CLINICAL STUDY PROTOCOL

CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM. THE COPE STUDY.

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SYNOPSIS

EudraCT/IND Number:

Protocol Number:	CRU_UniPg_2017
Study Title:	CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM
Short Title:	CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM
Study Aim:	The aim of the study is to assess contemporary management strategies in terms of diagnosis, risk stratification, hospitalization and treatment in Italy and assess a) their association with in-hospital and 30-day mortality and b) their adherence to current guidelines of the European Society of Cardiology.
Study Design:	This is a prospective, non-interventional, multicenter study in patients with acute pulmonary embolism admitted to Cardiology, Emergency and Internal Medicine Departments in Italy.
Study population:	Patients with acute, symptomatic, objectively diagnosed acute pulmonary embolism (either first or recurrent pulmonary embolism) will be eligible for the study. **Inclusion Criteria** - Age ≥ 18 years - Informed consent **Exclusion Criteria** - refusal of informed consent - participation in controlled trials on pulmonary embolism As this is a non-interventional study, no additional inclusion/exclusion criteria apply. **Patient Groups** There are no formal patient groups planned. However, all analyses will be run in the overall study population and comparisons will be made among:

	- patients admitted in Cardiology, Emergency or Internal Medicine Departments; - patients at low, intermediate or high risk for death according to the 2014 ESC Guidelines.
Study Outcome events:	The co-primary study outcomes are - in-hospital death and - death at 30 days from the diagnosis of pulmonary embolism. The secondary study outcomes are: - death or clinical deterioration at 30 days from the diagnosis of pulmonary embolism. - pulmonary embolism-related death or clinical deterioration at 30 days from the diagnosis of pulmonary embolism - Adherence to current guidelines on the management of acute pulmonary embolism released by the European Society of Cardiology regarding diagnosis, risk stratification, hospitalization and treatment. The cause of death will be classified as due to: - Pulmonary-embolism - Bleeding - Cancer - Cardiovascular events other than pulmonary embolism - Unexpected death - Other non-CV causes Pulmonary embolism-related death is defined as i) death where pulmonary embolism is the most probable cause or ii) based on objective diagnostic testing performed before death or iii) as assessed at autopsy (autopsy is not mandatory). Clinical deterioration is defined as the occurrence of at least 1 of the followings: (i) the need for cardiopulmonary resuscitation; (ii) systolic blood pressure <90 mm Hg for at least 15 minutes, or

drop of systolic blood pressure by at least 40 mmHg for at least 15 minutes, with signs of end-organ hypoperfusion (cold extremities, or urinary output <30 mL/h, or mental confusion);

(iii) the need for catecholamine infusion (except for dopamine at a rate of <5 μg kg−1 min−1) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg.

Adherence to ESC guidelines 2014 will be assessed concerning:
- diagnosis
- risk stratification
- treatment
- global management (the composite of diagnosis, risk stratification and treatment).

Safety Study Outcomes:	The primary safety outcome is: - Major bleeding according to ISTH definition, occurring up to 30 days from diagnosis of pulmonary embolism. Major bleeding, defined (as per ISTH guidelines), as acute clinically overt bleeding (i.e. bleeding that is visualized by examination or radiologic imaging) associated with one or more of the following: • decrease in hemoglobin of 2 g/dl or more; • transfusion of 2 or more units of packed red blood cells; • bleeding that occurs in a critical site [intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal]; • bleeding that is fatal; • bleeding that necessitates acute surgical intervention. Major bleeding events will also be further sub-classified as life-threatening or non-life threatening.

	The secondary safety outcome is: - Clinically relevant non-major bleeding Clinically relevant non-major bleeding event is defined as acute clinically overt bleeding that does not meet the criteria for major and consists of: • any bleeding compromising hemodynamics; • spontaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause; • intramuscular hematoma documented by ultrasonography; • epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes; • hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures; • hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention; • or any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.
Study visits:	Patients will be evaluated at the time of diagnosis of pulmonary embolism (baseline), at discharge and at 30 days (±4) from index pulmonary embolism. For some patients discharge may occur beyond 30 days from index pulmonary embolism. These patients will have two study assessments only (baseline and 30 days).
Planned Sample Size:	In order to - achieve information on the clinical course of high, intermediate and low-risk patients with acute pulmonary embolism, - observe a number of patients with intermediate / low-risk pulmonary embolism who died at 30 days from diagnosis and

	adequate to evaluate around 10 variables able to possibly predict poor patients' outcome by means of logistic regression analysis expecting an incidence of death of 3% and 0.5% for patients with intermediate or low-risk pulmonary embolism, respectively, it is estimated that 2100 patients with intermediate pulmonary embolism and 2500 with low-risk pulmonary embolism should be included in the study. In the same time frame, it is estimated that around 400 patients with high-risk pulmonary embolism will be observed. The expected mortality in these patients is 10-15%. According to these estimates, we would be able to have about 100 deaths in study patients and this will empower assessment of independent predictors of death. Besides already known predictors (hypotension, right ventricle dysfunction – imaging and BNP – and increased troponin), the role of comorbidities and clinical features as well as adherence to current guidelines on pulmonary embolism (risk stratification adequate, appropriateness of acute treatment) as determinants of prognosis will be assessed. The same features will be tested as predictors of death or clinical deterioration.
Statistical Analysis:	The impact of clinical characteristics on death and on death or clinical deterioration will be evaluated by means of univariate and multivariable logistic regression models. Variables with a p-value<0.10 at the univariate analysis will be considered for the multivariable model and covariates will be selected for the final model by means of a step-ward selection procedure. A time-to-event analysis will be also performed. Kaplan-Meier plots will be generated where applicable to characterize the risk over time for each outcome. Time-to-event variables will be analysed by Cox proportional hazard regression model presenting hazard ratios and corresponding 95% confidence intervals and p-values for comparisons of the pre-defined subgroups.
Study Sites and Location:	About 200 study centers in Italy are planned to participate in the study. Study centers will be composed as it follows: Cardiology (around 80 sites)

	Emergency (around 40 sites) Internal Medicine (around 80 sites). The patient recruitment period consists of 24 months, followed by a 1 month follow up period per patient, summing up to 25 months of study duration.

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RATIONALE AND BACKGROUND

Pulmonary Embolism

Acute pulmonary embolism is a common and potentially life-threatening disease (1-4). The incidence is estimated to be 0.5 to 1.5% person-years (1). The estimated short-term mortality in patients with acute pulmonary embolism ranges from less than 1% to more than 30% during the hospital stay (2-4). Recent guidelines recommend to tailor diagnosis (according to hemodynamic status and pre-test clinical probability assessment), hospitalization (intensive care unit vs. medical wards vs. short hospital stay) and acute treatment (thrombolysis vs. anticoagulant treatment) based on the estimated risk for short-term death (5-6). However, recent studies suggested that the clinical course and the clinical management of the disease in terms of duration of hospitalization and treatment have been changing over the last years (7). Thus, the assessment of the contemporary clinical management of patients with acute pulmonary embolism across different specialties would be of crucial value.

The guidelines

According to latest guidelines, the first step in the management of patients with suspected pulmonary embolism is the assessment of hemodynamic status (6).

Patients with acute pulmonary embolism and shock or hemodynamic impairment have a short term risk for death varying from 30 to more than 50% and should be categorized as at 'high risk' for death. These patients should rapidly proceed to a definitive diagnosis by CT angiography if the patient is not critically ill. In critically ill patients, the absence of right ventricle dysfunction at bedside echocardiography exclude the diagnosis of pulmonary embolism as the cause of hemodynamic impairment. This diagnostic algorithm is based on clinical sense more than on evidence from clinical trials. In those hemodynamically unstable patients candidates to percutaneous revascularization, the diagnosis could be confirmed by pulmonary angiography performed at the time of the invasive procedure. Moreover, the role of other bedside ultrasound examinations in these patients could be of help, and in particular ultrasonography of the lower limbs.

As shown by several studies, the diagnostic work-up in hemodynamically stable patients should be driven by pre-test clinical probability, as assessed by means of either validated rules or clinical gestalt. In patients with a low pre-test probability, a negative d-dimer will exclude the diagnosis of pulmonary embolism. This strategy allows avoidance of expensive examination for the healthcare and exposure to radiation in about 30% of the overall population with suspected pulmonary embolism evaluated in a standard emergency department, with a failure rate at 3 months (diagnosis of fatal or non-fatal venous thromboembolism) of 0.14% (95% CI 0.05 to 0.41) (8). All patients with high pre-test probability should proceed to CT angiography. The 3-month failure rate of a negative CT angiography in patients with high

pre-test probability is about 1.5% (9-10). In these patients, ultrasonography of the lower limbs could reduce the failure rate. Whether ventilation/perfusion lung scan or pulmonary angiography may further reduce this rate remains undefined.

Risk stratification should be used in hemodynamically stable patients for decision making concerning hospitalization and treatment. Those patients who are hemodynamically stable and have low risk of death according to clinical scores have an estimated risk for death at 30 days of about 1% (11). The need for the assessment of right ventricle dysfunction or injury (as assessed by echocardiography, CT angiography or troponin levels) in these low-risk patients is controversial (12). In these patients, regular hospitalization or out-patient management (hospitalization <48 hours), as reported by one randomized clinical trial, were associated with similar 3-month mortality, recurrent venous thromboembolism or major bleeding (13). Based on these results and on those from cohort studies, low-risk patients are candidates to short-term hospital stay or home treatment. The additional prognostic value of BNP over the HESTIA clinical model for the selection of patients candidates to outpatient management appeared to be limited (14).

Patients who are hemodynamically stable but have evidence of right ventricle dysfunction or injury should be admitted as the risk for death in the short term is about 2-fold that of patients with no signs of right ventricle overload (OR 1.94 95% CI 1.23-3.06 for echocardiography, OR 1.64 95% CI 1.06-2.52 for CT-angiography, OR 5.90 95% CI 2.68-12.95 for increased troponin) (intermediate risk) (6). Nevertheless, in clinical practice risk stratification by means of the above mentioned measures seems to be performed in less than half of the patients with acute pulmonary embolism (3).

Early reperfusion by thrombolytic therapy should be given in hemodynamically unstable patients to reduce mortality (OR 0.53, 95% CI 0.32-0.88) (15). Percutaneous manoeuvre for pulmonary revascularization should be reserved for hemodynamically unstable patients with absolute contraindication for systemic thrombolysis or in centers with specific expertise with these procedures.

Anticoagulant treatment reduces recurrent venous thromboembolism by more than 90% and should be given to all patients with acute pulmonary embolism and no absolute contraindications (6). Initial anticoagulation with heparin (mainly low-molecular weight) followed by vitamin K antagonists (VKAs) has been the standard treatment for the majority of the patients with venous thromboembolism for several decades (7). Long term treatment with low-molecular weight heparin is usually preferred in patients with cancer-associated venous thromboembolism (6).

Direct oral anticoagulants (DOACs) with the potential for administration in fixed doses with no need for monitoring have been evaluated in phase III clinical trials for the treatment of venous thromboembolism. These agents have been developed for clinical use according to 2 different regimens for the treatment of venous thromboembolism (6,16-21). The ‘single drug approach’ includes potential for parenteral anticoagulation for less than 48 hours and the use of initial increased doses of apixaban (10mg twice

daily for 7 days) or rivaroxaban (15 mg twice daily for 3 weeks) followed by a maintenance dose (5 mg twice daily for apixaban and 20 mg once daily for rivaroxaban). The 'sequential' regimen includes potential for parenteral anticoagulation for at least 5 days followed by a maintenance dose of dabigatran (150 mg twice daily or edoxaban 60 once daily). A direct comparison of the efficacy and safety of these regimens in patients with acute pulmonary embolism has not been performed. Whether initial parenteral anticoagulation is associated with an improved clinical outcome in the short term in patients with acute intermediate- or high-risk pulmonary embolism is undefined. A meta-analysis of studies in patients presenting with acute pulmonary embolism randomized to receive treatment with DOACs or conventional treatment (11,539 patients) showed a 2.4% and a 2.6% recurrence rate of venous thromboembolism at 6-12 months in patients randomized to DOACs or conventional anticoagulation, respectively (OR 0.89, 95% CI 0.7-1.12; I-squared 0%) (22). However, data on pulmonary embolism severity according to clinical scores, right ventricle dysfunction or injury were not reported in these large studies except for a subgroup of 1000 patients with acute pulmonary embolism included in the Hokusai trial. About 30% of patients in this subgroup showed evidence of right ventricle dysfunction at computed tomography or by means of increased BNP levels (23). In a sub-analysis of the Einstein PE study more than 50% of patients was at low risk for death as assessed by means of the simplified PESI score (24). Thus, it remains to be addressed whether NOACs can be an appropriate treatment for the overall severity spectrum of patients with acute pulmonary embolism.

Moreover, the real-life adherence to current guidelines on the management of patients with acute pulmonary embolism concerning diagnosis, risk stratification and treatment (including physicians preferences on anticoagulation therapies) is undefined. Final, risk factors for adverse outcome in patients with low- or intermediate-risk need to be better evaluated.

Comparison with recent or ongoing non-interventional studies

Several large cohort studies and registries have been completed or are currently ongoing in patients with acute venous thromboembolism.

The PREFER in VTE disease registry (Prevention of Thromboembolic Events –European Registry in Venous Thromboembolism) was a prospective, observational, multicentre registry performed in seven European countries to assess the characteristics and the management of patients with venous thromboembolism, the use of health care resources, as well as the costs for 12 months treatment following a first-time and/or recurrent VTE. Three hundred and eighty one centres enrolled 3,464 patients with a symptomatic, objectively confirmed first time or recurrent acute VTE defined as either distal or proximal deep vein thrombosis, pulmonary embolism or both. However, PREFER in VTE was not focused on patients with acute pulmonary embolism and on the short-term management and course of

the disease. As a consequence, limited acute phase data and their influence on mortality and on decision making will be available from this study.

The Global Anticoagulant Registry in the Field of Venous Thromboembolism Event (GARFIELD – VTE) is a perspective, multicentre, international registry of patients with newly diagnosed deep vein thrombosis and/or pulmonary embolism aimed at describing acute and long-term (up to 3 years) management and outcomes in patient populations representative of everyday clinical practice in more than 20 countries. The primary objective of this registry is to determine the extent to which the treatment of venous thromboembolism varies in the real-world setting and to assess the impact of such variability on clinical and economic outcomes.

The RIETE registry, an ongoing, international, multicentre, prospective cohort of consecutive patients presenting with symptomatic venous thromboembolism (deep-vein thrombosis, pulmonary embolism, or both) is aimed at evaluating the clinical course of patients with acute venous thromboembolism treated with an anticoagulant. RIETE is mainly run in Angiology and Internal medicine Departments and not in the Cardiology or Emergency settings.

ETNA-VTE is a non-interventional, non-randomized single arm study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe. This study has similar strengths and limitations as the previously described registries.

AIM OF THE STUDY

The aim of the study is to assess contemporary management strategies in terms of diagnosis, risk stratification, hospitalization and treatment in Italy and assess

a) their association with in-hospital and 30-day mortality and

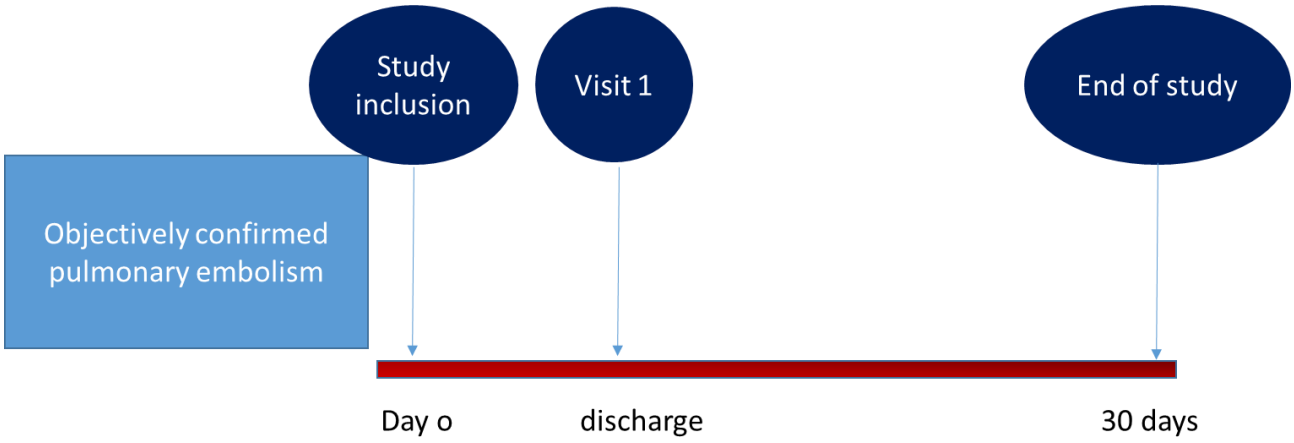
b) their adherence to current guidelines of the European Society of Cardiology (6)

EXPERIMENTAL DESIGN

Study Design

This is a prospective, non-interventional, multicenter study in patients with acute pulmonary embolism admitted to Cardiology, Emergency and Internal Medicine Departments in Italy.

Figure: Study design



Setting

In order to include the overall spectrum of patients with pulmonary embolism, the study will be performed in Cardiology, Internal Medicine and Emergency Departments.
Consecutive patients meeting the inclusion/exclusion criteria will be included in the study.
Diagnostic work-out, risk stratification strategies and treatment strategies are at the discretion and responsibility of the attending physician. Physicians will be encouraged to prescribe all medications according to the usual standard of care.

STUDY POPULATION

Eligibility Criteria

Patients with acute, symptomatic, objectively diagnosed acute pulmonary embolism (either first or recurrent pulmonary embolism) will be eligible for the study.
Patients will be included after screening for inclusion and exclusion criteria and the signature of the informed consent form. Patients will be encouraged to ask any questions regarding the study aims and procedures, to be answered straightforwardly by one of the Investigators.

Criteria for objective diagnosis of acute pulmonary embolism are :
- an intraluminal filling defect at CT angiography or
- a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scan (VQ scan)
- a perfusion defect of at least 75% of a segment with a normal chest X Ray
- Intermediate probability perfusion lung scan associated with objective diagnosis of deep vein thrombosis in patients with symptoms of acute pulmonary embolism
- Right ventricle dysfunction in patients with cardiogenic shock.
- an intraluminal filling defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter at pulmonary angiogram
- a proximal deep vein thrombosis in a patient with symptoms of acute pulmonary embolism.

Patients with acute, symptomatic, objectively diagnosed acute pulmonary embolism (either first or recurrent pulmonary embolism) will be eligible for the study.

Inclusion Criteria

- Age ≥ 18 years
- Informed consent

Exclusion Criteria

- refusal of informed consent
- participation in controlled trials on pulmonary embolism

As this is a non-interventional study, no additional inclusion/exclusion criteria apply.

A simultaneous participation in any other non-interventional study/registry is allowed. No other explicit exclusion criteria exist to avoid selection bias and to allow for documentation of routine clinical practice.

Patient Groups

There are no formal patient groups planned.

However, all analyses will be run in the overall study population and comparisons will be made among

- patients admitted in Cardiology, Emergency or Internal Medicine Departments;
- patients at low, intermediate or high risk for death according to the 2014 ESC Guidelines (6)

STUDY OBJECTIVES AND OUTCOMES

Primary Objectives

This study, in patients with acute PE admitted in Cardiology, Emergency and Internal Medicine Departments, has two co-primary objectives:

- assess predictors of in-hospital mortality
- assess predictors of 30-day mortality.

These items will be evaluated in the overall study population and compared between patients admitted in every-day clinical practice in Cardiology, Emergency or Internal Medicine Departments.

Secondary Objectives

Secondary objectives of this study, in patients with acute pulmonary embolism in every-day clinical practice in Cardiology, Emergency and Internal Medicine Departments, are as it follows:

- assess predictors for death or clinical deterioration at 30 days with specific attention to adherence to current guidelines on the management of acute pulmonary embolism released by the ESC.
- assess predictors for pulmonary embolism-related death or clinical deterioration at 30 days with specific attention to adherence to current guidelines on the management of acute pulmonary embolism released by the ESC.
- assess contemporary clinical management strategies in every-day clinical practice in Cardiology, Emergency and Internal Medicine Departments with specific attention to
    - Diagnostic strategies

- Use of risk stratification procedures
- Treatment strategies in the acute in-hospital phase across the full spectrum of severity of patients with acute pulmonary embolism.

- Adherence to current guidelines on the management of acute pulmonary embolism released by the European Society of Cardiology concerning diagnosis, risk stratification, hospitalization and treatment.

These items will be evaluated in the overall study population and compared between patients admitted in every-day clinical practice in Cardiology, Emergency or Internal Medicine Departments.

Primary study outcome

The co-primary study outcomes are

- in-hospital death and
- death at 30 days from the diagnosis of pulmonary embolism.

Secondary study outcomes

The secondary study outcome are:

- death or clinical deterioration at 30 days from the diagnosis of pulmonary embolism.
- pulmonary embolism-related death or clinical deterioration at 30 days from the diagnosis of pulmonary embolism
- Adherence to current guidelines on the management of acute pulmonary embolism released by the European Society of Cardiology regarding diagnosis, risk stratification and treatment.

For all patients, the cause of death will be reported as assessed by the attending physician and classified as:

- Unexpected
- Pulmonary-embolism related
- Due to bleeding
- Due to cardiovascular events other than pulmonary embolism
- Due to cancer
- Other non-cardiovascular causes

Pulmonary embolism-related death is defined as i) death where pulmonary embolism is the most probable cause or ii) based on objective diagnostic testing performed before death or iii) as assessed at autopsy (autopsy is not mandatory).

Documentation on study outcome events (in-hospital and 30 day deaths) will be centrally collected in order to allow an independent adjudication committee to definitely adjudicate the cause of death.

Clinical deterioration is defined as the occurrence of at least 1 of the following (25):

(iv) the need for cardiopulmonary resuscitation;

(v) systolic blood pressure <90 mm Hg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes, with signs of end-organ hypoperfusion (cold extremities, or urinary output <30 mL/h, or mental confusion);

(vi) the need for catecholamine infusion (except for dopamine at a rate of <5 μg kg−1 min−1) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg.

Adherence to ESC guidelines 2014 will be assessed concerning:

- diagnosis
- risk stratification
- treatment
- global management (the composite of diagnosis, risk stratification and treatment)

Six process indicators were selected, based on recommendations from ESC guidelines (6). The indicators are:

(1) Time from diagnosis to initiation of anticoagulant treatment. The time of CT angiography or of lower limbs ultrasonography will be considered as time of diagnosis.

(2) Number of diagnostic tests applied and their order within the diagnostic work-up based on estimated pre-test probability of pulmonary embolism.

(3) Type, number and timing (within 24 hours) of tests performed for prognostic assessment.

(4) Use of systemic thrombolysis or percutaneous manoeuvre associated with intravenous heparin for at least 48 hours in hemodynamically unstable patients.

(5) home treatment or short hospital stay (<48 hours) in patients with low-risk pulmonary embolism

(6) The number, dose and sequence of antithrombotic agents according to currently validated regimens.

Safety Objective

The safety objective of this study is to collect and evaluate real-world safety data on bleeding events in patients with acute pulmonary embolism.

Safety Outcomes

The primary safety outcome is:

- Major bleeding according to ISTH definition, occurring up to 30 days from the diagnosis of index pulmonary embolism.

Major bleeding, defined (as per ISTH guidelines), as acute clinically overt bleeding (i.e. bleeding that is visualized by examination or radiologic imaging) associated with one or more of the following:

- decrease in hemoglobin of 2 g/dl (1.2 mmol/L) or more;
- transfusion of 2 or more units of packed red blood cells;
- bleeding that occurs in at least one critical site [intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal];
- bleeding that is fatal;
- bleeding that necessitates acute surgical intervention

Major bleeding events will also be further sub-classified as life-threatening or non-life threatening. A life-threatening major bleed is defined as a bleeding event that is either intracranial or is associated with haemodynamic compromise requiring intervention.

The secondary safety outcome is:

- Clinically relevant non-major bleeding.

Clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major and consists of:

- any bleeding compromising hemodynamics;
- spontaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause;
- intramuscular hematoma documented by ultrasonography;
- epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;
- hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;
- hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
- or any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.

STUDY PROCEDURES

Patient information and informed consent

Before being admitted to the study, the subject must consent to participate after full information about the nature, scope, and possible consequences of the study.

The documents must be in a language understandable to the subject and must specify who informed the subject. A copy of the signed informed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

Moreover, a letter will be provided to every patient to inform his/her primary physician about the subject's participation in the study - provided the subject agrees to the primary physician being informed.

After reading the informed consent document, the subject must give consent in writing.

No personal patient's contact details (like mobile phone number) will be recorded in the study data-base.

Visits schedule and follow-up

Patients will be evaluated at the time of diagnosis of pulmonary embolism (baseline), at discharge (FU 1) and at 30 days (±4) from index pulmonary embolism (FU 2).

For some patients, discharge may occur beyond 30 days from index pulmonary embolism. These patients will have two study assessments only (baseline and 30 days).

At baseline, patient status at presentation (hemodynamics, respiratory failure, etc.), the relevant patient history (including concomitant medications), diagnostic strategies and assessments for risk stratification will be recorded.

Telephone call is allowed for the 30-day follow-up using standardized interview (Appendix 1).

The Table outlines the data to be collected at different timings. The data sources used in this study are clinical records, and data from telephone interviews.

The patient is asked within the ICF, whether he/she is willing to get contacted by the treating physician for standardized telephone interviews and needs to agree to provide contact details as long this procedure is in line with the clinical practice

Table: Study schedule

	Visit 1	Visit 2	Visit 3
	Enrollment	**Discharge**	**30-days**
			from diagnosis (± 4 days)
Informed consent	x		
Demography	x		
Medical History	x		
Pulmonary embolism Diagnosis (a)	x		
Physical Examination	x		x
Vital Signs (b)	x	x	x
Serum chemistry (c)	x		x
Hematology	x (d)		x (e)
Eligibility criteria	x		
Inclusion/Exclusion criteria	x		
Risk stratification procedures (f)	x	x	
Hospitalization (g)	x	x	
Assess study outcomes (i.e. death, clinical deterioration, bleeding) (h)		x	x
Prior and Concomitant Medications	x		

(a) i.e. Symptoms of pulmonary embolism, number and sequence of confirmatory tests
(b) i.e. Blood pressure, Heart Rate, Oxygen saturation, Respiratory rate, urinary output.
(c) i.e. Total Bilirubin (Direct and Indirect), ALT, AST, ALP, Serum creatinine, Creatinine clearance (Cockcroft Gault equation)
(d) At enrollment: Hematocrit, WBC, Hb, Plts, INR, PTT, d-dimer, etc
(e) At enrollment and 4-wks: Hematocrit, WBC, Hb, Plts, etc
(f) i.e. echocardiography, cardiac enzymes, assessment at CT angiography.
(g) i.e. home-treatment or hospitalization, department of hospitalization
(h) at 4-wks telephone query of health status (alive, occurrence of efficacy and safety endpoints and AEs/SAEs) is allowed. Subjects who have new symptoms should undergo further assessment as clinically appropriate, preferably at the study site whenever feasible.

Observations and measurements

Scheduled assessments for the study are presented in the Study schedule Table. All data will be collected from information routinely recorded in the patient files/medical records or during telephone follow-up interviews. All these data are available as part of the routine treatment. All examinations performed depend on the discretion and clinical routine of the physician. No diagnostic or monitoring procedures and no examinations, laboratory tests or procedures are applied to the patients as part of this non-interventional study others than those performed as standard of care.

Baseline/Enrolment

The following data will be collected at baseline for all enrolled patients:

• Demographics i.e. Age, Gender, pregnancy or lactation

• Vital Signs i.e. Blood pressure, Heart rate, oxygen saturation in room air, saturation in oxygen, respiratory rate, hourly urinary output, Height, Weight

• Medical History (past and current status) i.e. o Relevant comorbidities present at baseline (e.g. cancer, COPD, diabetes, dyslipidemia, previous major bleedings), recent history (recent trauma or hospitalization or surgery)

• Pulmonary embolism, Diagnosis and Interventions (past and current status) i.e. o Type of past VTE (DVT or/and PE, first or recurrent), date of diagnosis, symptoms at diagnosis, etc. ; diagnostic work-out,

• Risk stratification i.e. echocardiography, clinical models, cardiac evaluation at CT angiography

• Anticoagulant treatment (agents, time of initiation, dose, duration)

• Concomitant CV and non CV treatments, including non-pharmacological treatments

• Laboratory examinations i.e. renal function, hemoglobin, cardiac enzymes.

• Other VTE-relevant patient information e.g. Bleeding disposition, Thrombocytopenia, Alcohol consumption, frailty

• Hospitalisations related to current pulmonary embolism i.e. Emergency Room, Intense Care Unit, Cardiology, Internal Medicine .

Study visit at discharge

The following data are planned to be collected at discharge:

• Date of documentation

• Vital status and Current vital signs i.e. dead/alive

• Clinical deterioration, bleeding during the hospital stay i.e. date, treatment strategies

• Anticoagulant treatment during the hospital stay i.e. agent, dose, initiation/stop date,

• Anticoagulant treatment at discharge i.e. agent, dose, initiation/stop date,

-concomitant CV and non CV treatments

Study visit at 30 days

The following data are planned to be collected at discharge:

• Date of documentation

• Vital status and Current vital signs i.e. dead/alive

• Clinical deterioration, bleeding during the hospital stay i.e. date, treatment strategies

• Anticoagulant treatment during the hospital stay i.e. agent, dose, initiation/stop date,

• Anticoagulant treatment at discharge i.e. agent, dose, initiation/stop date,

-concomitant CV and non CV treatments, including non-pharmacological treatments

• Follow-up examinations i.e. laboratories (renal function, hemoglobin, cardiac enzymes), cardiac (EKG, echocardiography, CT).

• Hospitalisations i.e. related to index pulmonary embolism or other causes

• Adverse drug reactions

Data from routine patient data collection points or telephone interviews at the respective site should be documented directly in the Medical Records and entered shortly thereafter into the eCRF.

Early Study Termination

In case a patient terminates the study early, reason for early study termination (lost to follow-up, investigator's decision, adverse events, withdrawal of consent etc.) will be recorded.

The treating physician should at least get awareness of the patient's vital status at the time of the early termination of patient participation in the study.

Withdrawal of Consent

In accordance with the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw consent for participation in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

If a patient withdraws consent to participate in the study, the investigator will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final contact with the patient. The investigator will clearly document the reason (if given) for consent withdrawal in the medical record and will complete the associated electronic case report form (eCRF) section.

Data Management

An electronic CRF system will be used for data capture.

A data management plan will be created in the study start phase and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include automated plausibility checks (e.g. range checks, conditional checks, etc.) at data entry to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous and allow for correction or confirmation by the site. Concurrent manual data review will be performed based on parameters defined in the data management plan. If necessary, queries will be manually generated within the eCRF system and followed up for resolution.

Critical fields will be defined that need to be filled in by the site prior to signing the eCRF.

Data Entry/Electronic Data Capture

Data will be collected and entered directly into the eCRF system. Each participating site will have access to the data of its own enrolled patients. All sites will be fully trained on using the on line system, including eCRF completion guidelines and other help files. Sites will be responsible for entering patient data into the secure internet-based eCRF. Investigators and other site personnel will access their account with a unique username and password. All eCRFs should be completed by designated and trained personnel, as appropriate. Each eCRF has to be reviewed and electronically signed and dated by the investigator.

File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms, and source documents. The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study that is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 10 years or according to local legislation respectively after completing the participation in the study. Documents to be archived include the patient identification list, screening log and the signed informed consent form (ICF).

STATISTICAL CONSIDERATIONS

Sample Size

In order to

- achieve information on the clinical course of high, intermediate and low-risk patients with acute pulmonary embolism,
- observe a number of cases with intermediate / low-risk PE died at 30 days from diagnosis and adequate to evaluate around 10 variables able to possibly predict poor patients' outcome by means of logistic regression analysis

expecting an incidence of death of 3% and 0.5% for patients with intermediate or low-risk, respectively, it is estimated that 2100 patients with intermediate pulmonary embolism and 2500 with low-risk pulmonary embolism should be included in the study. In the same time frame, it is estimated that around 400 patients with high-risk pulmonary embolism will be observed. The expected mortality in these patients is 10-15%. According to these estimates, we would be able to have about 100 deaths in study patients and this will empower assessment of independent predictors of death. Besides already known predictors (hypotension, right ventricle dysfunction – imaging and BNP – and increased troponin), the role of comorbidities and clinical features as well as adherence to current guidelines on pulmonary embolism (risk stratification adequate, appropriateness of acute treatment) as determinants of prognosis will be assessed. The same features will be tested as predictors of death or clinical deterioration.

The inclusion of patients in each risk category (low, intermediate and high risk for death) will be stopped when the predicted number of patients is complete. An alert signal will appear in the e-CRF once the estimated sample is completed.

Planned analyses

The following analyses are planned:

1. Final analysis on the data

2. Three data snapshots of the study data are planned and will be analysed before the final analysis will take place after data base lock:

1. Snapshot: Q4 2018

2. Snapshot: Q3 2019

3. Snapshot: Q1 2020

All analyses will contain a summary of all data plus a summary of data per patient groups.

The writing of the SAP for the study will start immediately after the finalisation of the observational plan and a version 1.0 of the SAP will be available before the start of the study. If the SAP needs to be revised for a snapshot or the final analysis, the adaptation will always be finalised and signed before the extraction of data for the respective snapshot or the final data base lock, respectively.

Statistical methodology

All variables collected in the CRFs as well as all derived parameters will be used in the statistical analysis. Categorical variables will be summarized by the number and percentage (%) of patients in each category. Continuous variables will be summarized using number of non-missing observations, mean, SD, median, first quartile and third quartile, minimum and maximum values. The 95% CIs will also be provided for selected variables.

The association of clinical characteristics with death and death or clinical deterioration will be evaluated by means of univariate and multivariable logistic and multinomial logistic regression models, respectively. Variables with a p-value<0.10 at the univariate analysis will be considered for the multivariable model and covariates will selected for the final model by means of a step-ward selection procedure.

A time-to-event analysis will be also performed. Kaplan-Meier plots will be generated where applicable to characterize the risk over time for each outcome.

Time-to-event variables will be analysed via a Cox proportional hazard regression model presenting hazard ratios and corresponding 95% confidence intervals and p-values for comparisons of the pre-defined subgroups.

Analysis of primary endpoint

For the primary endpoint, the overall rate of in-hospital deaths and deaths at 30 days from diagnosis of pulmonary embolism (including the 95% confidence interval) will be presented.

Furthermore, the following subgroups will be descriptively compared:

- patients admitted in Cardiology, Emergency or Internal Medicine Departments
- patients at low, intermediate or high risk for death according to ESC guidelines definition.

Further comparisons of the above subgroups will be done via Cox proportional hazard regression models presenting hazard ratios and corresponding 95% confidence intervals. If relevant differences in Baseline characteristics are detected, these variables will be added to the model as additional covariates.

Analysis of secondary endpoints

The analyses will follow the above outlined analysis of the primary endpoint. Absolute and relative frequencies of death or clinical deterioration at 30 days from diagnosis of pulmonary embolism and of pulmonary embolism-related death or clinical deterioration at 30 days from diagnosis of pulmonary embolism (including the 95% confidence interval).

For all secondary endpoints, summary statistics, frequencies and rates (including the 95% confidence interval) will be presented overall and within the different patients' groups (see 9.3.1 for details). Kaplan-Meier estimates will be calculated for the occurrence of death or clinical deterioration at 30 days from diagnosis of pulmonary embolism and of pulmonary embolism-related death or clinical deterioration at 30 days from diagnosis of pulmonary embolism.

In analogy to the primary endpoint, comparisons of patients will be performed for the following subgroups

- patients admitted in every-day clinical practice in Cardiology, Emergency or Internal Medicine Departments
- patients at low, intermediate or high risk for death according to ESC guidelines definition.

For all secondary endpoints results of the Cox proportional hazard regression models will be evaluated as well (hazard ratios and corresponding 95% confidence intervals). If relevant differences in baseline characteristics are detected, these variables will be added to the model as additional covariates. Further data like patient characteristics or laboratory data will be summarized as appropriate, i.e. by means of absolute numbers and percentages or by means of standard statistics.

Furthermore, it will be looked at safety endpoints

- major bleedings
- clinically relevant non-major bleedings .

Definition of adherence

Firstly, the number of indicators that each patient will have met will be counted and divided by the total number for which the patient was eligible, obtaining the proportion of adherence.
The adherence score is defined as the ratio of the diagnostic tests/prognostic evaluations/treatment actually prescribed to those that should theoretically have been prescribed. Adherence will be calculated separately for each step (diagnosis/prognostic stratification/treatment) and globally for the overall patient's management. The theoretical diagnostic/prognostic/treatment/global scores will be calculated for every patient, taking into account diagnostic/prognostic/treatment eligibility criteria, guideline-based contraindications to tests/drugs or treatments.
We define as adherent to the care pathway a patient with a proportion of met indicators equal or greater than 80%. Sensitivity analyses will be performed at different cut-offs, and considering adherence

as an ordinal and a continuous variable. A directed acyclic graph will be constructed (DAG) (26) to represent assumptions regarding the underlying causal relationships between guideline adherence, survival and a set of clinical and socioeconomic variables. The DAG utilizes these assumptions to select the potential confounders, rather than relying on the statistical associations observed in the data. The selected confounders are then used in the statistical analysis aiming at evaluating the 'causal' impact of receiving a care adherent to guidelines on survival.

The adherence score will be corrected:

- for diagnosis by the sequence of tests over time.
- for treatment by sequence of different anticoagulant agents according to validated regimens and use of recommended dosages.

Diagnosis

The score will be calculated for each patient by summing the points attributed as follows: 0.5 points for use of non validated sequence or 1 point for use of recommended sequence of diagnostic tests. Non-administration of recommended tests due to specific contraindications or intolerance (i.e. allergy to contrast media) will be scored as adherence to guidelines.
The score ranges from 0 (very poor) to 1 (excellent) and we define three levels of adherence: good adherence (score =1); moderate adherence (score >0.5 to <1) and poor adherence (score ≤0.5).
In this study, the term 'adherence' relates solely to physicians following guidelines, not to patient compliance.

Risk stratification

The score will be calculated for each patient by summing the points attributed as follows: 0.5 points for use of not recommended tests or 1 point for use of recommended tests.
The score ranges from 0 (very poor) to 1 (excellent) and we define three levels of adherence: good adherence (score =1); moderate adherence (score >0.5 to <1) and poor adherence (score ≤0.5).
In this study, the term 'adherence' relates solely to physicians following guidelines, not to patient compliance.

Treatment

The score will be calculated for each patient by summing the points attributed as follows: 0 points for non-prescription of a given treatment (i.e. thrombolysis) in the absence of contraindications, 0.5 points for use of non validated regimen or 1 point for use of validated regimen. Non-administration of recommended drugs due to specific contraindications or intolerance will be scored as adherence to

guidelines. The score ranges from 0 (very poor) to 1 (excellent) and we define three levels of adherence: good adherence (score =1); moderate adherence (score >0.5 to <1) and poor adherence (score ≤0.5). In this study, the term 'adherence' relates solely to physicians following guidelines, not to patient compliance or persistence.

QUALITY CONTROL

This study will be conducted according to the rules of 'Good Clinical Practice' (GCP).

The physician will comply with the confidentiality policy and with the observational plan described in the protocol. The physician is ultimately responsible for the local conduct of all aspects of the study and verifies by signature the integrity of all data.

All monitoring details will be described in a separate Clinical Operations Plan (COP).

On-site monitoring will be performed according to a risk-based approach. During on-site monitoring the monitor will verify 100% of informed consent documentation and a selected, limited set of very relevant variables will be checked on the patient's medical records.

Data quality checks will be performed on an ongoing regular basis. Queries will be raised by the responsible CRO and shall be answered by the site in due course. The purpose is to ensure that the rights of the patients are protected and that the reported data is accurate and complete.

An independent adjudication committee will centrally review documentation on study outcome events in order to allow to definitely adjudicate the cause of in-hospital and 30 day deaths.

Limitations of the Research Methods

As this study aims at collecting real-world evidence, some limitations common to non-interventional studies apply. In addition, the following aspects need to be considered:

• Although sites will be selected to guarantee representativeness for their medical activities as much as possible, sites also need to have sufficient capabilities, interest and capacities to participate in the study and they need to be able to comply with the study protocol at the site. This may influence the sites' representativeness in some regions.

• Eligible patients not giving their informed consent to participate in the study cannot be enrolled. Therefore this may impact the consecutive enrolment at a site.

• For rating adherence to ESC guidelines, there might be differences due to different type of sites, namely hospital and departments. The respective tables will be stratified by type of site to detect these discrepancies (if any) and to allow for a careful and appropriate interpretation of the results.

• Also differences between the regions might occur, especially when rating adherence. Therefore, especially for adherence the analysis by region will careful looked at. In case that there will be mentionable differences the interpretation has to be very careful.

• As the study is non-interventional, only data from the clinical routine treatment can be obtained. Therefore, some information may be missing or unavailable and comparisons between treatments concerning efficacy and/or safety un-appropriate. This needs to be taken into account when data are analysed and reported.

No explicit non-eligibility criteria are defined to avoid selection of patients and thus violation of the 'real-life' principle.

PROTECTION OF HUMAN SUBJECTS

Review by Ethics Committees/Competent Authorities

Notification to or approval by institutional ethics committees (IECs) and competent authorities (CAs) or other organizations will be performed as required by national and local regulations in the participating countries before commencement of enrolment at a study centre.

All treatments of patients included in this study are local standard of care and occur as part of the routine clinical practice. The study is non-interventional and does not foresee any change of treatment nor additional examinations apart from the standard of care.

Patient Information, Informed Consent

Written Informed Consent (ICF) will be obtained from all patients before or on baseline data collection point and not thereafter.

The ICF should be approved by the Independent Ethics Committee (IEC) prior to being provided to potential patients.

The patient's written informed consent will be documented in the patient's medical records of the investigator. Two ICF forms should be signed and personally dated both by the patient and by the investigator who conducted the informed consent discussion. One original signed ICF should be retained at the study centre (preferably in the patient's medical records). The second original of the signed consent form should be provided to the patient. The date informed consent was given will also be recorded in the Case Report Forms (eCRF).

In addition, the patient has to agree with his/her signature to provide his/her contact details (address, phone number, email) to the investigator to allow his/her for future study contacts for follow up. The patients must declare with a signature to agree to the follow-up by calls or email.

Data Protection

The patients' privacy will be kept according to the requirements of Directive 95/46 EC and national legislation for data protection. Data will be collected in a pseudonymous way. An identification

number assigned to each patient will be used in lieu of the patient's name to protect the patient's identity.

All patient contact information required for follow-up calls will be kept strictly confidential and will only be accessible by the site personnel. This personalized data will be stored separately from the project specific database and the data will be destroyed after the completion of the study.

Only authorised personnel at the site has access to the identification list or original source documents (medical records). Representatives of the sponsor, the contract research organisation (CRO), and authorities are allowed access in case of audit or inspection or for monitoring purposes. The patient will agree to this by signing a respective statement on the ICF.

Numbering and Identification of Patients

A unique identification number (patient ID) will be assigned to each patient when reporting data in the eCRF or on the paper patient questionnaires.

At each study centre a patient identification list will be kept linking the identification number to the patient's identity.

Assessments

The investigators will be instructed about the correct documentation of the required variables for each patient in the eCRF. These data are available as part of the routine treatment. All examinations performed depend on the discretion and clinical routine of the physician. No diagnostic or monitoring procedures are applied to the patients in the study others than those performed as standard of care.

STUDY ORGANIZATION

The study will be coordinated by the University of Perugia (Sponsor) and the Steering Committee.

The Steering Committee will be composed by three members from the Sponsor, 4 members from Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), 2 members from Società Italiana Medicina Emergenza Urgenza (SIMEU) and 2 members from Federazione Assistenti Dirigenti Ospedalieri medicina Interna (FADOI).

An independent adjudication committee will be designated to definitely adjudicate the cause of death.

FEASIBILITY

The study is promoted by the University of Perugia (Sponsor) and ANMCO, with the collaboration of SIMEU and FADOI.

About 200 hospital- in Italy are planned to participate in the study. For comparisons, the following specialties are pre-specified:

Cardiology (around 80 sites)

Emergency (around 40 sites)

Internal Medicine (around 80 sites).

Sites who have not recruited any patient in the first 6 months after site initiation can be excluded from further participation.

The total study period from first patient in to last patient out is 25 months. The individual start per center depends on Ethical Committee and Institutional review Board approvals and will range approximately from Q1 2018 to Q2 2018.

The patient recruitment period consists of 24 months, followed by a 1 month follow up period per patient, summing up to 25 months.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For publishing the study results a separate publication plan will be set up by the scientific Steering Committee. The final study report will be made publicly available within 6 months after LPO. Full manuscripts are planned to be submitted for the baseline data and for final data.

Publication of sub-studies and secondary analyses should have the approval of the Steering Committee. Aside from the main publication, participating investigators in the study can propose ancillary analyses and related second level publications. Such publications may be produced by a dedicated team of authors in common agreement with and governed jointly by the SC of the study.

DOCUMENTATION AND ARCHIVING

The sponsor is responsible for archiving study specific documentation (Observational Plan, amendments, copy of eCRF burned on CD, Final Report and Database) for at least ten years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.

The investigator is responsible for archiving the patient identification list, all signed ICFs, copy of his eCRF burned on a CD for at least ten years and in accordance with local legislation.

Physicians are obliged to keep patient files according to national requirements.

Registration

This study will be listed in in public study database which meets International Committee of Medical Journal Editors requirements.

PREMATURE TERMINATION OF THE STUDY

In the case of a premature termination of the entire study by the SC of the study, the project leader has to inform all participating sites, Ethics Committees, and authorities. In case the study is terminated by the authorities, the project leader informs all participating sites and Ethics Committees.

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Appendix 1

Appendix 2 – Protocol Signature Page (protocol writers)

Protocol Title:

CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM. THE COPE STUDY.

The present research protocol was subject to critical review and has been approved in the present version by the persons who undersigned. The information contained is consistent with the moral, ethical and scientific principles governing clinical as set out in the Declaration of Helsinki and the principles of ICH/GCP.

Signatures:

_____ Date: _____

Cecilia Becattini MD, Study Chairman
University of Perugia, Italy

_____ Date: _____

Michele Gulizia MD,
Fondazione per il tuo Cuore Onlus –ANMCO, Italy

Appendix 3 – Protocol Signature Page (principal investigator)

Protocol Title:

CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM. THE COPE STUDY.

Declaration of Principal Investigator

I have read the present research protocol and agree to conduct the study according to the protocol.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled.

I pledge to obtain written consent for study participation from all subjects.

I pledge to retain all study-related documents and source data as described.

Principal Investigator (Head of the study center):

Name : _____

Study Center: _____

Signature: _____Date: _____