 per 100 adult older than 60 years in the Region of Madrid (Table 4).

Table 4. Incidence of Hospitalised Pneumonia Cases in Adults 60 Years and Older

Madrid Region, CMBD 2015[a]	60-64y	65-74 y	>74y	Total Cases/Incidence rate per 10^5
480–viral	9	25	37	71/4.98
481-pneumococcal	110	345	1192	1,647/115.53
482-Other bacteria	96	316	707	1,119/78.49
483-Other organism	7	13	20	40/2.81
484-Other	17	36	53	106/7.44
485-Broncopneumonia	52	136	583	771/54.08
486-Non specify	1,094	3,508	14,131	18,733/1,314
Total	1,385	4,379	16,723	22,487/1,577.37

a. The ICD codes in this column as well as 487.0, 510, 513 will be used to retrospectively screen for missed CAP events to ensure completeness of surveillance.

The equivalent codes for hospitalised pneumonia under ICD-10 (Table 5) are as follows:

Table 5. Codes for Hospitalised Pneumonia Under ICD-10

ICD-10 codes[a]	
J12	Viral pneumonia, unspecified
J09.X1	Influenza due to identified novel influenza virus with pneumonia
J10.00 J10.01 J10.08	Influenza due to other identified influenza virus with unspecified type of pneumonia Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia. Influenza due to other identified influenza virus with other specified pneumonia.
J11.00 J11.01 J11.08	Influenza due to unidentified influenza virus with unspecified type of pneumonia. Influenza due to unidentified influenza virus with other respiratory manifestations. Influenza due to unidentified influenza virus with specified pneumonia.
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Hemophilus influenzae*
J15	Unspecified bacterial pneumonia
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Bronchopneumonia, unspecified organism

a. The ICD codes in this column as well as J1100, J129, 5100, 5109, and 5130 will be used to retrospectively screen for missed CAP events to ensure completeness of surveillance.

For this study surveillance region, we expect approximately 1800 all-cause CAP patients in the age group of the study are hospitalised yearly based on 2018 data. This would represent 162 PCV13-type cases per year overall considering 9% of VT-CAP cases as per the CAPA study[1] and 648 PCV13-type cases in 4 years of expected duration of the study. Approximately, 36% of CAP admissions are expected to be immunocompromised persons, so we expect ~104 immunocompetent CAP cases annually (~416 over 4 years).[20] The following table (Table 6) estimates accrual of cases and controls for the VE analysis for immunocompetent subjects varying the key inputs. For these calculations, 2.5% alpha was used to split alpha allocated between interim analysis and final analysis (ie, 2.5% to each analysis).

Table 6. Sample Size Scenarios for VE Calculations At Interim

Scenario by input varied		Vaccine Coverage Among Controls	Projected Vaccine Effectiveness	Vaccinetype (VT) Serotype Prevalence	Case:Control Ratio based on VT Serotype Prevalence	Needed Cases	Expected non-VT Controls	Total Evaluable subjects	Enrolled,[b] n	% CAP inpatients enrolled	CAP inpatients needed,[c] n	Years to Enroll[d]
Expected VE	1	15%	70%	9%	1:10	117	1165	1282	1349	70%	1928	1.7
	2[a]	15%	60%	9%	1:10	170	1692	1862	1960	70%	2800	2.4
	3	15%	50%	9%	1:10	259	2584	2843	2993	70%	4275	3.7
	4	15%	40%	9%	1:10	427	4261	4688	4935	70%	7050	6.1
% CAP VT	5	15%	60%	7%	1:13	167	2160	2327	2449	70%	3499	3.0
	6	15%	60%	11%	1:8	173	1380	1553	1635	70%	2335	2.0
	8	15%	60%	13%	1:7	176	1224	1400	1474	70%	2105	1.8
% Vax	9	10%	60%	9%	1:10	252	2516	2768	2914	70%	4162	3.6
	10	20%	60%	9%	1:10	129	1283	1412	1486	70%	2123	1.8
90% Power	11	15%	60%	9%	1:10	208	2070	2278	2398	70%	3426	3.0
% enrolled	12	15%	60%	9%	1:10	170	1692	1862	1960	50%	3920	3.4
	13	15%	60%	9%	1:10	170	1692	1862	1960	30%	6533	5.7

a. Base case values are highlighted in gray; 2.5% alpha was used for all scenarios and 80% power was used for all scenarios except #11. All calculations done with OpenEpi, Version 3, open-source calculator (Sample Size-Unmatched Case Control Study; available @ https://www.openepi.com/SampleSize/SSCC.htm) and used Fleiss method with continuity correction, which is consistent with estimates based on Fischer's exact test. For these calculations, 2.5% alpha was used to split alpha allocated between interim analysis and final analysis (ie, 2.5% to each analysis).

b. Includes projected 5% of subjects with no valid pneumococcal serotype specimen result.

c. Number of "CAP inpatients needed" is based on the percentage of CAP patients enrolled in prior column, which accounts for loss of potential subjects who declined participation or were not offered participation due to incomplete surveillance.

d. Estimate 1800 CAP admissions annually in the surveillance area and 36% would be immunocompromised, leaving ~1150 immunocompetent CAP admissions annually and ~104 vaccine-type pneumococcal CAP cases.

In conclusion, assuming 9% VT-CAP, Scenario 1 sample size would be reached in 1.7 years after enrolling 1349 immunocompetent subjects (~2107 subjects overall), Scenario 2 (base case) in 2.4 years after enrolling 1960 immunocompetent subjects (~3063 subjects overall), and Scenario 3 in 3.7 years after enrolling 2993 subjects (~4,677 subjects overall). An increase in percentage of cases that VT-serotype to ≥11% or the vaccinated proportion to 20% would reduce the time to accrue the needed cases for the interim analysis to 2 years or less. Lower proportion of VT-serotypes, lower VE point estimate, lower percentage of PCV13-vaccinated persons, or lower number of patients enrolled or subjects with valid urine specimens could all increase the time to achieve the needed number of vaccine serotype CAP cases. As the required number of enrolled subjects is highly dependent on the proportion of CAP subjects that have VT pneumococcal CAP 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 if needed. An interim analysis will be conducted after accrual of 170 VT-cases (scenario 2 above), but, given additional subjects may be needed to allow for adequate statistical power, 4 years of enrolment is planned, which would bring the number of subjects enrolled to 5,400 (based on 1,800 potential subjects annually and 70% enrolled).

If the anticipated PCV20 is approved during the enrolment of cases for VE analysis as

expected (projected to be in use no sooner than late 2022), subjects with PCV20 exposure will be excluded from both the cases and the controls for the PCV13 VE analysis. We expect substantial number of persons with a history of PCV13 vaccination to remain in the population in this age group and, thus, event accrual for VE analysis would not be significantly impact immediately following the PCV20 launch.

12.1.3. Analysis Populations

12.1.3.1. Vaccine Effectiveness CAP Population (Primary Analysis Population)

The Primary Analysis Population will include all participants who:

1. Meet all inclusion and exclusion criteria.
2. Have a final diagnosis consistent with CAP (CAP-Radiologically Confirmed; CAP-Not Radiologically Confirmed or CAP-no chest radiology done).
3. Meet the definition of either case or test-negative control from Section 12.1.1.
4. Have ≥5 combined years of pneumococcal vaccination history available.
5. Did not receive any pneumococcal vaccination ≤30 days prior to urine sample collection.
6. Have not received PCV20 if available in surveillance region during study.

This population will be analysed overall and restricted to immunocompetent subjects which will be all subjects not noted to the immunocompromised in Table 7.

Table 7. Categorization of Risk Factors by Immunocompetence[3]

Risk factor	Spain's Categorization
Age	60 +
Diabetes mellitus	immunocompetent
Alcoholism	immunocompetent
Chronic heart disease	immunocompetent
Chronic liver disease	immunocompetent
Chronic lung disease	immunocompetent
Smoking	immunocompetent
Congenital or acquired asplenia	immunocompromised
Cerebrospinal fluid leak	immunocompetent
Cochlear implant	immunocompetent
Congenital or acquired immunodeficiencies	immunocompromised
HIV infection	immunocompromised
Chronic renal failure	immunocompromised
Nephrotic syndrome	immunocompromised
Leukemia	immunocompromised
Hodgkin's disease	immunocompromised
Lymphoma	immunocompromised
Generalize malignancy	immunocompromised
Iatrogenic immunosuppression	immunocompromised
Solid organ transplant	immunocompromised
Multiple myeloma	immunocompromised
Antineoplastic chemotherapy	not specified
Occupational risk with exposure to metal fumes	not specified
Bone marrow transplantation	immunocompromised
Neurologic diseases (eg, cerebral palsy and seizures)	not specified
Prior IPD	immunocompetent

These populations will serve as the primary analysis population for the primary endpoint and the secondary objective of calculating VE for PPV23.

[3] Official Regional Immunisation Programme in the Community of Madrid, 2019.

12.1.3.2. Five-year PPV23-naïve Population

The Five-year PPV23-naïve Population is a subset of the Primary Analysis Population and will include participants from the Primary Analysis Population that have not received PPV23 within the last 5 years. To better understand the impact of PPV23 use on PCV13 VE, the primary endpoints will be analysed in this population in addition to the primary analysis population as a sensitivity analysis.

12.1.3.3. Radiologically Confirmed CAP Population

The VE populations endpoints will be analysed in this population as a sensitivity analysis to determine the impact of requiring radiographic confirmation for the diagnosis of CAP. All requirements will be the same as the "All CAP" population but the events must have a final diagnosis of "CAP-radiologically confirmed" consistent with the definition provided in Section 10.2.

12.1.3.4. Serotype Distribution CAP Population (Secondary Analysis Population)

The Primary Analysis Population will include all events who:

1. Participant meets all inclusion and exclusion criteria.
2. Event has final diagnosis consistent with CAP.
3. Did not receive any pneumococcal vaccination ≤30 days prior to event urine sample collection.
4. Event with valid UAD1/2 test results or other pneumococcal serotype result (eg, from bacterial isolate).

Events with same serotype result involving rehospitalisation ≤30 days will be considered same event for this analysis.

12.1.3.5. Incidence CAP Population (Exploratory Analysis Population)

The calculation of incidence will include all CAP events identified on the screening log as residents of the hospitals' geographical catchment area either prospectively or retrospectively through ICD discharge code review.

12.1.4. Endpoints

See Section 8 for details of endpoints per study objective.

12.2. Data Management

An electronic database will be created for this study. Details of the database creation are included in the Data Management Plan.

12.3. Case Report Forms/Data Collection Tools/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 eCRF is required and should be completed for each included subject. The completed original eCRFs 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 eCRFs 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 eCRFs 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 eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs 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 eCRFs must match those charts.

In some cases, thee 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 eCRF, and for which the eCRF will stand as the source document.

12.3.1. 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, eCRFs and hospital records), all original signed informed consent [/assent] documents, copies of all eCRFs, 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 Council for 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 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.

12.4. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

12.4.1. Vaccine Effectiveness

If either PCV13 or PPV23 coverage is <10% or >90%, we will assess whether valid VE estimates can be generated for the involved vaccine. If appropriate, we will proceed as follows; odds ratio of having received PCV13 and PPV23 for cases and controls with 95% CI for odds ratio will be calculated. See details on case and control assignment in Section 12.1.1. We will calculate VE as 1-OR x 100. In addition to constructing crude OR and VE estimates, we will perform unconditional logistic regression modelling to assess VE after adjustment for potentially confounding factors. Because of the risk-based approach to catch up vaccination in the over 60 cohort, we will also perform a second adjusted analysis, selecting non-vaccine-type controls similar the VT-serotype cases based on propensity score matching. Further, we will use a two-sided alpha of .025 for all analyses if final VE analysis is not conducted at the interim analysis. If interim analysis is final VE analysis, a two-sided alpha of .05 will be used in the final tables. A second model will be developed excluding immunocompromised persons to evaluate VE without those that may not be able to respond to the vaccine. Only adjusted estimates will be considered the final VE. Time from vaccination will be accounted for in the adjusted analyses. The comparison of the estimates of the effectiveness between PCV13 and PPV23 will be performed using the z-score test. The null hypothesis will be that there is no difference between the two estimates.

For the other study objectives, descriptive analysis will be carried out, presenting the absolute and relative frequencies of the qualitative variables and main measures of centralisation and dispersion in case of quantitative variables. 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.

12.4.2. CAP Incidence Rate

Incidence rates (IR) per 100,000 inhabitants of the study age group will be calculated with their respective 95% confidence intervals.

Numerator: The numerator will include all CAP events – both involving study subjects and other unconsented patients captured on screening log as residents of the hospitals' geographical catchment area. Frequent retrospective review of admissions assigned pneumonia ICD discharge codes will be undertaken monthly to ensure no CAP events are missed from the screening log. Efforts will also be made to assess how many persons from the district were hospitalised for pneumonia outside of the surveillance region.

For SP+CAP, the proportion of CAP events among study subjects with pneumococcus identified by any means, will be multiplied by the calculated CAP incidence rate. For radiologically confirmed CAP, the proportion of CAP events among study subjects that is radiologically confirmed will be multiplied by the calculated CAP incidence rate. Other more complex adjustment processes will also be explored if there is adequate detail captured in the screening log, such as calculation the proportion with pneumococal infection within specific risk/age strata or multiple imputation.

Denominator: Annual population data over 60 years old and estimated person-years data for this age group will be obtained from INE (National Statistical Institute). To determine denominators (catchment area), calculations will be made based on the following parameters: age-specific strata of the total population in the region of Madrid; age-specific strata of total hospital discharges in the region of Madrid; age-specific strata of hospital discharges of the Móstoles (2 hospitals) and Alcorcón (1 hospital). Catchment area is calculated as the proportion of the Móstoles and Alcorcón hospital discharges compared to total hospital discharges in the region of Madrid. These percentages are then applied to the total population of the region of Madrid and hence, catchment population in the Móstoles and Alcorcón hospitals by age group are estimated. If population denominators for adults aged ≥60 years are available for underlying at-risk and high-risk medical conditions, incidence will be calculated specifically for these risk groups in aggregate and for individual risk conditions that are of sufficient size as outlined in the SAP.

While every effort will be taken to prospectively and retrospectively capture pneumonia events, incidence estimates will be considered conservative, given established multiple risks for under ascertainment of pneumonia events in studies in this setting (for example, due to misdiagnosis, CXR false negative, or hospitalisation on a different inpatient ward).

12.4.3. Additional COVID-19 and RSV Exploratory Analyses

Additional statistical methods and data analysis for the COVID-19 and RSV exploratory analyses will be described in the SAP. These analyses will be undertaken if COVID-19 continues to occur at a sufficient frequency during enrolment in the surveillance region to allow for a meaningful analysis.

12.5. Interim Analysis

An interim analysis will be conducted after accrual of the number of cases required to assess VE with expected VE of 60% (scenario 2 above, Table 5). Currently, this is expected to require ~170 evaluable VT cases. Because the study will assess VE among all subjects and limited to the immunocompetent, we will need 170 evaluable immunocompetent VT cases available at the interim analysis. As per Table 5, this would expect to take approximately 2.4 years (Q1 2023) to enrol the needed cases, and, given the required time for UAD testing, the study team would be aware of this in Q2 2023. The target number of cases for the interim may be adjusted based on UAD testing results and vaccine exposure data obtained during the conduct of the study. If VE point estimate is lower than 60% at the interim analysis, the required number of cases will be re-assessed.

Other descriptive analyses of eCRF and laboratory data may be done on an ad hoc basis throughout the enrolment period.

13. 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) and/or Good Pharmacoepidemiology Practices (GPP), as relevant, are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs 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 IRB/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.

14. LIMITATIONS OF THE RESEARCH METHODS

The actual proportion of participants who would follow their healthcare practitioner vaccination recommendation is not known, so this aspect might influence the size of the vaccinated group and therefore the global results.

Differential enrolment based on clinical status (eg, severity of illness) and age can introduce bias in the global results obtained, likely an underestimation of incidence.

Under ascertainment of incidence estimates is expected, given established multiple risks for under ascertainment of pneumonia events in studies in this setting (for example, due to misdiagnosis, CXR false negative, or hospitalisation on a different inpatient ward).

15. PROTECTION OF HUMAN SUBJECTS

15.1. Patient 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 patient personal data. Such measures will include omitting patient names or other directly identifiable data on any sponsor forms, reports, publications, or in any 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 subject's personal data consistent with the clinical study agreement (CSA) 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 his or her legally acceptable representative 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 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.

Whenever consent is obtained from a subject's (legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject (or the subject's legally acceptable representative and the subject's assent, when applicable,) before any study-specific activity is performed (unless a waiver of informed consent has been granted by an IRB/EC). The investigator will retain the original of each subject's signed consent(/assent) document.

15.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if applicable. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

15.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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

15.4. 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 Organisations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

16. MANAGEMENT AND REPORTING OF ADVERSE EVENTS (AEs)/ADVERSE REACTIONS

Table 8. Summary of Study AE Reporting Requirements[a]

Safety event	Recorded on the Case Report Form	Reported on the CT SAE Report Form Report Form to Pfizer Safety within 24 hours of awareness
SAE	1. All SAEs occurring within 15 minutes of study sample collection (ie, study urine or saliva specimens). 2. SAEs determined to be related to a Pfizer product during entire study period. 3. Research-related injuries during entire study period.	Only SAEs determined to be related to a Pfizer product.

Non-serious AE	AEs occurring within 15 minutes after study sample collection (ie, study urine or saliva specimens).	None.

Safety event	Recorded on the Case Report Form	Reported on the CT SAE Report Form Report Form to Pfizer Safety within 24 hours of awareness
Scenarios **involving exposure to a Pfizer product**, including exposure during pregnancy or breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure.	All involving exposure to a Pfizer product (regardless of whether associated with an AE), **except occupational exposure**, during entire study period.	All (regardless of whether associated with an AE) involving exposure to a Pfizer product. **Note:** Any associated AE (either serious or non-serious) is reported together with the exposure scenario.

a. See full detail on reporting requirements and definitions in Protocol Section 16.1, Section 16.2, and 16.3.

16.1. Adverse Events

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

This study includes qualifying diagnostic or monitoring procedures required per protocol to collect clinical data needed to meet the study objectives, which are not standard-of-care but that do not pose more than a minimal risk or burden to the study participant. The qualifying procedures in this study are:

Qualifying diagnostic or monitoring procedure(s)	Recording Time Period
Urine collection	15 minutes
Saliva sample collection	15 minutes

Any AE that occurs up to 15 minutes after a study-related urine or saliva sample collection must be recorded.

The investigator is required to assess whether the AE may be related to the participant's participation in the study. All AEs (ie, serious and non-serious, including those attributed to a qualifying procedure identified as RRI) are collected in the clinical study database.
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 an RRI requiring immediate notification to Pfizer as described below.

16.2. Research-Related Injury (RRI)

Should a participant, in the investigator's opinion, suffer a medically important RRI caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately and the AE documented in the eCRF.

A medically important RRI is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- 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 hospitalisation. However, if it is determined that the event may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as an RRI.

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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

16.3. Reporting of Selected Exposures and AEs Related to Pfizer Products

If during the conduct of this study, the investigator or study staff becomes aware (for example, during the course of medical record review or through spontaneous, non-solicited reports from the patient) of an serious AE that has been noted to be **related** to a Pfizer product or certain exposures to a Pfizer product, these events must be reported to CT SAE Report Form Report Form to Pfizer Safety (local Drug Safety Unit) within 24 hours of awareness (immediately if fatal or life-threatening). This includes reports related to PCV13 as well as other Pfizer drugs. These AEs should also be recorded in the eCRF. For each subject, the safety event reporting period for these events begins at the time of the patient's informed consent and lasts through the end of the observation period of the study (Visit 3). The investigator or his/her staff might become aware of such events during the participant interview (for example, participant spontaneously mentions a serious vaccine

or drug reaction related to a Pfizer product) or during study-related medical record review (for example, reads a medical note that mentions a diagnosis of a serious vaccine or drug reaction involving a Pfizer product). The investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. Additional information on safety reporting will be provided in the Study Reference Manual.

16.4. Definition of Serious Adverse Events (SAEs)

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of hospitalisation (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

16.5. Selected Exposures to Pfizer Product that Require Reporting to Pfizer Safety

The selected Pfizer product exposures that require reporting to Pfizer Safety/local Drug Safety Unit even in the absence of an AE are as follows: exposure during pregnancy or breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. Additional information on these definitions will be provided in the Study Reference Manual.

17. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

17.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

17.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the 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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19. LIST OF TABLES

20. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.