STATISTICAL ANALYSIS PLAN

Significance of puLmonary embolIsm in COPD Exacerbations

Short title: SLICE

ClinicalTrials.gov Number: NCT02238639

Supported by:
Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal

Protocol Version Number: 5.0

03 SEP 2018

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LIST OF ABBREVIATIONS

AE	*Adverse Event*
AR	*Adverse Reaction*
CI	*Confidence Interval*
COPD	*Chronic Obstructive Pulmonary Disease*
CRF	*Case Report Form*
CT	*Computed Tomographic*
DVT	*Deep Vein Thrombosis*
FEV_1	*Forced Expiratory Volume in one second*
ITT	*Intention-To-Treat*
PE	*Pulmonary Embolism*
PP	*Per Protocol*
PROBE	*Prospective Randomized Open, Blinded Endpoint*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAR	*Serious Adverse Reaction*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
SLICE	*Significance of puLmonary embolIsm in COPD Exacerbations*
V/Q	*Ventilation/Perfusion*
VTE	*Venous Thromboembolism*

VERSION HISTORY

Version	Version Date	Updated Part	Change*	Reason	Author
00	01/09/2014	all	Creation		Alfonso MURIEL and David JIMÉNEZ
01	16/05/2015	all	Addition	Inclusion of clinically relevant non-major bleeding as a secondary safety event	David JIMÉNEZ
02	07/11/2015	all	Addition	Inclusion of breastfeeding as an exclusion criterion	David JIMÉNEZ
03	10/02/2016	all	Modification	Modification of the end point “Readmission”	David JIMÉNEZ
04	21/09/2016	all	Modification	Clarification of the definition “Initial suspicion of PE”	David JIMÉNEZ
05	03/09/2018	all	Modification	New sample size calculation	Alfonso MURIEL

**Change:*

A: Addition

M: Modification

D: Deletion

1. INTRODUCTION

As stated in the summary of the rational in the protocol version 5 dated 3rd September 2018:

Chronic obstructive pulmonary disease (**COPD**) is a leading cause of morbidity and mortality worldwide and represents a huge economic burden for the healthcare system. COPD patients may suffer from exacerbations, defined as acute worsening of respiratory symptoms that results in additional therapy. COPD exacerbations are independent predictors of mortality in COPD and also drive disease progression, with approximately 25% of the lung function decline attributed to exacerbations.

The exact prevalence of PE in unexplained exacerbations of COPD is unclear based on the current data. Over the past decade, several studies have reported the prevalence of venous thromboembolism (**VTE**) in COPD, primarily from hospitalized patients. However, due to the heterogeneities in race, sample size, study design, research setting, and enrollment criteria, there were remarkable differences in reported data among these studies.

In patients with clinical suspicion of PE, there are some data suggesting that some PE diagnoses are less severe, and these patients might not benefit from anticoagulation therapy. For instance, in the PIOPED study, the prevalence of PE was 10% in patients with a nondiagnostic ventilation/perfusion (**V/Q**) scan and a low clinical probability of PE. Nevertheless, such patients have a low-3-month thromboembolic risk provided they have no proximal deep vein thrombosis (**DVT**). This highlights the important point that not all PEs are clinically important, especially if the main site for potential recurrence is free of clots. Particularly for patients with COPD exacerbations, some PE might be clinically unimportant, and the risk of submitting a patient with a clinically insignificant PE to anticoagulant treatment might outweigh the benefit.

Data from randomized controlled trials regarding the clinical effectiveness of an active search for PE in patients who have unexplained exacerbations of COPD are lacking. We hereby propose comparing health outcomes in patients with unexplained exacerbations of COPD who required hospital admission and who will be randomly assigned to an active search for PE with the use of D-dimer and computed tomography (**CT**) pulmonary angiogram, or to usual care.

The objectives of this Statistical Analysis Plan (**SAP**) are:

- To clearly define all variables, end points/outcomes, parameters, thresholds used for the statistical analyses.
- To define strategies employed regarding missing data on end points and possibly on adjustment variables.
- To describe statistical methods performed during the analyses.
- To define the populations of patients used during the analyses.

2. TRIAL DESIGN AND OBJECTIVES

2.1 Type of study

- Typology: comparison of two strategies of care
- Experimental design: investigator-initiated, phase III, prospective, multicenter, randomized (1:1), open-label with blind end-point evaluation (**PROBE**), parallel-group trial
- Planned intervention: active search for pulmonary embolism
- Control: usual care
- NCT (clinicaltrials.gov): NCT02238639

2.2 Sample size and power consideration

Previous studies have shown short-term rates of death, thromboembolic events, or readmission of approximately 40% at day 90 among patients who required hospital admission because of an exacerbation of COPD (1, 2). An estimated 355 participants will be needed in each trial group to detect a clinically important 10% absolute reduction in the primary outcome (i.e., from 40% to 30%) with 80% power at 5% significance level. The 10% reduction was based on consultation with primary and secondary care colleagues (general practitioners and pulmonologists) who considered a 10% reduction to be small but clinically important. Since an interim analysis showed that 3% of patients were lost to follow-up, the Steering Committee anticipated a 5% loss to follow-up. This inflated each study group to 373 patients, giving 746 patients in total.

2.3 Randomization

In a patient with unexplained exacerbations of COPD requiring hospital admission, randomization should occur in the first 24 hours after admission. The trial will use a computer-generated randomization scheme. Randomization will be stratified by center and, within the centers, performed in blocks of 4 and 6 to ensure balanced distribution of the management groups. Randomization will be

performed centrally via the Internet (www.estudioslice.org), and management allocation will be concealed from all investigators.

2.4 Study design

- Population of patients who will benefit the study results: patients with unexplained exacerbations of COPD requiring hospital admission
- Number of centers: 18 centers in Spain
- Study length: inclusion = 48 months; participation = 3 months (Day 90 +/- 7 days).
- Visit schedule: Cf. section 3 protocol version 5 dated 3rd September 2018.

2.5 Objectives and end points

2.5.1 Primary objective

- To demonstrate the clinical benefits of an active strategy for the diagnosis and treatment of PE compared to usual care in patients with unexplained exacerbations of COPD who require hospital admission.

2.5.2 Primary end points

Primary efficacy end point

- Clinical composite endpoint of death from any cause, non-fatal (recurrent) symptomatic VTE, or readmission for COPD exacerbation within 90 days after enrollment.

Primary safety end point

- Major bleeding within 90 days after enrollment.

2.5.3 Secondary objectives

- To assess the prevalence of PE in patients with unexplained exacerbations of COPD who require hospital admission.

- To identify those clinical variables associated with a diagnosis of PE in patients with unexplained exacerbations of COPD who require hospital admission.
- To determine the positive predictive value of D-dimer testing for the diagnosis of PE in patients with unexplained exacerbations of COPD who require hospital admission.

2.5.4 Secondary end points

Secondary efficacy end points

- Death from any cause within 90 days after enrollment.
- Nonfatal (recurrent) symptomatic VTE within 90 days after enrollment.
- Need of readmission for COPD exacerbation within 90 days after enrollment.
- Length of hospital stay.

Secondary safety end points

- Clinically relevant non-major bleeding within 90 days after enrollment.
- Serious adverse events (**SAE**) within 90 days after enrollment.

2.5.5 Ancillary objectives

- To perform a cost-effectiveness analysis comparing both strategies (i.e., active search for PE versus usual care).

2.5.6 Definition of end points

Confirmation of **(recurrent) symptomatic PE** requires symptoms of PE and a new or an extension of a previous intraluminal-filling defect in (sub)segmental or more proximal branches on PE-protocol chest CT pulmonary angiography. Confirmation of **(recurrent) symptomatic DVT** requires symptoms of DVT and the following criteria: 1) In the absence of previous DVT investigations at baseline, a non-compressible venous segment on ultrasonography; 2) if there

were previous DVT investigations at baseline, abnormal lower limb CCUS where compression had been normal; or, if previously non-compressible, a substantial increase (≥4 mm) in diameter of the thrombus during full compression.

Major bleeding is defined according to the guidelines of the International Society of Thrombosis and Haemostasis (3), as acute clinically overt bleeding associated with one or more among the following: a decrease in hemoglobin of 2 g/dL or more, a transfusion of two or more units of packed red blood cells, bleeding that occurs in at least one of the following critical sites (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal), bleeding that is fatal (defined as a bleeding event that the central independent committee adjudicate as the primary cause of death or contributing directly to death) and bleeding that necessitates surgical intervention.

A bleeding event is classified as a **clinically relevant non-major** bleeding event if it is overt (i.e., is symptomatic or visualized by examination) not meeting the criteria for major bleeding, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life.

Adverse event (AE): any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication/procedure, whether or not considered related to the study medication.

Adverse reaction (AR): all untoward and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product"

means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication/procedure qualify as adverse reactions.

Serious adverse event: an event that fulfils one or more of the following criteria:

- Fatal.
- Immediately life-threatening.
- Results in persistent or significant disability/incapacity.
- Requires or prolongs in-patient hospitalization.
- Is a congenital anomaly/birth defect.
- Any other reason representing a significant hazard comparable to the criteria mentioned above.

Serious adverse reaction (SAR): an adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

Suspected unexpected serious adverse reaction (SUSAR): a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product).

Length of hospital stay: defined as the interval (in days) from diagnosis of PE at the emergency department to discharge (i.e., date of discharge minus date of diagnosis).

3. STATISTICAL METHOD

3.1 General considerations

The statistical analysis will be performed by the statistician of the Biostatistics Department at Ramón y Cajal Hospital, under the supervision of the Coordinating Investigator. The strategy for the design and the analysis will be made in compliance with the CONSORT statement (http://www.consort-statement.org/).

All statistical analyses will be carried out with SAS (SAS Institute, Cary, NC, USA) and R (R Core Team. R Foundation for Statistical Computing, Vienna, Austria) softwares. A p-value inferior to 0.05 will be considered as statistically significant unless stated otherwise.

3.2 Missing data

Missing data won't be replaced, and analysis will be made on all evaluable patients. In addition, sensitivity analyses will be made on the primary and secondary end points using worst case and/or multiple imputations (see 3.5.3). Missing or incomplete data for survival analyses will be managed by censored data analyses.

3.3 Protocol deviations

All protocol deviations will be listed and summarized in a blinded manner before the database lock preliminary to the final statistical analysis. Deviations will be classified as minor or major. The process will enable the population inception for the analyses (global, randomized, per-protocol).

The description of the protocol deviations may be found in section 7 of the SAP.

3.4 Baseline demographics and clinical characteristics

Baseline characteristics will be summarized by strategies on the randomized population. Only descriptive analyses will be provided (no inferential statistics).

Results will be presented as mean ± one standard deviation if the variable follows a normal distribution and median [interquartile range] in case of other distribution. For the qualitative or categorical quantitative variables, results will be presented as numbers (proportions in %).

3.5 Hypotheses and statistical methods

3.5.1 Hypothesis

The primary aim of the trial is to demonstrate superiority in the intent-to-treat analysis of an active search for PE over usual care with regard to primary end point as the composite of death from any cause, non-fatal (recurrent) symptomatic VTE, or readmission for COPD exacerbation within 90 days after enrollment (90daycomposite).

The null and alternative hypotheses are as follows:

H_0: $90daycomposite_{intervention} = 90daycomposite_{control}$

H_1: $90daycomposite_{intervention} \neq 90daycomposite_{control}$

3.5.2 Statistical analysis

The principal analysis of the primary and secondary end points will be performed on the evaluable patients from the randomized population with application of the intent-to-treat principle. In addition, safety analyses will be performed in the safety analysis set, which included all the patients in the control arm, and all the patients in the intervention arm who had received a D-dimer testing. The alpha level of the two-sided test is set to 0.05. The primary efficacy and safety end points will be analyzed by means of a two-sided chi-square test of proportions. The results for the primary end points will be also stratified according to center (4). Secondary end points will not be adjusted for multiplicity, and therefore these results should not be used to infer intervention

effects (5). Kaplan-Meier survival curves until 90 days after randomization will be compared with a log-rank test. For each end point, results will be presented as the relative risk (intervention:control) for percentages and difference (intervention-control) for means, and its 95% confidence interval (**CI**).

Cost-effectiveness will not be analyzed for the main presentation of the SLICE study but will be performed later as an ancillary study.

3.5.3 Sensitivity analyses

For the intention-to-treat population, sensitivity analyses will be made on the primary and secondary end points using worst case and/or multiple imputations. In addition, the analysis of the primary and secondary end points will be replicated in the per protocol population.

3.6 Subgroup analyses

Several analyses will be run by subgroups, as follows:

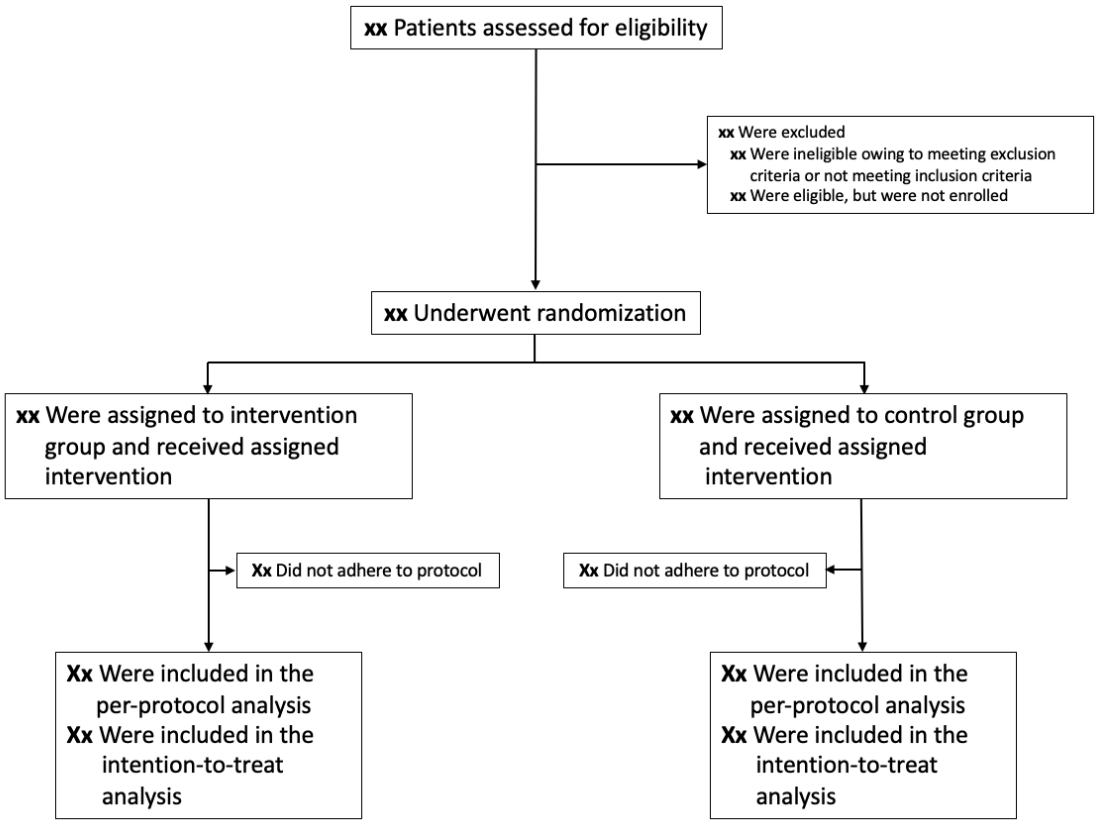
Subgroup	**End point**
Age <75 ≥75 years	Primary and secondary end points
Sex Women Men	Primary and secondary end points
COPD severity FEV_1 ≥80% 50% ≤FEV_1 <80% 30% ≤FEV_1 <50% FEV_1 <30%	Primary and secondary end points
Hospital size <300 beds ≥300 beds	Primary and secondary end points
Season	Primary and secondary end points

Autumn Winter Spring Summer	

FEV_1: volumen espiratorio máximo en el primer segundo.

4. POPULATION TO BE ANALYZED

4.1 Flow diagram



4.2 Definition of populations

4.2.1 Global included population

All included patients having a free and informed written consent adjudicated as conform.

4.2.2 Randomized population

All randomized patients. Following the intention-to-treat principle, patients will be analyzed according to the strategy assigned by the randomization.

4.2.3 Per-protocol population

All randomized patients without any major protocol deviation. The major protocol deviations were pre-specified prior to unblinding treatment codes and database lock for analyses. (Cf. table in section 7).

4.3 Populations used in analyses

The populations for statistical analysis will be:

Population	**Analysis**
Global set	Descriptive purpose (study inclusion flowchart)
Randomized set	*With intention to treat principle:* Demography and clinical characteristics at baseline All analyses *With 'as-treated' principle:* Safety analyses
Per protocol set	Sensitivity analyses

5. DATA REVIEW

5.1 General considerations

- The investigator completes patient's data in an electronic Case Report Form (**eCRF**).
- The Clinical Research Associate (**CRA**) visualizes the data remotely.
- Data management and queries will be done under the responsibility of SH Medical.
- Moreover, a data-management plan, written jointly by the data-manager, the coordinating investigator, the scientific director and the statistician, will be implemented.
- After correcting the errors shown after data-management plan implementation, a data review meeting will be held to validate the entire database with the investigator.
- The database will be frozen for statistical analysis.
- The statistical analyses will be done by the personnel of the Biostatistics Department at Ramón y Cajal Hospital in charge of the study.

5.2 Blind review

In order to ensure the smooth progress of the blind review meeting, some descriptions of the data will be done:

- Missing data on variables and consistencies.
- Chronological order.
- "Hat" variables of variables of type "if yes, please specify" or "if no, please specify".
- Missing visit.

6. REFERENCES

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5. https://www.fda.gov/media/102657/download

7. PROTOCOL DEVIATIONS

Category	Excluded from
Inclusion/exclusion criteria	
Informed consent not available/not done/declined	All
Anticoagulant therapy at the time of hospital admission	All
Other exclusion criteria violated	PPS
COPD not objectively confirmed	PPS
Management strategies	
Randomization more than 24 hours after admission	PPS
D-dimer testing more than 24 hours after randomization	PPS
Missing CT pulmonary angiogram in patients with a positive D-dimer (intervention group)	PPS
End points	
Missing data on primary end points	PPS
Missing data on secondary end points	PPS

PPS: leading to the exclusion from the per-protocol population analysis.