Non-Interventional Study Protocol

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Prospective multicenter study to determine the impact of pneumococcal vaccination on acute COPD exacerbations (IMPACE study)

Statistical Analysis Plan
(SAP)

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CONTENTS

1 AMENDMENTS TO PREVIOUS VERSIONS

Not applicable: this is version 1.

2 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to give a detailed description of the statistical analyses that will be carried out to generate the final report of the IMPACE study. This includes, on the one hand, a brief summary of the main characteristics of the study and, on the other, the objective of the SAP, which corresponds to the planning of the statistical analysis of the study.

Patients with chronic obstructive pulmonary disease (COPD) have been demonstrated to have an increased risk of pneumococcal disease.[1,2] Pneumonia is frequent among patients hospitalized for COPD exacerbations and is associated with increased health care utilization and higher mortality. Nonpneumonic COPD exacerbations predict increased risk of subsequent exacerbations.[3] Among community-acquired pneumonia (CAP) patients with the highest severity of disease who require hospitalization, COPD is the most common comorbidity. These two diagnoses, CAP and acute exacerbations of COPD (AECOPD), come together when a COPD patient has an exacerbation caused by CAP.[4]

Exacerbations are a significant component of the clinical course in COPD. Furthermore, as the disease progresses, exacerbations become more frequent.[5]

COPD exacerbations are defined as a complex of two or more respiratory symptoms (worsening dyspnea, cough, sputum production, chest tightness, or wheezing) related to the underlying COPD, with duration of 3 days or more, that require a change in treatment.[6] AECOPD have a great impact on health status,[7] disease progression,[3] and prognosis.[8] Up to 50%–70% of AECOPD can be attributed to respiratory infections by viruses or bacteria, even more in the most severe patients.[9] They are often associated with the colonization of airways by multiple bacteria or viruses of low virulence that in normal conditions are part of the normal flora of the upper airway.[10]

Some studies have identified factors independently associated with bacterial growth, such as smoking and *H. influenzae*; longer periods between exacerbations and *S. pneumoniae*; or decrease in FEV1 and *P. aeruginosa*.[11] Traditionally, bacterial identification has been defined depending on the severity of the COPD, since *S. pneumoniae* and *M. catharralis* are isolated in patients with predicted FEV1 >50%, and *H. influenzae*, Enterobacteriaceae and *P. Aeruginosa* in those with predicted FEV1 <50.[11,12]

Therefore, considering *S. pneumoniae* appears to be more frequent in patients with mild/moderate COPD, these subjects might benefit from a preventive approach targeting this pathogen.

In terms of costs, COPD represents a significant burden on the healthcare system. Different studies relate the costs to the severity of the disease.[13] The clinical course of COPD with multiple exacerbations has generated many economic studies analyzing these episodes. Anderson et al. in 2002 concluded that severe exacerbations represent 10 times the cost of a moderate exacerbation and around 60 times the cost of a mild-moderate episode. Similarly, exacerbations in severe COPD are 45 times more costly than in mild stages of the disease. The largest proportion of the cost of exacerbations is associated with hospitalizations, representing 65-85% of the total expense per acute episode.[14]

All this evidence supports the current recommendations for immunization of patients with COPD with vaccines against influenza and *Streptococcus pneumoniae*, aimed to help prevent infectious exacerbations.[15,16] Existing studies suggest an additive effect in the prevention of all-cause mortality with influenza and pneumococcal vaccines given together in elderly people, including in those with chronic diseases. Although no significant reduction in mortality rate was seen with the pneumococcal vaccine (PPV23) alone, there was a decrease in mortality rate of 27.0% (20.0–34.0) in subjects who received both vaccines compared to 16.0% (6.0–24.0) in those who received the influenza vaccine alone.[17] However, despite the existing recommendation, these vaccines are generally under-used, probably due to some persistent uncertainty about the benefits of vaccination.[18]

There are two types of pneumococcal vaccines, a 23-valent polysaccharide vaccine and a 13-valent conjugate vaccine. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is approved and recommended for use in persons ≥2 years of age for the prevention of pneumonia and pneumococcal disease.[19] In the past decades many studies have evaluated the effect of PPV23 in adults, and effectiveness in preventing invasive pneumococcal disease (IPD) has been reported, but with a short duration of protection and limited impact on the total burden of disease, even in countries with high uptake.[20,21]

Regarding the prevention of noninvasive pneumococcal pneumonia, the most common clinical presentation of the disease in adults, studies assessing the effectiveness of PPV23 show inconsistent results.[22] The available studies focused specifically on COPD patients, do not show a clear effect on any of the outcomes evaluated (developing pneumonia or acute exacerbations).[23]

The 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the EMA for the prevention of IPD in adults ≥50 in 2011, and subsequently in 2013 for adults ≥18 years of age, based on immunogenicity studies.[24] Following the publication of the results of the CAPiTA study in 2015, showing the efficacy of the vaccine for the prevention of

vaccine-type community-acquired pneumonia (45.6%) and nonbacteremic (45%) pneumococcal pneumonia, and IPD (75%) caused by vaccine serotypes in subjects ≥65 years old, the EMA approved the indication for the prevention of pneumonia in adults aged ≥18 years.[25,26]

Recent exploratory studies have shown a beneficial effect of PCV13 in reducing the number of exacerbations in COPD and other respiratory diseases.[27,28] Results from a group of 90 COPD patients vaccinated with PCV13 and followed for 2 years in Spain showed a reduction of 50% in the number of severe exacerbations in the second year after immunization.[29] A prospective comparative open-label study carried out in Russia, evaluating PCV13 safety and effectiveness to prevent CAP in COPD patients compared with non-vaccinated patients, found in a group of 25 patients a 4.8-fold reduction in the incidence of exacerbations one year after vaccination.[28]

The limitations of these preliminary results require larger studies, specifically designed for this purpose, to assess which subgroups might benefit most from this preventive approach.

The aim of this study is to generate evidence to support vaccination of COPD patients with PCV13 and/or against influenza in terms of clinical benefits and quality of life.

2.1 STUDY DESIGN

Prospective observational study, which will be carried out in 6 different geographical areas in Spain (Salamanca, Cantabria, Palma de Mallorca, Madrid, Barcelona and Seville), involving 1 hospital in each region.

Subjects identified with COPD will be invited to participate by investigators at the time of their routine follow-up visits. All therapies will be prescribed in line with routine clinical practice according to the updated National COPD Guidelines (GesEPOC),[1] indicating among other therapies active reduction of risk factors, and influenza and pneumococcal vaccination (with PCV13) in all patients with mild, moderate or severe COPD. All patients will be advised to quit smoking and recommended healthy lifestyle habits.

Study will include periodic visits for all patients, to complete a total follow up of 2 years.

2.2 STUDY OBJECTIVES

The study objectives are to:

- **Primary objectives**

1. Evaluate the impact of routine clinical practice vaccination with PCV13 on the reduction of the risk of moderate/severe COPD exacerbations, after 2 years of follow-up.
2. Determine which subgroup of patients (based on the severity of COPD) benefit most from vaccination with PCV13

   COPD severity (GOLD)[18]
   - GRADE 1: Mild/unknown [FEV1≥80%, FEV1/FVC < 0.7 or no spirometry record]
   - GRADE 2: Moderate [50% ≤ FEV1< 80%, FEV1/FVC < 0.7]
   - GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0.7]
   - GRADE 4: Very severe [FEV1< 30% or FEV1< 50% plus respiratory failure, FEV1/FVC < 0.7])

- **Secondary objectives**

1. Evaluate the impact of influenza and PCV13 vaccination on the reduction of the risk of exacerbations
2. Evaluate the impact of vaccination with PCV13 on patients' quality of life
3. Evaluate the impact of vaccination with PCV13 on the decrease in FEV1
4. Estimate the potential savings for the healthcare system derived from vaccination of COPD patients with PCV13
5. Determine the prevalence of PCV13 vaccination in COPD patients.

3 INTERIM ANALYSES

Depending on recruitment and data availability, an interim analysis will be performed after the first year, if at least 75% of subjects included have completed one year of follow up.

4 HYPOTHESIS AND ROLE OF DISCUSSION

The statistical significance value is set at $p<0.05$. The SPSS statistical package version 19.0 or later will be used.

5 ANALYSIS SYSTEMS / POPULATIONS

Considering that 37% of COPD patients will have one moderate/severe exacerbation per year, and assuming that at least 35% of patients will follow their doctor's vaccination

recommendation,[3] to have at least 200 vaccinated COPD patients with moderate/severe exacerbations, a total of 1541 eligible subjects should be included in the analysis.

With 35% of patients vaccinated with PCV13, enrolling 1541 eligible subjects with COPD would provide approximately 540 patients in the PCV13 cohort and 1000 patients in the unexposed cohort.

Assuming that 37% of unexposed patients will present one moderate/severe exacerbation per year,[2] with 70% of the patients remaining in the study after 1 year, this sample size would provide 91% power to detect a statistically significant reduction of 10% in moderate/severe COPD exacerbations with PCV13 after 1 year. Assuming an additional 30% dropout in the second year, the study sample size would provide 91% power to detect a statistically significant reduction of 14% in moderate/severe COPD exacerbations with PCV13 after 2 years.

Time	**PCV13**		**Unexposed**		**Power**	**Retention rate**
	Sample size	% exacerbation	Sample size	% exacerbation		
Enrollment	540		1000			
1 year	378	27%	700	37%	91.43%	70% from enrollment
2 years	264	60%	490	74%	91%	70% from year 1

5.1 FULL ANALYSIS

The statistical analysis of this study will be carried out with all those evaluable patients with COPD, recruited by the Spanish sites participating in the study and who meet the following selection criteria:

5.1.1 Inclusion Criteria

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

1. *Aged 18 years or older at the time consent is given*
2. *Patient diagnosed with COPD (any stage, subgroups for analysis will be based on COPD severity)*
3. *Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.*
4. *Ability to understand and complete the required quality of life questionnaires*
5. *Patients with at least 2 years of previous clinical history available relating to (if applicable) history of moderate/severe exacerbations, influenza and pneumococcal vaccination history, comorbidities and previous treatments*
6. *Spirometry data* (maximum 6 months old, or if not available at enrollment, to be performed as per normal clinical practice at visit 1 ± one month)*

*Total proportion of subjects with FEV1 <40 should be less than 20% of the total study population (related to the microbiological etiology dependent on severity)[14,15]

5.1.2 Exclusion criteria

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

1. *Impossibility to perform prospective follow up*
2. *Present any immunocompromising condition*
3. *Present any other respiratory disease as a comorbidity (subjects with overlap syndrome COPD-asthma will be excluded. Mixed phenotype defined as: symptoms of increased variability of airflow and incompletely reversible airflow obstruction)[33]*

5.2 SAFETY ANALYSIS

NA

5.3 OTHER ANALYSES

NA

5.4 SUBGROUPS

The statistical analyses described in this SAP will be carried out according to the following analysis groups:

Exposed/unexposed (patients vaccinated/not vaccinated with PCV13):
The results will be evaluated through a cohort study, considering the subjects not vaccinated with PCV13 included in the study as the unexposed group.

COPD severity (GOLD):

- GRADE 1: Mild/unknown [FEV1 ≥80%, FEV1/FVC < 0.7 or no spirometry record]
- GRADE 2: Moderate [50% ≤ FEV1< 80%, FEV1/FVC < 0.7]
- GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0.7]
- GRADE 4: Very severe [FEV1< 30% or FEV1< 50% plus respiratory failure, FEV1/FVC < 0.7])

6 OBJECTIVES AND VARIABLES

Given that the primary objective of this study is to evaluate the impact of routine clinical practice vaccination with PCV13 on the reduction of the risk of moderate/severe COPD exacerbations, after 2 years of follow up, and to determine which subgroup of patients (based on the severity of COPD) benefit most from vaccination:

Primary endpoint to be analyzed:

- COPD severity (GOLD)[18]
  - GRADE 1: Mild/unknown [FEV1 ≥80%, FEV1/FVC < 0.7 or no spirometry record]
  - GRADE 2: Moderate [50% ≤ FEV1< 80%, FEV1/FVC < 0.7]

  - GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0.7]
  - GRADE 4: Very severe [FEV1< 30% or FEV1< 50% plus respiratory failure, FEV1/FVC < 0.7])
- Number and severity of exacerbations
- Frequency of total exacerbations (moderate and severe) in previous years and during follow-up.

6.1 OTHER OBJECTIVES

For other study objectives, such as to determine the prevalence of PCV13 vaccination in COPD patients or to determine the impact of vaccination on quality of life or the decrease in FEV1:

Secondary endpoints:

- Demographic and epidemiological data;
- Anthropometric data (weight, height, body mass index [BMI], waist circumference)
- Smoking habit, alcohol consumption
- Spirometry data (FEV1, FVC, FEV1/FVC)
- Pharmacological treatment
- Associated comorbidity
  - high blood pressure
  - dyslipidemia
  - type 2 diabetes mellitus
  - metabolic syndrome
  - heart failure
  - ischemic heart disease
  - chronic kidney disease
  - cirrhosis

- History of neoplasia (solid organ and hematologic)
- Pneumococcal vaccination
- Influenza vaccination
- Quality of Life questionnaire (shortened SGRQ, CAT) (completed by the subject and transcribed into the study CRF)

7 HANDLING OF MISSING VALUES

In the Saint George Quality of Life scale, ideally there would be no missing values and the questionnaire would be complete; however, if there are missing values, the effect of the missing elements has been examined and the following methods of action are recommended:

Symptoms

The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total weight for the Symptoms category (662.5) and from the Total weight (3989.4).

Activity

The Activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total weight for the Activity category (1209.1) and from the Total weight (3989.4).

Impacts

The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total weight for the Impacts category (2117.8) and from the Total weight (3989.4).

No criteria for replacement of missing values will be used for the rest of the study variables.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSIS

8.1 STATISTICAL METHODOLOGY

The results will be evaluated through a cohort study, considering the subjects not vaccinated with PCV13 included in the study as the unexposed group.

- A descriptive analysis of all variables will be performed. Qualitative variables will be analyzed by absolute and relative frequencies. Quantitative variables will be studied using the usual measures of central tendency and dispersion (mean, median, standard deviation, confidence intervals, minimum, maximum and interquartile range).

- For comparison of independent samples, the Pearson's Chi-squared test or the Fisher's exact test for 2x2 tables or likelihood ratio for mXn tables will be used for qualitative variables. The Student's t-test, one-way ANOVA or its non-parametric equivalents, the Mann-Mann U test or Kruskal-Wallis H test, will be used for quantitative variables.
- For comparison of paired samples, the McNemar's test will be used for qualitative variables and the Student's t-test or Wilcoxon's test for quantitative variables.
- The study will seek to identify factors associated with the occurrence of exacerbations throughout the follow-up period; to that end, a multivariate logistic regression analysis will be performed, where the dependent variable will be the occurrence of exacerbations (Yes/No) during the study. Vaccination with PCV13 and significant variables in the univariate model will be used as possible risk factors: demographic characteristics, influenza vaccination, smoking habit, etc. In addition, potential confounding variables will be considered: exacerbator phenotype, comorbidities, COPD severity, FEV1 (no control possible based on the study design).
- Appropriate tests will be performed accordingly to determine if the necessary requirements are fulfilled for the use of parametric tests.
- Estimates will be performed with a 95% confidence interval. The SPSS statistical package, version 19.0 or later, will be used.

8.2 STATISTICAL ANALYSIS

8.2.1 Patient disposition

The absolute and relative frequency of evaluable patients will be determined. In the subpopulation of non-evaluable patients, the frequency distribution will be presented based on the reasons for non-evaluation:

- Patient under 18 years of age at the time of obtaining informed consent
- Not diagnosed with COPD of any grade (patients diagnosed with COPD less than 2 years after inclusion in the study should not be included)
- At least two years of prior medical records are not available relating to (if applicable):
    - History of moderate/severe exacerbations
    - History of influenza vaccination (date)
    - History of pneumococcal vaccination (date)
    - Comorbidities
    - Previous treatments
- No spirometry data available
- Inability to understand and complete the required quality of life questionnaires
- No evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study
- Impossibility to perform prospective follow-up
- Present any immunocompromising condition

- Present any other respiratory disease as comorbidity

In the subpopulation of evaluable patients, the frequency distribution will be given according to the analysis groups:

Exposed/unexposed patient:

- Patient with COPD of any grade vaccinated with PCV13
- Patient with COPD of any grade not vaccinated with PCV13

  In the subpopulation of exposed patients and provided that we have a sufficient frequency, a new analysis group will be established based on:
  - **PCV13 only**
  - ***PCV13+ PPV23***
  - ***PCV13+ Influenza (same summer period)***
  - ***PCV13+ PPV23+influenza (same summer period)***

COPD severity:

- GRADE 1: Mild/unknown [FEV1≥80%, FEV1/FVC < 0.7 or no spirometry record]
- GRADE 2: Moderate [50% ≤ FEV1< 80%, FEV1/FVC < 0.7]
- GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0.7]
- GRADE 4: Very severe [FEV1< 30% or FEV1< 50% plus respiratory failure, FEV1/FVC < 0.7])

The statistical analysis detailed below will be performed both with the total sample of evaluable patients and divided based on the two analysis groups established: exposed/unexposed and severity of COPD.

Additionally, a flow chart will be presented on the total number of patients analyzed at each of the study follow-up visits:

- Month 1
- Month 6
- Month 12
- Month 18
- Month 24

In the subpopulation of ineligible patients at each of the scheduled visits, the frequency distribution will be given based on the reason for ineligibility:

- Does not meet one or more of the inclusion criteria:

a) Aged ≥18 years at the time of obtaining informed consent
b) Diagnosed with COPD of any grade
c) With at least 2 years of previous clinical history available relating to (if applicable): history of moderate/severe exacerbations, history of influenza vaccination (date), history of pneumococcal vaccination (date), comorbidities and previous treatment
d) Spirometry data (if available at enrollment, should be a maximum of 6 months old. If not available at enrollment, perform as per routine clinical practice at visit 1 ± 1 month.
e) Ability to understand and complete the required quality of life questionnaires
f) Existence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study

- Meets one or more of the inclusion criteria:

g) Impossibility to perform prospective follow-up
    a. Death
    b. Moved to another region
    c. Other reason
h) Present any immunocompromising condition
i) Present any other respiratory disease as a comorbidity (subjects with asthma-COPD overlap syndrome will be excluded)

8.2.2 Baseline descriptive statistics

8.2.2.1 Demographic/anthropometric variables

The variables age, weight, height, BMI and waist circumference will be described by the mean, median, standard deviation, minimum, maximum, interquartile range and 95% confidence interval.

The study will examine whether there are statistically significant differences in these variables according to the severity of COPD and type of patient (exposed/unexposed), using the Student's t-test and one-way ANOVA test in the case of compliance with the assumptions necessary for the use of parametric tests, or the Mann-Whitney U test and the Kruskal-Wallis H test if otherwise, as appropriate.

The frequency distribution of patients will be given according to sex:

- Male
- Female

The likelihood ratio test will be used to study whether there are statistically significant differences in the sex of patients depending on the severity of COPD, while Pearson's Chi-square test or Fisher's exact test will be used to examine statistically significant differences between sex and the type of patient (exposed vs. unexposed).

8.2.2.2 Alcohol consumption

The absolute and relative frequency of patients who consume alcohol will be presented, considering as such those with an intake of ≥80 g/day for at least the previous year. Using Pearson's Chi-squared test or Fisher's exact test for 2x2 tables or likelihood ratio for mXn tables, we will study whether statistically significant differences are observed in alcohol consumption and the two patient subpopulations established according to the severity of COPD and type of patient (exposed/unexposed).

8.2.2.3 Relevant medical history

The absolute and relative frequency of patients with at least one relevant condition in their history will be given, as well as each of the personal histories described:

- High blood pressure
- Dyslipidemia
- Type II diabetes mellitus
- Metabolic syndrome
- Heart failure
- Chronic kidney disease
- Cirrhosis
- History of neoplasia (solid organ and hematologic)
- Previous pneumonia in the last year
- Other relevant history

The study will examine whether there are statistically significant differences in the presence of a relevant history depending on the severity of COPD and type of patient (exposed/unexposed) using the likelihood ratio test and Pearson's Chi-Square test or Fisher's exact test, as appropriate.

8.2.3 Effectiveness analysis

8.2.3.1 Study of exacerbations

A detailed analysis of the total number of exacerbations reported by the study patients will initially be performed. The absolute and relative frequency of patients who have reported at least two moderate exacerbations or one severe exacerbation per year (exacerbator patient) will be given.

The following indices will be calculated:

- NEPA (number of exacerbations patient/year) =Total no. of exacerbations reported by patients/ Patient follow-up time*)
- NEPA $_{Mild}$ = Total no. of mild exacerbations/Patient follow-up time
- NEPA $_{Moderate}$ = Total no. of moderate exacerbations/Patient follow-up time
- NEPA $_{Severe}$ = Total no. of severe exacerbations/Patient follow-up time
- NEPA $_{Moderate/severe}$ = Total no. of moderate_severe exacerbations/Patient follow-up time

The following will also be calculated in the subpopulation of exposed patients:

- NEPA$_{_pre_PCV13}$ = Total no. of exacerbations reported by the patient prior to receiving the PCV13 / Time to vaccination with PCV13**)
- NEPA$_{_pre_PCV13\ (moderate/severe)}$ = Total no. of moderate/severe exacerbations reported by the patient prior to receiving the PCV13 / Time to vaccination with PCV13**)
- NEPA$_{_post_PCV13}$ = Total no. of exacerbations reported by the patient after receiving the PCV13 / Time since vaccination with PCV13***)
- NEPA$_{_post_PCV13\ \ (moderate/severe)}$ = Total no. of moderate/severe exacerbations reported by the patient prior to receiving the PCV13 / Time since vaccination with PCV13***)

*) Time from the date of COPD diagnosis to the date of the last follow-up visit. If the date of diagnosis of the disease is unknown, it will be computed as two years before the date of inclusion of the patient in the study

**) Time from date of COPD diagnosis to date of PCV13 vaccination

***) Time from vaccination with PCV13 to date of the last follow-up

Each of the indices calculated above will be described using the main measures of central tendency and dispersion (mean, median, standard deviation, confidence intervals, minimum, maximum and interquartile range).

The Student's t test, one-way ANOVA or its non-parametric equivalents, the Mann-Mann U test or Kruskal-Wallis H test will be used to determine if statistically significant differences are observed in NEPA, NEPA $_{Mild,}$ NEPA $_{Moderate,}$ NEPA $_{Severe}$ and NEPA $_{Moderate/Severe}$ according to the severity of COPD and type of patient (exposed/unexposed).
In order to determine the impact of PCV13 vaccination on exacerbations, paired data comparisons will be made between (NEPA$_{_pre\ _PCV13}$ vs. NEPA$_{_post_\ PCV13}$) and (NEPA$_{_pre_\ PCV13\ (moderate/severe)}$ vs. NEPA$_{_post_PCV13\ (moderate/severe)}$), using the Student's t-test for paired data or its non-parametric equivalent, the Wilcoxon test.
In order to study which subgroups of patients obtain a greater benefit from vaccination

with PCV13 according to COPD severity, paired data comparisons will be made between ($NEPA_{\_pre\_PCV13}$ vs. $NEPA_{\_post\_PCV13}$) and ($NEPA_{\_pre\_PCV13\ (moderate/severe)}$ vs. $NEPA_{\_post\_PCV13\ (moderate/severe)}$), in each of the four patient subpopulations established based on disease severity.

In order to determine the factors associated with the presence of an exacerbator patient, a logistic regression model will be constructed, whose dependent variable is (exacerbator/non-exacerbator patient) and, as independent variables, all those possible factors that have been significant in the univariate models (p_value <0.25), following the methodology of Hosmer-Lemeshow.

- Vaccine exposure (PCV13 yes/no)
- COPD severity (Grade I, Grade II, Grade III, Grade IV)
- Age
- Sex
- Time since diagnosis of the disease
- Patient with stable treatment for at least three months
- ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,

8.2.3.2 Change in post-bronchodilator spirometry test

Changes in the spirometry data at the different follow-up visits will be given and analyzed using the main measures of central tendency and dispersion (mean, median, standard deviation, confidence intervals, minimum, maximum and interquartile range).

- FEV1
- FVC
- FEV1/FVC

The study will examine whether there has been a significant change in the spirometry data over time, both in the total sample of evaluable patients and in each of the subpopulations established based on the severity of the COPD and type of patient, using the Student's t-test for paired data or its non-parametric equivalent, the Wilcoxon test.
The % reduction in the parameters FEV1, FVC and FEV1/FVC will be calculated at the 24-month visit relative to baseline ((final value-baseline value)*100/baseline value).

The Student's t-test, one-way ANOVA or its non-parametric equivalents, the Mann-Mann U test or Kruskal-Wallis H test will be used in order to determine if statistically

significant differences in FEV1, FVC, FEV1/FVC (% reduction compared to the FEV1, FVC and FEV1/FVC baseline values) are observed, depending on the severity of the COPD and type of patient (exposed/unexposed).

8.2.3.3 Smoking habit

The study will explore if there have been changes in the patients' smoking habit during the follow-up, presenting the frequency distribution of the patients for each of the study visits according to the smoking habit described in said visit.

- Regular smoker (currently smokes tobacco daily)
  - How many cigarettes per day? Mean (SD)
- Occasional smoker (does not smoke daily)
- Never-smoker: Has not been exposed to smoking.
- Former smoker: Has quit smoking more than 6 months ago.
  - Pack-years: Mean (SD)

Both for the total sample of evaluable patients and for each of the analysis subpopulations, the study will determine whether there has been significant change during the study in terms of the patient's smoking habit, using the sign test.

In order to determine whether there are statistically significant differences in smoking habits in patients, depending on the severity of COPD as well as on the type of patient (exposed/unexposed), the Pearson's Chi-squared test or the Fisher's exact test for 2x2 tables or likelihood ratio for mXn tables will be used.

8.2.3.4 COPD treatment

A detailed descriptive analysis of the treatments used by COPD patients will be performed. The absolute and relative frequency of patients who have received any of the following at some point during the disease will be given:

- Short-acting bronchodilators
  - Anticholinergics (SAMA) (ipratropium bromide, umeclidinium)
  - Short-acting β-2 agonists (SABA) (salbutamol, terbutaline)
- Long-acting bronchodilators
  - β-2 adrenergics (LABA) (salmeterol, formoterol indacaterol, vilanterol, olodaterol)
  - Anticholinergics (LAMA) (tiotropium bromide, aclidinium, glycopyrronium, umeclidinium)

- LABA+ LAMA
- Theophyllines
  - Theophylline +LABA+LAMA
  - Purified α-1-antitrypsin (AAT) replacement therapy
- Inhaled corticosteroids (IC): budesonide, fluticasone propionate, fluticasone furoate, beclomethasone, ciclesonide
  - IC+LABA
  - IC+LAMA
  - IC+LABA+LAMA
  - IC+ Theophylline
- Phosphodiesterase 4 (PDE4) inhibitors (Roflumilast)
  - PDE4 inhibitor+LABA
  - PDE4 inhibitor+LAMA
  - PDE4 inhibitor+LABA+LAMA
  - N-acetylcysteine (NAC)
- Antibiotics
  - Macrolides
  - Quinolones
- Other_____specify

Additionally, the compliance of the patient will be described for each of the study progress visits through frequency distribution:

- Complies with treatment
- Does not comply with treatment
- Probably complies with treatment.

Using the Pearson's Chi-squared test or the Fisher's exact test for 2x2 tables or likelihood ratio for mXn tables, the study will examine whether there are statistically significant differences in the use of each of the treatments and the compliance of the patient according to the different analysis groups.

8.2.3.5 Vaccination history

The absolute and relative frequencies of patients who have a vaccination history of the following will be given:

- Pneumococcal vaccination
- Influenza vaccination

In the subpopulation of patients with pneumococcal vaccination, the frequency

distribution will be presented according to the type of pneumococcal vaccine:

- ✓ Polysaccharide
  - 1 dose
  - 2 doses
  - 3 doses
  - 4 doses
  - No. of doses unknown
- ✓ Conjugate
  - History of influenza vaccination, in the same year in which the conjugate vaccine is received

The study will look at whether there are statistically significant differences in the patient's vaccination history according to the severity of COPD, using the significance level test.

8.2.3.6 Disease-related costs

The mean, standard deviation, median, minimum, maximum, IR and $CI_{95\%}$ of the costs derived from the following will be shown:

- Hospital admission and cost of exacerbations
- Treatment

The Student's t test, one-way ANOVA or its non-parametric equivalents, the Mann-Mann U test or Kruskal-Wallis H test, will be used to determine if statistically significant differences are observed in the disease-related costs according to the severity of COPD and type of patient (exposed/unexposed).

For the subpopulation of vaccinated patients, the related costs per patient and year will be calculated in the pre-vaccination/post-vaccination period.

In order to determine the impact of vaccination with PCV13 on the disease-related costs, paired data comparisons will be made between (related cost patient $year_{\_pre\_PCV13}$ vs. related cost patient $year_{\_post\_PCV13}$), using the paired Student t-test or its non-parametric equivalent, the Wilcoxon test.

8.2.3.7 Quality of life questionnaires

8.2.3.7.1 ST. GEORGE'S Respiratory Questionnaire

To study the patient's quality of life, the abbreviated Saint George's Respiratory Questionnaire (SGRQ-C) was used. This questionnaire is self-administered. The SGRQ consists of 50 items, where 10 of them are multiple choice and 40 are true or false. This instrument is divided into three domains:

a) ***Symptoms,*** which consists of eight items and refers to all symptoms presented due to lung disease; these include cough, sputum production, dyspnea or shortness of breath or breathlessness and wheezing, as well as duration, frequency and severity.

b) ***Activity***, containing 16 true or false questions and refers to activities that are limited due to dyspnea

c) ***Impacts***, which has 26 items and refers to other situations or aspects related to social or psychological functioning affected by the respiratory problems that may alter the patient's lifestyle.

The sum of the three components gives us the total Quality of Life score. Each item in the questionnaire corresponds to a weight or score (Appendix 1) depending on the option chosen by the subject; for the true-false questions, only those with a true response have a score. The score corresponding to each subject is calculated by sub-scales. For the *Symptoms* component, the scores obtained from all the items in part 1 (questions 1 to 8) are added together, divided by 662.5, and multiplied by 100. In *Activity*, the score obtained in section 2 and section 6 are added (questions 11 and 15), divided by 1209.1 and multiplied by 100. *Impacts* is calculated with the sum of the scores of sections 1, 3, 4, 5 and 7 (questions 9, 10, 12, 13, 14, 16 and 17), divided by 2117.8, and multiplied by 100. The total results from the sum of the score of the three categories and the division of this sum by 3989.4, multiplied by 100. The score ranges from 0 to 100%. The lower the percentage, the higher the quality of life and vice versa: the higher the percentage, the lower the quality of life.

The change in the quality of life of the patients according to the Saint George's questionnaire will be studied, presenting the main measures of central tendency and dispersion (mean, standard deviation, median, minimum, maximum, IR and 95%CI), both for the total score obtained and for the three domains of Symptoms, Activity and Impacts.

We will explore whether there are statistically significant differences in the quality of life of patients depending on the severity of COPD and the type of patient using the Student's t-test or its non-parametric equivalent Mann-Whitney U test, depending on the distribution of the variables.

We will examine whether there has been a significant change over time in quality of life, both for the total sample of evaluable patients and in each of the subpopulations established based on the severity of COPD and the type of patient, using the paired Student's t-test or its non-parametric equivalent, the Wilcoxon test.

8.2.3.7.2 CAT

Questionnaire used to measure the impact COPD (chronic obstructive pulmonary disease) is having on the patient's wellbeing and daily life. The answers and test score can be used by the patient and the healthcare professional to help improve the management of the COPD and get the greatest benefit from treatment.

The study will look at the change in the quality of life of the patients according to the CAT questionnaire, presenting the main measures of central tendency and dispersion (mean, standard deviation, median, minimum, maximum, IR and 95%CI), for the total score obtained as the sum of the scores obtained in the 8 items that compose it.

We will study whether there are statistically significant differences in the quality of life of patients depending on the severity of COPD and the type of patient using the Student's t-test or its non-parametric equivalent Mann-Whitney U test, depending on the distribution of the variables.

We will study whether there has been a significant change over time in quality of life, both for the total sample of evaluable patients and in each of the subpopulations established based on the severity of COPD and the type of patient, using the paired Student's t-test or its non-parametric equivalent, the Wilcoxon test.

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11 APPENDICES

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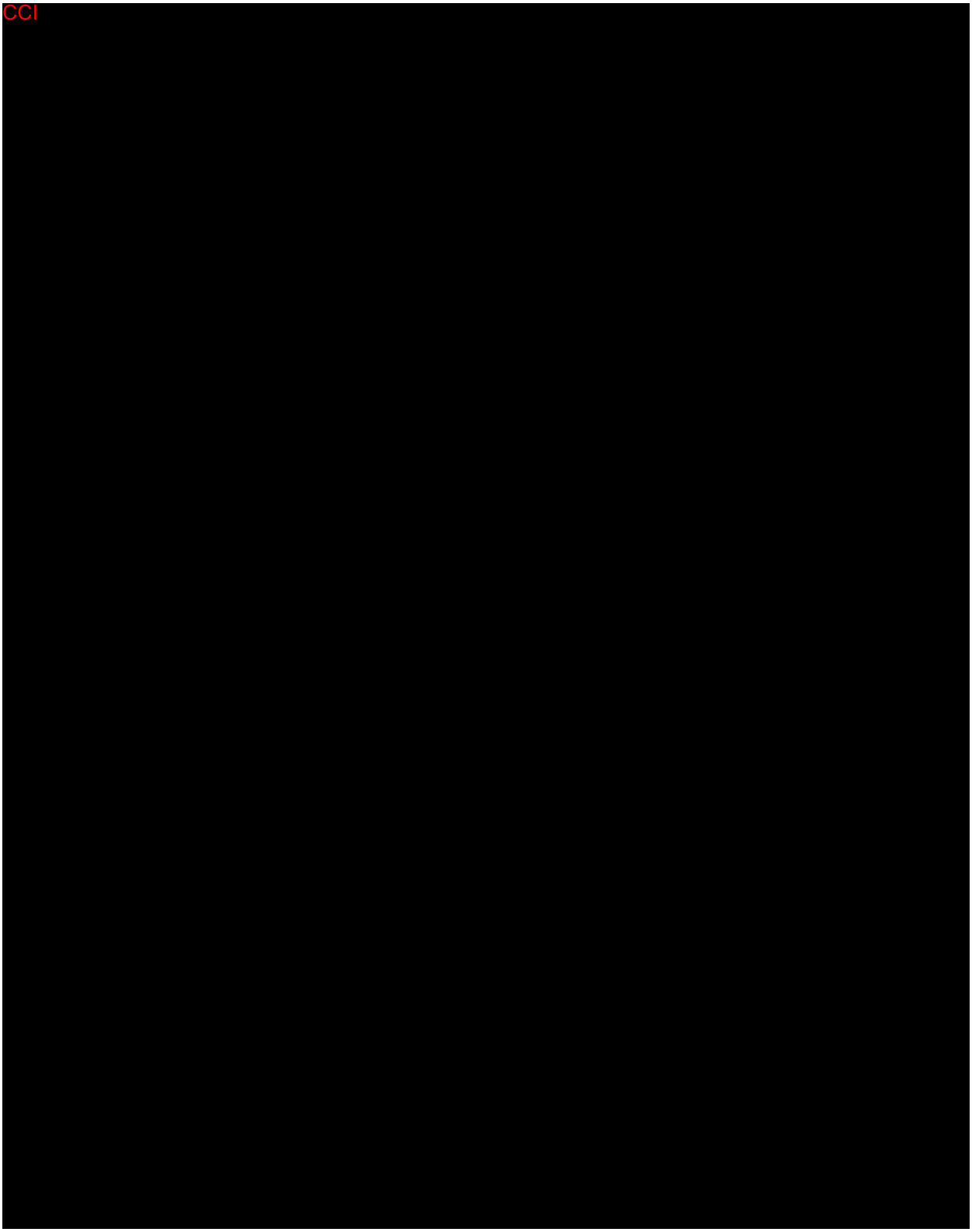

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