PROTOCOL

Significance of puLmonary embolIsm in COPD Exacerbations

Short title: SLICE

ClinicalTrials.gov Number: NCT02238639

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SUMMARY OF CHANGES

Document	Date of issue	Summary of change
Revised protocol 05	03 September 2018	Incorporates amendment 05
Amendment 05	03 September 2018	This amendment was written to: Include the new sample size calculation[a]
Revised protocol 04	10 February 2016	Incorporates amendment 04
Amendment 04	10 February 2016	This amendment was written to: Modify the end point "readmission"[b] Clarify the definition of initial suspicion of PE[c]
Revised protocol 03	10 February 2016	Incorporates amendment 03
Amendment 03	10 February 2016	This amendment was written to: Modify the end point "readmission"[b] Clarify the definition of initial suspicion of PE[c]
Revised protocol 02	07 November 2015	Incorporates amendment 02
Amendment 02	07 November 2015	This amendment was written to: Include breastfeeding as an exclusion criterion
Revised protocol 01	16 May 2015	Incorporates amendment 01
Amendment 01	16 May 2015	This amendment was written to: Include clinically relevant non major bleeding as a safety event[d]
Original protocol	01 September 2014	Not applicable

[a]New sample size calculation:

After the last interim analysis, the DSMB increased the expected evaluability rate from 75% to 95%. Therefore, the final sample size decreased to 746 patients (373 per arm).

[b]Primary efficacy outcome:
“Readmission for any cause” was changed by “readmission for COPD exacerbation”.

[c]Definition of initial suspicion of PE
Defined as the indication of a D-dimer testing or a multidetector computed tomography (**CT**) angiogram by the attending physician in the Emergency Department.

[d]Definition of clinically relevant non major bleeding
Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: 1) requiring medical intervention by a healthcare professional; 2) leading to hospitalization or increased level of care; or 3) prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.

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TRIAL OBJECTIVES

The objectives of the trial are:

To assess the clinical effect of an active strategy for the diagnosis and treatment of pulmonary embolism (**PE**), compared to usual care, in patients with unexplained exacerbations of chronic obstructive pulmonary disease (**COPD**) who require hospital admission.

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.

STUDY PLAN

	Screening: Visit 1 Day -1	**Enrollment: Visit 2 Day 0**	**Follow-up: Visit 3 Day 7 ± 2**	**Follow-up: Visit 4 Day 30 ± 5**	**Follow-up: Visit 5 Day 90 ± 7**
Medical history	**X**				
Demographic variables	**X**				
Physical examination	**X**		**X**	**X**	**X**
COPD diagnosis	**X**				
Inclusion and exclusion criteria	**X**				
Informed consent	**X**				
Hematology tests	**X**				
Biochemistry tests	**X**				
Coagulation tests	**X**				
Chest X-ray	**X**				
Randomization		**X**			
D-dimer		**Intervention group**			
Multidetector CT pulmonary angiogram		**Intervention group**			
ASSESSMENT OF:					
Recurrent VTE			**X**	**X**	**X**
Death			**X**	**X**	**X**
Bleeding[a]			**X**	**X**	**X**
Adverse events[a]			**X**	**X**	**X**
Length of hospital stay			**X**	**X**[b]	
Readmission			**X**	**X**	**X**

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; VTE, venous thromboembolism.

[a]See definitions in the protocol.

[b]If hospital admission longer than 7 ± 2 days.

ABBREVIATED PROTOCOL

Title: Efficacy and safety of an active strategy for the diagnosis and treatment of acute pulmonary embolism (**PE**) in patients with unexplained exacerbations of chronic obstructive pulmonary disease (**COPD**): a randomized clinical trial.

Investigators: Multicentre.

Participating sites: Approximately 18 study centers.

Clinical phase: III

Objectives: The primary objective is to assess the benefit 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.

The secondary objective is to assess the safety 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.

Methodology: Prospective, international, multicenter, randomized (1:1), open-label with blind end-point evaluation (**PROBE**), parallel-group trial.

No. de subjects: Approximately 746 patients.

Each strategy: Approximately 373 patients.

Diagnosis and main criteria for exclusion: Patients admitted to the hospital because of COPD exacerbation. COPD exacerbation is defined as any worsening of respiratory symptoms sufficiently severe to warrant an admission to the Emergency Department in a patient with known COPD. Patients with an initial clinical suspicion of PE or deep vein thrombosis (**DVT**), a diagnosis of pneumothorax, pneumonia, or lower respiratory tract infection will be excluded from the trial.

Strategies:

Intervention group: All included patients will undergo D-dimer testing. A negative plasma D-dimer value (defined as a D-dimer level below the manufacturers assay threshold) will rule out pulmonary embolism, and no further examination will be performed. For patients with a positive D-dimer value, a thoracic multidetector helical computed tomography scan will be performed.

Control group: All included patients will undergo standard clinical management of their exacerbations, as deemed appropriate by the attending physician.

Criteria for efficacy:

Primary end point

- Clinical composite endpoint of all-cause mortality or venous thromboembolism recurrence or need for COPD readmission within 90 days.

Secondary end points

- All-cause mortality within 90 days.
- Venous thromboembolic recurrence within 90 days.
- Need for COPD readmission within 90 days.
- Length of hospital stay.

Criteria for safety:

Primary end point

- Major bleeding within 90 days.

Secondary end points

- Clinically relevant non-major bleeding within 90 days.
- Serious adverse events within 90 days.

Statistical analysis: Intent-to-treat (**ITT**) analysis on superiority of an active strategy for the diagnosis and treatment of PE in patients with unexplained exacerbations of COPD requiring hospital admission.

Primary criteria

The primary ITT analysis on the primary end points will be carried out by a two-sided chi-square test on proportions. In addition, the 95% confidence interval on the relative risks will be presented.

Secondary efficacy criteria

The secondary ITT analysis on the secondary efficacy end points will be carried out by a two-sided chi-square test on proportions. In addition, the 95% confidence interval on the relative risks will be presented. The survival status during 90 days follow-up will be analyzed by showing Kaplan-Meier curves, and management differences will be compared by means of log-rank test.

Secondary safety analysis

Safety end points will be tabulated by management group. All (dichotomized) end points will be analyzed by chi-square test on proportions, and the 95% confidence interval on the relative risks will be presented. In addition, continuous safety monitoring will be done by the Data and Safety Monitoring Board.

Interim analysis

Interim analysis will be made by the Data Center after recruitment of 50% of the total number of patients. Theses analyses will be made in order to allow sample size reassessment or early stop of the trial for efficacy or futility.

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LIST OF ABBREVIATIONS

AE	*Adverse Event*
AR	*Adverse Reaction*
CCUS	*Complete Compression UltraSound*
COPD	*Chronic Obstructive Pulmonary Disease*
CRF	*Case Report Form*
CT	*Computed Tomographic*
DSMB	*Data Safety Monitoring Board*
DVT	*Deep Vein Thrombosis*
FEV_1	*Forced Expiratory Volume in one second*
FVC	*Forced Vital Capacity*
GCP	*Good Clinical Practice*
GP	*General Practitioner*
ICH	*International Conference on Harmonization*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
ITT	*Intention-To-Treat*
PE	*Pulmonary Embolism*
PP	*Per Protocol*
PROBE	*Prospective Randomized Open, Blinded Endpoint*
QALY	*Quality-Adjusted Life Year*
SAE	*Serious Adverse Event*
SAR	*Serious Adverse Reaction*
SEPAR	*Sociedad Española de Neumología y Cirugía Torácica*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
SLICE	*Significance of puLmonary embolIsm in COPD Exacerbations*
V/Q	*Ventilation/Perfusion*
VTE	*Venous Thromboembolism*

1. BACKGROUND

1.1 Study justification

Chronic obstructive pulmonary disease (**COPD**) is a leading cause of morbidity and mortality worldwide and represents a huge economic burden for the healthcare system (1-3). COPD patients may suffer from exacerbations, defined as acute worsening of respiratory symptoms that results in additional therapy (4, 5). 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 (6).

The most common triggers of exacerbations are infections and air pollution, but noninfectious factors were thought to cause approximately 20% of acute exacerbations of COPD in a hospital study (7). In addition, other frequent clinical conditions may mimic the symptoms of COPD exacerbations, including congestive heart failure, pneumonia, pneumothorax, pleural effusion and pulmonary embolism (**PE**) (8).

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 (9-12). 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. Tillie-Leblond et al evaluated PE in a series of 197 consecutive patients with COPD and exacerbation of unknown origin, and found that the frequency of PE was 25% (13). However, that study was performed in a highly selected subgroup of patients. Rutschmann et al. showed that the prevalence of PE and deep vein thrombosis (**DVT**) in patients who were admitted to Emergency Department and with acute exacerbations of moderate-to-severe COPD was only 3.3% and 2.2%, respectively (14). In fact, a recent meta-analysis found a lower

prevalence of PE of 16% in exacerbations of compared with previous studies (15).

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 (16). For instance, in the PIOPED study (17), 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 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 (18).

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. The objective of the Significance of Pulmonary Embolism in COPD Exacerbations (**SLICE**) is to compare health outcomes in patients with unexplained exacerbations of COPD who required hospital admission and who were randomly assigned to an active search for PE with the use of D-dimer and computerized tomography (**CT**) pulmonary angiogram, or to usual care.

1.2 Hypothesis

For patients with unexplained exacerbations of COPD who required hospital admission, an active search for PE with the use of D-dimer and, if positive, contrast-enhanced, PE-protocol, multidetector CT will improve health outcomes, compared to usual care.

1.3 Objectives

The primary objective of the SLICE trial is:

- 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.

Secondary objectives of the SLICE trial are:

- 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.

Primary end point

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.

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.

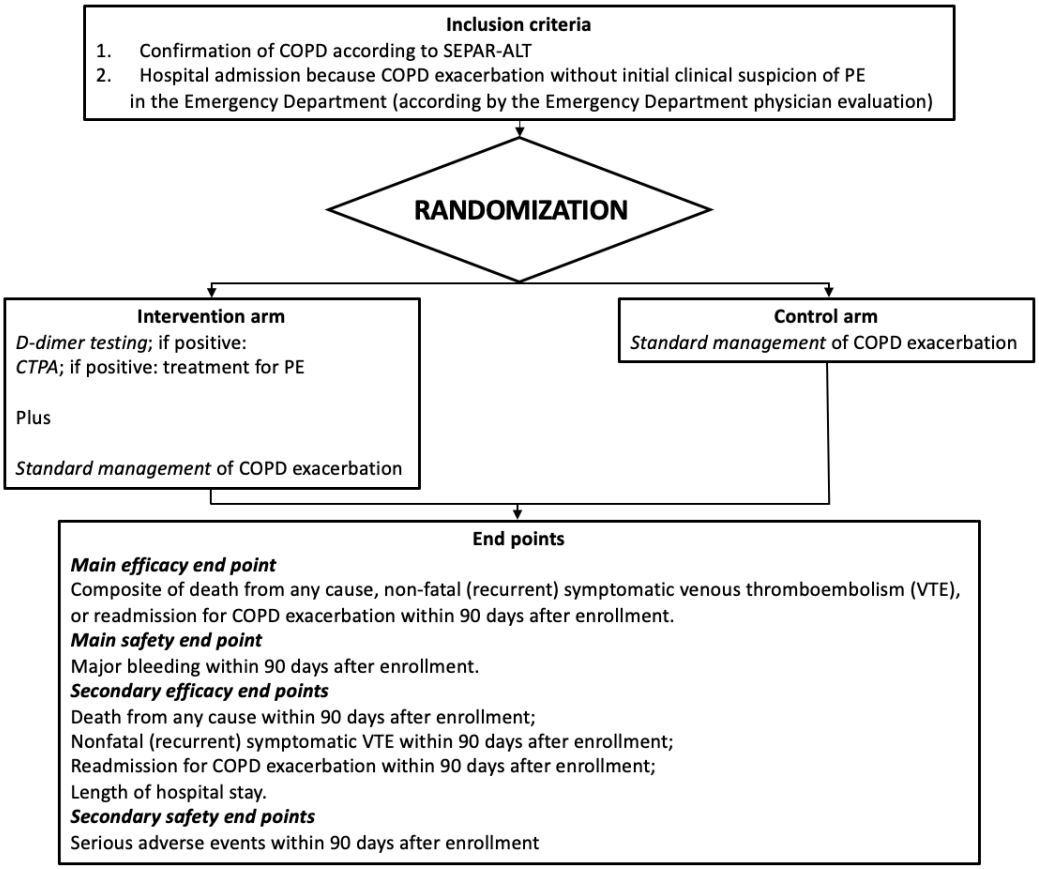
Secondary safety end points

- Clinically relevant non-major bleeding within 90 days after enrollment.
- Serious adverse events within 90 days after enrollment.

2. METHODOLOGY

2.1 Design

SLICE is an investigator-initiated, phase III, prospective, multicenter, randomized (1:1), open-label with blind end-point evaluation (**PROBE**), parallel-group trial comparing the efficacy and safety of an active search for PE (intervention group) with usual care (control group) in patients with unexplained exacerbations of COPD who require hospital admission (ClinicalTrials.gov identifier NCT02238639).



2.2 Setting

Emergency, Respiratory and Internal Medicine Departments in 18 Spanish University Hospitals.

2.3 Study subjects

*Inclusion criteria (**Table 1**)*

Patients are required to fulfill the following inclusion criteria:

1. Confirmation of COPD according to SEPAR-ALT criteria: post-bronchodilator forced expiratory volume in one second (**FEV1**)/forced vital capacity (**FVC**) < 0.7.
2. Hospital admission because COPD exacerbation without initial clinical suspicion of PE in the Emergency Department (according by the Emergency Department physician evaluation).

*Exclusion criteria (**Table 2**)*

A patient will be excluded from the study if ANY of the following apply:

1. Contraindication to multidetector CT pulmonary angiography (allergy to intravenous contrast medium, or renal failure defined as a creatinine clearance less than 30 mL/min, according to the Cockroft-Gault formula [**appendix 1**]).
2. Refusal to give informed consent.
3. Pregnancy, or breast feeding.
4. Life expectancy less than 3 months.
5. Anticoagulant therapy at the time of hospital admission.
6. Diagnosis of pneumothorax, or pneumonia (fever [temperature >38ºC two times at least 12 hours apart], and purulent sputum, and new infiltrate in chest X-ray) at the time of hospital admission.
7. Diagnosis of lower respiratory tract infection (fever [temperature >38ºC two times at least 12 hours apart], or increased sputum volume and increased sputum purulence) at the time of hospital admission.
8. Indication of invasive mechanical ventilation at the time of hospital admission.
9. Participation in any other investigational drug or device study in the past four weeks.
10. Geographic inaccessibility that precludes follow-up.

2.4. 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.

2.5 Study procedures

All patients will receive standard clinical management (usual care) for their COPD exacerbation according to the clinician's preference and local standards.

Intervention group

Patients in the intervention group will have blood samples collected from an antecubital vein, and will undergo D-dimer testing within 12 hours after randomization. Cut-off levels for defining elevated D-dimer will be defined by the Department of Clinical Chemistry at each participating site. For patients with a negative D-dimer, a diagnosis of PE will be ruled out. For patients with a positive D-dimer, a contrast-enhanced, PE-protocol, multidetector CT will be performed. CT pulmonary angiography results will be categorized as positive for PE if an intraluminal filling defect is seen in (sub)segmental or more proximal branches, and will be considered negative if no filling defect is observed. Scans will be considered technically inadequate only if main or lobar pulmonary vessels are not visualized. Though not mandatory, the protocol suggests the use of complete lower limb compression ultrasonography (**CCUS**) to detect concomitant DVT for patients with isolated subsegmental PE.

If the diagnosis of PE is confirmed, patients will receive anticoagulant treatment according to guideline recommendations: parenteral anticoagulation (i.e.,

unfractionated heparin, low-molecular-weight heparin, or fondaparinux) overlapped and followed by vitamin K antagonists; or parenteral anticoagulation followed by dabigatran or edoxaban; or monotherapy with apixaban or rivaroxaban (19).

Control group

Patients in the control group will receive standard clinical management (usual care) for their COPD exacerbation according to the clinician's preference and local standards.

After hospital discharge, all patients (in the intervention and control arms) will be treated according to the national and international recommendations for the management of stable COPD (1, 2).

2.6 Criteria for termination of the trial

Premature termination of the trial may happen under the following conditions:

- Occurrence of unknown or increase of known adverse events that render the risk/benefit ratio unacceptable.
- Interim analysis indicates reason.
- An unacceptable high number of SAEs.
- Ethical justification.
- Recruitment rate is too low such that it is unrealistic to consider completion of the trial within an acceptable period of time.
- Decision of the authorities.

2.7 Definition of study end points

Efficacy

The primary efficacy end point is the composite of death from any cause, non-fatal (recurrent) symptomatic VTE, or readmission for COPD exacerbation within 90 days after enrollment.

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.

Secondary efficacy end points include:

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

Safety

The primary safety end point is major bleeding within 90 days after enrollment.

Major bleeding is defined according to the guidelines of the International Society of Thrombosis and Haemostasis (20), 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.

Secondary safety end points include:

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

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).

A central independent adjudication committee whose members are unaware of management allocation will adjudicate all suspected study outcomes during the study period.

Causality and expectedness

The relationship of each adverse event to the trial intervention must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial intervention. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

Procedures for recording AEs

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study intervention, will be recorded on the e-CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study intervention, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study intervention as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

The relationship of AEs to the study intervention will be assessed by a medically qualified investigator. Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect.

Reporting procedures for SAEs

All SAEs must be reported to the Steering Committee or designated organization within one working day of discovery or notification of the event. The Steering Committee or designated organization will perform an initial check of the report, request any additional information. All SAE information must be recorded on an SAE forms and faxed to the Steering Committee or designated organization. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and faxed to the Steering Committee or designated organization.

It may be appropriate that some SAEs do not require immediate reporting, but this must be justified. Justification might be determined, for example, by admission to hospital, or prolongation of hospitalization, where this is to be expected in the underlying disease or condition.

Type and duration of follow-up of subjects after SAEs

SAEs will be followed until resolved or considered stable. All SAE case report forms will be included in the e-CRF and will trigger an alert at the Data and Safety Monitoring Board.

2.8 Surveillance and follow-up

The study requires the following scheduled visits (see Section 3. Study procedures for details): enrollment, 1 week, 1 month, and 3 months after randomization. Additional visits are performed if new symptoms and/or signs of VTE or bleeding occur during the study period or anytime it is deemed necessary by the investigator. Clinical examination, laboratory and diagnostic imaging are performed if the patient develops symptoms or signs suggestive of (recurrent) VTE.

2.9 Cost-effectiveness analysis

The study will calculate the incremental cost-effectiveness ratio (**ICER**) according to the following formula:

$$\frac{\text{Cost}_{\text{active strategy}} - \text{Cost}_{\text{usual care}}}{\text{Effectiveness}_{\text{active strategy}} - \text{Effectiveness}_{\text{usual care}}}$$

where $\text{Cost}_{\text{active strategy}}$ and $\text{Cost}_{\text{usual care}}$ represent costs associated with the active strategy and usual care, respectively; while $\text{Effectiveness}_{\text{active strategy}}$ and $\text{Effectiveness}_{\text{usual care}}$ represent the clinical consequences as quality-adjusted life year (**QALY**) in both arms.

2.10 Statistical plan

Statistical design

SLICE is an investigator-initiated, phase III, prospective, international, multicenter, randomized (1:1), open-label with blind end-point evaluation, parallel-group trial comparing the efficacy and safety of an active search for PE (intervention group) with usual care (control group) in patients with unexplained exacerbations of COPD who require hospital admission

Null and alternative hypotheses

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

Analyses

The intention-to-treat (**ITT**) analysis dataset will be the source of data for all analyses. This will include all randomized participants regardless of actual receipt or compliance with the intervention. Safety analyses will also be performed in the safety analysis set, which will consist of all participant who receive D-dimer testing. In addition, a per-protocol (**PP**) analysis of all patients randomized and managed without major protocol violations/deviations will be carried out; this dataset will support sensitivity analyses to complement the primary ITT analyses.

Protocol deviations (minor) refer to incidents involving non-compliance with the protocol that are unlikely to have a significant impact on the

participant's rights, safety or welfare, or on data integrity. Examples of deviations include forgetting to complete a procedure at a specified visit or a patient receiving an inadequate management strategy.

Protocol violations (major) refer to more serious incidents involving non-compliance with the protocol that may result in significant effect on the participant's rights, safety, or welfare or data integrity. Protocol violations could result in the participant being excluded from the eligibility analysis and/or result in the participant being discontinued from the trial. Examples of violations include non-compliance with inclusion/exclusion criteria or inadequate risk classification.

Efficacy analyses

The primary ITT analyses will be carried out by the chi square test on proportions, or the Fisher exact test. In addition, the corresponding 95% on the relative risks will be presented.

Safety analyses

The secondary ITT analyses will be carried out by the chi square test on proportions, or the Fisher exact test. In addition, the corresponding 95% on the relative risks will be presented.

Patient accountability

Disposition of patients, patient status and patients excluded from ITT will be summarized by group (intervention and control). Descriptive statistics for primary reason for patient's withdrawal will be also presented by group (intervention and control) as well as a list of these patients sorted by group (intervention and control).

Drop-outs

Reasons for drop-outs in each group (intervention and control) will be displayed. A detailed list of drop-out patients will also be provided.

Baseline characteristics

Baseline characteristics will be tabulated and comparability / differences between the treatment groups will be examined by means of descriptive statistics.

Subgroup analysis

The following subgroup analyses will be carried out: age (<75 versus ≥75), sex (women versus men), COPD severity (FEV_1 ≥80%, 50% ≤FEV_1 <80%, 30% ≤FEV_1 <50%, and FEV_1 <30%), hospital size (<300 beds versus ≥300 beds) and season (autumn, winter, spring, summer).

Interim analysis

We will conduct an interim analysis after recruitment of 50% of the study population. To preserve an overall type I error rate of 0.05 for the entire trial, the O'Brien-Fleming type boundary (alpha of 0.005) will be used for early trial stoppage. Futility will be assessed with conditional power, an approach that quantifies the probability of rejecting the null hypothesis of no effect. Stopping rule for futility will be based on a conditional power less than 20%.

Handling of missing data

Missing data won't be replaced, and analysis will be made on all evaluable patients. If necessary, 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.

Sample size

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 (21, 22). 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.

3. STUDY PROCEDURES

The study is divided in three distinct periods: screening (visit 1), enrollment and in-hospital period (visits 2 and 3), and follow-up period (visits 4 and 5).

3.1 Informed consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information and the opportunity to question the Investigator, their general practitioner (**GP**) or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorized to do so by Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

3.2 Screening and eligibility assessment

Start of period: When a given patient is admitted to the hospital because unexplained COPD exacerbation.

End of period: Twenty-four hours after decision to admit to hospital.

Setting: Emergency Department.

e-CRF entries:

- Demographics: date of birth, gender
- Medical history
- Concomitant medication
- Physical examination: height, weight, heart rate, systolic blood pressure, temperature, respiratory rate, arterial oxyhemoglobin saturation
- Inclusion and exclusion criteria
- Laboratory tests: hemogram, biochemistry, and hemostasis
- Chest X-ray
- Informed consent

3.3 Enrollment and in-hospital period

Start of period: When a given patient is randomized.

End of period: When a given patient is discharged.

Setting: Hospital.

e-CRF entries:

- Randomization group: intervention or control group
- D-dimer test results (Intervention group)
- CT pulmonary angiogram result (Intervention group)
- Symptomatic new or recurrent VTE
- Death
- Primary cause of death
- Major bleeding

- Clinically relevant non-major bleeding
- Serious adverse events
- Treatment for COPD exacerbation
- Hospital discharge

At day 7, it will be recorded if the patient was discharged or not. Hospital discharge is defined as end of hospitalization or if the patient is transferred for long-term rehabilitation.

3.4 Subsequent assessments

Visits: Day 30 ± 5 and Day 90 ± 7.

Setting: Outpatient basis.

e-CRF entries:

- Recording of concomitant medications
- Symptomatic new or recurrent VTE
- Death
- Primary cause of death
- Major bleeding
- Clinically relevant non-major bleeding
- Serious adverse events
- Rehospitalization
- Primary cause of rehospitalization

3.5 End of trial assessment

The end of trial is the date of the last visit of the last participant.

Visits: Day 30 ± 5 and Day 90 ± 7.

Setting: Outpatient basis.

e-CRF entries:

- Recording of concomitant medications
- Symptomatic new or recurrent VTE
- Death
- Primary cause of death
- Major bleeding
- Clinically relevant non-major bleeding
- Serious adverse events
- Rehospitalization
- Primary cause of rehospitalization

4. STUDY ORGANIZATION

4.1 Steering Committee

The Steering Committee will meet periodically to assess the progress, provide scientific input on the protocol and possible amendments as well as on the "state of the art" and any ongoing development during the study which could have consequences for the performance of the study, and address policy issues and operational aspects of the protocol and recommendations of the Data safety Monitoring Board (**DSMB**).

4.2 Investigators

Participating investigators will be responsible for enrollment of patients who meet the inclusion and none of the exclusion criteria, obtaining informed consent, and management of patients randomized to the intervention. Participating investigators will not be allowed to manage patients randomized to usual care.

4.3 Adjudication

A committee of two clinical experts from Ramon y Cajal Hospital (Spain) who will be unaware of the study-group assignments will confirm all outcomes and classify the cause of all deaths as due to PE, due to COPD, due to bleeding, or due to another cause.

4.4 Data Safety Monitoring Board

The DSMB will consist of independent clinicians and statisticians. At regular intervals the DSMB will review safety and outcome data provided by SH Medical and report to the Chairman of the Steering Committee. The DSMB will also conduct analyses of data at the request of the Steering Committee.

In order to assure patient safety, the DSMB will be provided in a timely fashion with data on safety end points in periodic cumulative reports.

4.5 Data management

Study data will be entered into the electronic case report forms (e-CRFs), embedded in the SLICE database by the authorized principal investigators or sub-/co-investigators (www.estudioslice.org). The data-management of the study database maintenance will be performed by the CRO (SH Medical) according to its own Standard Operating Procedures. Data evaluated by the DSMB will be extracted periodically from the trial database. After data base lock, the database will be transferred to the Chairman.

4.6 Central readings

Image interpretations for all radiological tests except venous ultrasonography will be based on agreement of two certified readers in the SLICE trial who were from Ramón y Cajal Hospital. Readers will be unaware of all clinical information and of the study arm.

5. CALENDAR

It is estimated that the trial duration will be 4 years. After legal approvals, it is expected that enrollment will begin the last trimester of 2014.

6. LEGAL ISSUES

The trial will be carried out:

- In compliance with the protocol.
- In compliance with Conventions of the Council of Europe on Human Rights and Biomedicine, UNESCO Declaration.
- In accordance with the Declaration of Helsinki, version as of Oct. 1996, the International Conference on Harmonization (**ICH**) Harmonized Tripartite Guideline for Good Clinical Practice (**GCP**) and in accordance with applicable Spanish regulatory requirements.

-*Informed consent*: Ethical and legal requirements in accordance with international declarations (e.g., Declaration of Helsinki, Conventions of the Council of Europe on Human Rights and Biomedicine, UNESCO Declaration) will be fulfilled in this study. The person who informs the subject should be a physician. An informed consent document that includes both information about the trial and the consent form will be prepared and given to the subject. This document will comply with all local requirements and the requirements set out in GCP. The document must be in a language understandable to the subject and must specify who informed the subject. After reading the informed consent document, the subject is asked to give consent in writing.

The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject or the subject's legally authorized representative (means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in research). A copy of the signed consent document must be given to the subject or the subject's legally authorized representative. The original signed consent document will be retained by the investigator (a copy may be requested by the sponsor).

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors appointed by the Sponsor, or by appropriate IEC/IRB members or by inspectors from regulatory authorities. Should a protocol amendment be made, the subject consent form and subject information form may need to be revised to reflect the changes to the protocol. It is the responsibility of the investigator to ensure that an amended consent form is reviewed and received approval/favorable opinion from the ICE or IRB, and that it is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the amendment.

-*Confidentiality*: Individual subjects medical information obtained as a result of this study is considered confidential (according to Spanish regulations, LOPD 15/1999) and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this trial are to be available for inspection on request by the participating physicians, the Sponsor’s representatives, by the IEC/IRB and the regulatory health authorities.

-*Insurance cover*: The Sponsor will take out no-fault insurance cover for all subjects included in the trial. The conditions of this insurance cover are available to the investigators on request. The investigator can make this information available to subjects on request.

-*Adverse events*: Following the subject’s written consent to participate in the study, which must be obtained before any screening procedures, all SAEs must be collected, including those thought to be associated with clinical study

procedures. All SAEs must be reported to the Sponsor (Hospital Ramón y Cajal) within 24 hours of awareness.

-*Publication policy*: The Sponsor is dedicated to supporting the process of free exchange of relevant scientific information. Any publication of the results of this trial must be consistent with the publication policy of the Sponsor (Hospital Ramón y Cajal) and Executive Committee. Some general rules are laid down below.

This study represents a joint effort between the Sponsor and the investigators. A publication policy will be presented by the Writing Committee and approved by the Steering Committee:

- All investigators and members of these committees agree to abide by the policy.
- Agreement on authorship of the main paper -Conditions for secondary manuscripts.
- It is foreseen that the Study Chairman, Co-chairman and the Writing Committee will prepare a manuscript plan to ensure timely and high-quality presentation and publication of the study results and provide this to the Sponsor for due consideration. Local publication of part(s) of the results is not allowed before the publication of the main study.
- The Study Chairman and Co-chairman will submit any manuscript to members of the Steering Committee for comment and release prior to the actual submission to a learned society or scientific journal.
- After this, Investigators may submit secondary papers, but these should be provided according to the publication policy for review and approval.

One week should be allowed for review by the Sponsor of abstracts planned to be submitted to a learned society, and 3 weeks should be allowed for review of papers planned to be submitted to a scientific journal.

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Table 1. Inclusion criteria

Inclusion criteria
Previous diagnosis of COPD: post-bronchodilator forced expiratory volume in one second (**FEV1**) / forced vital capacity (**FVC**) < 0.7
Hospital admission because COPD exacerbation without initial clinical suspicion of PE in the Emergency Department (according to the Emergency Department physician evaluation)

Definition of initial suspicion of PE

Defined as the indication of a D-dimer testing or a multidetector computed tomography (**CT**) angiogram by the attending physician in the Emergency Department.

Table 2. Exclusion criteria

Exclusion criteria
Unable to provide informed consent
Contraindication to a contrast-enhanced, PE-protocol, multidetector computerized tomography **(CT)** pulmonary angiogram: allergy to intravenous contrast medium, or renal failure defined as a creatinine clearance < 30 mL/min, based on the Cockroft-Gault equation
Anticoagulant therapy at the time of hospital admission
Pregnancy, or breast feeding
Life expectancy of less than 3 months
Diagnosis of pneumothorax, or pneumonia (fever [temperature ≥ 38ºC], and purulent sputum, and new infiltrate in chest X-ray)
Diagnosis of lower respiratory tract infection (fever [temperature ≥ 38ºC], increased sputum volume and/or increased sputum purulence).
Indication of invasive mechanical ventilation at the time of hospital admission
Inability to comply with study assessments

Appendix 1. Cockroft-Gault formula

CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72)

CrCl (female) = CrCl (male) × 0.85