A randomized trial of ultrasound-facilitated, catheter-directed, thrombolysis versus anticoagulation for acute intermediate-high risk pulmonary embolism: The higher-risk pulmonary embolism thrombolysis study

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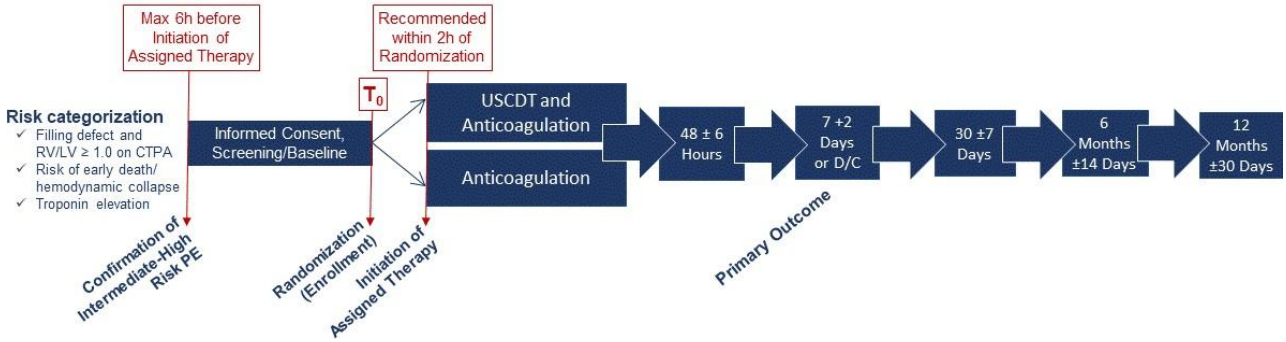
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B	**March 16, 2021**	[redacted]	**Header**	**Added document #**	**Administrative**
C	**August 19, 2021**	[redacted]	Safety Reporting: - 18.3 Definitions and Classifications - Table 18.2 Criteria for Assessing Relationship - 18.5 Investigator Reporting Requirements - Table 18.3 Communication Requirements for Safety Event Reporting Committees: - 20.2 Data Safety Monitoring Board 20.3 Clinical Events Committee	- References to MDR: MDCG 2020-10/1 - Instructions for safety reporting if EDC is unavailable - Updated device deficiency definition - Reporting timeline for adverse event vs adverse device effect - Correction to function and makeup of DSMB - Clarified communication to and from DSMB - Removed list of events for CEC adjudication.	- Alignment with MDR reporting requirements and definitions - Addition of instructions for timely safety reporting - Updates to align with DSMB and CEC Charters

2. Protocol Synopsis

A randomized trial of ultrasound-facilitated, catheter-directed, thrombolysis versus anticoagulation for acute intermediate-high risk pulmonary embolism: The higher-risk pulmonary embolism thrombolysis study (HI-PEITHO)	
Study Objective(s)	Primary Objective: To assess whether ultrasound-facilitated, catheter-directed, thrombolysis and anticoagulation are associated with a significant reduction in the composite outcome of pulmonary embolism (PE)-related mortality, cardiorespiratory decompensation or collapse, or nonfatal symptomatic and objectively confirmed recurrence of PE compared to anticoagulation alone within seven days of randomization Secondary Objective: To contribute further evidence to the existing data on the treatment and outcomes of acute, intermediate-high risk PE and provide controlled data related to catheter-based interventions
Study Population	Patients with acute intermediate-high risk PE, i.e. with absence of overt hemodynamic instability at presentation, but with a combination of clinical, imaging and laboratory parameters indicating an elevated risk of early death, hemodynamic collapse, or PE recurrence will be included in the trial.
Device/ Experimental Arm	EkoSonic™ Endovascular System and Anticoagulation • Ultrasound-facilitated catheter-directed delivery of thrombolytic (alteplase*): 2 mg bolus/catheter + 1 mg/hour/catheter for 7 hours (total of 9 or 18 mg) • Low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) *EkoSonic™ Endovascular system is indicated for the delivery of physician-prescribed fluids, including thrombolytics. Alteplase was selected for this protocol in order to standardize the thrombolytic drug across investigational sites, as it is one of the most widely-used and commercially-available products in the selected regions of the trial.
Control Arm	Anticoagulation • LMWH or UFH

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Study Design	Post-market, randomized, controlled, adaptive, open-label, multicenter parallel-group trial with blinded adjudication of primary composite outcome (PROBE design). Patients who fulfill all inclusion criteria and meet none of the exclusion criteria will be enrolled in the study after providing written informed consent. They will be randomized with a 1:1 ratio to ultrasound-facilitated, catheter-directed thrombolysis (USCDT) combined with anticoagulation versus anticoagulation alone. Randomization and initiation of assigned therapy should follow as soon as possible, but no more than six (6) hours after confirmation of diagnosis of intermediate-high risk PE as defined by inclusion criteria #2-5. Randomization should occur as soon as practical after the Investigator confirms diagnosis. Initiation of assigned therapy should follow as soon as possible after randomization. For subjects randomized to receive USCDT, it is strongly recommended the intervention is initiated within two (2) hours of randomization. 
Planned Number of Subjects	Initially, enrollment of 406 subjects is planned. An interim analysis after 50% enrollment could lead to an increase in the number of subjects to 544.
Planned Number of Sites/ Countries	Subjects will be enrolled at approximately 65 sites in Europe and the United States.

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Primary Endpoint	The primary outcome is a composite of PE-related mortality, cardiorespiratory decompensation or collapse (as defined below), or nonfatal symptomatic and objectively confirmed recurrence of PE, within seven days of randomization. Cardiorespiratory collapse or decompensation is defined as at least one of the following criteria: a) cardiac arrest or need for cardiopulmonary resuscitation (CPR) at any time between randomization and day 7; b) signs of shock: new-onset persistent arterial hypotension (systolic blood pressure (SBP) below 90 mmHg or SBP drop by at least 40 mmHg, over at least 15 minutes and despite an adequate volume status; or need for vasopressors to maintain SBP of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time between randomization and day 7; c) placement on extracorporeal membrane oxygenation (ECMO) at any time between randomization and day 7; d) intubation, or initiation of noninvasive mechanical ventilation at any time between randomization and day 7; e) National Early Warning Score (NEWS) of 9 or higher, between 24 hours and 7 days after randomization, confirmed on consecutive measurements taken twice, 15 minutes apart.

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Additional Assessments	1. Change in the right ventricular (RV) to left ventricular (LV) end diastolic diameter ratio (RV/LV) as measured by echocardiography between baseline and 48±6 hours; 2. PE-related death within 7 days; 3. Cardiorespiratory decompensation within 7 days; 4. Placement on ECMO or mechanical ventilation within 7 days 5. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding scale major (moderate and severe) bleeding within 7 days; 6. International Society on Thrombosis and Haemostasis (ISTH) major bleeding within 7 days, 30 days, and 6 months; 7. Ischemic or hemorrhagic stroke within 7 days and 30 days; 8. All-cause mortality within 7 days, 30 days, 6 months, and 12 months; 9. Serious adverse events within 30 days; 10. All-cause mortality, cardiorespiratory collapse or recurrence of PE within 30 days; 11. Symptomatic PE recurrence within 30 days and 6 months; 12. Change from baseline in RV dysfunction on echocardiography at 6 months; 13. Duration of hospitalization for the index PE event; 14. Duration of stay at the intensive, intermediate or coronary care unit during hospitalization for the index PE event; 15. Functional status: World Health Organization (WHO) functional class and Post-Venous Thromboembolism (VTE) Functional Status (PVFS) scale at discharge, 30 days, 6 and 12 months; 6-Minute Walk Test (6MWT) at 30 days, 6 and 12 months; 16. Quality of life: Pulmonary Embolism Quality of Life (PEmb-QOL), Short Form 36 (SF-36), EuroQuol-5 Dimension (EQ-5D) at 6 and 12 months; 17. Diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) within 12 months; 18. Health economic analysis (length of hospital stay, resource utilization, indirect costs) at 30 days and at 12 months (selected sites and countries)
Method of Assigning	Patients who fulfill all of the inclusion criteria and meet none of the exclusion criteria will be enrolled in the study after providing written informed consent.

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Patients to Treatment	They will be randomized in a 1:1 ratio to receive USCDT combined with anticoagulation or anticoagulation alone. Randomization will be stratified by the following parameters: • Age: <75 years vs ≥75 years • RV/LV ratio on computed tomography pulmonary angiography (CTPA): <1.5 vs ≥1.5 Randomization and initiation of assigned therapy should follow as soon as possible after confirmation of intermediate-high risk PE as defined by inclusion criteria #2-5. Initiation of therapy must begin within six (6) hours of confirmation of intermediate-high risk PE; it is highly recommended it begins within two hours of randomization.
Follow-up Schedule	Subjects will be followed for the composite primary outcome through 7 days post-randomization. Additional follow up visits will occur at 30 days, and 6 and 12 months post-randomization. The visit schedule and list of assessments is found in Section 10.
Study Duration	Enrollment is expected to be completed in approximately 24 months; therefore, the total study duration is estimated to be approximately 36 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	1) Age 18-80 years, inclusive 2) Objectively confirmed acute PE, based on CTPA showing a filling defect in at least one main or proximal lobar pulmonary artery (PA) 3) Elevated risk of early death/hemodynamic collapse, indicated by at least two of the following new-onset clinical criteria: i. Electrocardiogram (ECG)-documented tachycardia with heart rate ≥100 beats per minute, not due to hypovolemia, arrhythmia, or sepsis; ii. SBP ≤ 110 mm Hg for at least 15 minutes; iii. respiratory rate > 20 x min^{-1} *or* oxygen saturation on pulse oximetry (SpO_2) < 90% (or partial arterial oxygen pressure < 60 mmHg) at rest while breathing room air; 4) Right-to-left ventricular (RV/LV) diameter ratio ≥ 1.0 on CTPA 5) Serum troponin I or T levels above the upper limit of normal

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	6) Signed informed consent.
Exclusion Criteria	1) Hemodynamic instability*, i.e. at least one of the following present: a) cardiac arrest or need for cardiopulmonary resuscitation; b) need for ECMO, or ECMO initiated before randomization c) PE-related shock, defined as: (i) SBP < 90 mmHg, or vasopressors required to achieve SBP ≥ 90 mmHg, despite an adequate volume status; and (ii) end-organ hypoperfusion (altered mental status; oliguria/anuria; increased serum lactate); d) isolated persistent hypotension (SBP < 90 mmHg, or a systolic pressure drop by at least 40 mmHg for at least 15 minutes), not caused by new-onset arrhythmia, hypovolemia, or sepsis * Patients who presented with *temporary* need for fluid resuscitation and/or low-dose catecholamines may be included, provided that they could be stabilized within 2 hours of admission and maintain SBP of ≥ 90 mmHg and adequate organ perfusion without catecholamine infusion. 2) Need for admission to an intensive care unit for a reason other than the index PE episode. Note: Patients who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be enrolled where the investigator believes that the pulmonary embolism is the dominant pathology in the patient's clinical presentation and qualifying cardiorespiratory parameters. 3) Temperature above 39ºC / 102.2ºF 4) Logistical reasons limiting the rapid availability of interventional procedures to treat acute PE (e.g., during the outbreak of an epidemic) 5) Index PE symptom duration > 14 days 6) Active bleeding 7) History of intracranial or intraocular bleeding at any time 8) Stroke or transient ischemic attack within the past 6 months, or previous stroke at any time if associated with permanent disability 9) Central nervous system neoplasm, or metastatic cancer 10) Major neurologic, ophthalmologic, abdominal, cardiac, thoracic, vascular or orthopedic surgery or trauma (including syncope-associated with head strike or skeletal fracture) within the past 3 weeks 11) Platelet count < $100 \times 10^9 \times L^{-1}$ 12) Patients who have received a *once-daily* therapeutic dose of LMWH or a therapeutic dose of fondaparinux within 24 hours prior to randomization 13) Patients who have received one of the direct oral anticoagulants apixaban or rivaroxaban within 12 hours prior to randomization

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	14) Patients who have received one of the direct oral anticoagulants dabigatran or edoxaban for the index PE episode, as these drugs are not approved for patients who have not received heparin for at least 5 days 15) Administration of a thrombolytic agent or a glycoprotein IIb/IIIa receptor antagonist during the current hospital stay and/or within 30 days, for any reason 16) Chronic treatment with antiplatelet agents other than low-dose acetylsalicylic acid or clopidogrel 75 mg once daily (but not both). Dual antiplatelet therapy is excluded. 17) Chronic treatment with a direct oral anticoagulant (apixaban, dabigatran, edoxaban or rivaroxaban) 18) Chronic treatment with a vitamin K antagonist, or known coagulopathy including severe hepatic dysfunction, with an International Normalized Ratio (INR) > 1.5 19) Pregnancy or lactation 20) Previous inclusion in the study 21) Known hypersensitivity to alteplase, LMWH or UFH, or to any of the excipients 22) Life expectancy less than 6 months
Statistical Methods	
Primary Statistical Hypothesis	The treatment group (i.e. USCDT combined with anticoagulation) will be associated with a significant reduction in the primary outcome compared to the control group (i.e. anticoagulation alone). The null hypothesis is that the probability of a primary outcome event in the control group (π_c) and in the treatment group (π_t) is identical; the alternative hypothesis is that the probability of an event is lower in the treatment group than in the control group: $\mathbf{H_0}$: $\pi_t = \pi_c$ $\mathbf{H_1}$: $\pi_t < \pi_c$
Statistical Test Method	Analysis of the primary endpoint will be performed on the Intention-To-Treat (ITT) and Per-Protocol (PP) populations. The ITT population will comprise all randomized patients who met study eligibility criteria. The PP population will

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	comprise all patients in the ITT population without significant protocol deviations. The primary analysis will be performed on the ITT population. A Pocock alpha-spending group sequential design will be used with one interim analysis after inclusion of 50% of the patients. Adaption of the trial, including a sample size increase, will be possible based on the results of the interim analysis. A chi-square test will be used to compare the primary endpoint between the treatment and control groups; the odds ratio and corresponding 95% confidence interval will be presented. A logistic regression which includes the stratification factors used at randomization as covariates, will be performed as a sensitivity analysis. Multicollinearity will be assessed using the variance inflation factor. **Safety analyses, including adverse events (AEs) and serious adverse events (SAEs),** will be performed on the treated population, comprising patients in the ITT population, who received USCDT (i.e. patients for whom the EkoSonic™ device was activated and thrombolytic infusion begun) or who received anticoagulation. **Subgroup analyses** to assess the heterogeneity of the treatment (USCDT) effect will be described in the statistical analysis plan. An **efficacy interim analysis** will be assessed by the independent Data and Safety Monitoring Board (DSMB) after 50% of the expected number of subjects (1). The superiority of the treatment group versus the control group will be tested by a chi-square test. If the interim analysis takes place with exactly 50% of the patients, the 1-sided significance level for the interim analysis is α_1=0.01469, and is α_2=0.01469 for the final analysis using Pocock alpha spending. A conditional power of ≤ 15% at the interim analysis could result in the study stopping early for futility. A sample size increase to 544 patients will be considered at the interim analysis following the Promising Zone methodology described in Mehta and Pocock (2), to ensure control of Type I error. **Adaptive design:** The following decisions can be made based on which of the zones, defined below, the results of the interim analysis fall into: • Futility zone: stop for futility if the conditional power is ≤ 15% • Unfavorable zone: if the conditional power is > 15% and < CP_{min*} the study will continue with the original sample size; the value of CP_{min} will be provided in the statistical analysis plan.

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	• Promising zone: if the conditional power is ≥ CP_{min} and < 90% the sample size will be increased to 544 patients • Favorable zone: if the conditional power is > 90% the study will continue with the original sample size • Efficacy: stop for efficacy if the 1-sided p-value is < 0.01469. *CP_{min} is the conditional probability of rejecting the null hypothesis at final analysis
Sample Size Parameters	The study is designed to detect a 15% versus 5% difference (i.e. odds ratio = 0.298) in the primary endpoint event rate. The expected rate of the primary efficacy endpoint for the control group was derived from the subset of patients in the placebo arm of the Pulmonary Embolism International Thrombolysis (PEITHO) study who had SBP ≤ 110 mmHg and respiratory rate > 20 x min^{-1} at baseline as approximately 15% (1). Due to uncertainty in the expected event rate in the treatment arm, a sample size re-estimation is planned, which would allow the sample size to increase in order to detect a 15% vs 6% difference in event rates (i.e. odds ratio = 0.362). A total of 406 patients will yield 90% power to detect the target difference in event rates (i.e. odds ratio = 0.298) with a one-sided alpha of 0.025 using a Pocock alpha spending group sequential design with one interim analysis. If the sample size is increased after the interim analysis, the final analysis will be performed with 544 randomized patients, which will result in 90% power to detect a reduction in the event rate from 15% to 6% (i.e. odds ratio = 0.362) with a final one-sided alpha of 0.01469. An adjustment to the sample size to take into account patients who will be lost to follow-up is not required since it can be reasonably assumed that all patients will be assessed for the primary endpoint at 7 days.

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4. Introduction

4.1. *Background*

Intravenously administered thrombolysis is the 'prototype' of reperfusion therapy for acute PE. Early studies reported significant hemodynamic improvement after full-dose systemic thrombolysis, and a meta-analysis of 15 randomized controlled trials with a total of 2057 patients confirmed that thrombolysis may improve early survival (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.36-0.96), and reduce PE-related death (OR 0.29; 95% CI 0.14-0.60) and recurrent PE (OR 0.50; 95% CI 0.27-0.94) compared to anticoagulation alone (3). Today, PE guidelines recommend primary systemic thrombolytic therapy only for 'high-risk' patients with overt right ventricular (RV) failure, i.e. those presenting with hemodynamic instability (4-6).

The majority of patients with acute PE appear hemodynamically stable at presentation (7). However, patients with imaging or laboratory findings of RV dysfunction may have an 'intermediate' but still substantial (up to 8%) risk of early death (7). It has been hypothesized that intermediate-risk patients may benefit from early thrombolysis. In the randomized, placebo-controlled, Pulmonary Embolism International Thrombolysis (PEITHO) trial, patients had combined echocardiographic and laboratory evidence of RV dysfunction. All-cause death or hemodynamic decompensation within 7 days was reduced in the thrombolysis group, from 5.6% to 2.6% (OR 0.44; 95% CI 0.23-0.88). However, this was offset by higher rates of hemorrhagic stroke (OR 12.10; 95% CI 1.57–93.39) (8). High rates of major and intracerebral bleeding were confirmed by a meta-analysis of thrombolysis trials, most of which employed systemic 'full-dose' thrombolysis (9).

Consequently, the **current state of the art on thrombolysis for PE** can be summarized as follows:

a) Acute intermediate-risk (submassive) PE remains potentially life-threatening when treated with anticoagulation alone.
b) Early reperfusion with standard-dose intravenous thrombolysis offers the potential of improving hemodynamics as well as early clinical outcomes.
c) Reperfusion treatment is nevertheless not recommended for patients without cardiogenic shock, because the bleeding risk of standard-dose thrombolytic treatment is considered prohibitive.

This unsatisfactory situation, which deprives many patients with acute PE of a potentially life-saving therapeutic option, can be resolved only if future research focuses on the following key aspects:

a) **Improve the safety of thrombolysis**. Pharmacomechanical reperfusion, notably ultrasound-facilitated catheter-directed thrombolysis (USCDT), has the potential of reversing RV dilation, pulmonary hypertension, and anatomic thrombus burden (10). In the randomized phase II Ultrasound Accelerated Thrombolysis of Pulmonary Embolism Trial (ULTIMA), which enrolled 59 patients with acute PE and a right-to-left ventricular

dimension ratio > 1.0, ultrasound-assisted local infusion of 10–20 mg recombinant tissue-type plasminogen activator (r-tPA) led to significant recovery of RV function at 24 hours, with no increased risk of major hemorrhage or stroke (11). Supportive of the efficacy and safety of this approach are also the results of (i) a prospective, single-arm multicenter trial on 150 patients with submassive or massive PE (12); (ii) a registry on catheter-directed, either purely mechanical or pharmacomechanical thrombus removal including 28 patients with massive and 73 with submassive PE (13); and (iii) the prospective multicenter, parallel-group optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism (OPTALYSE-PE) trial which randomized 101 hemodynamically stable adult patients, testing four USCDT regimens using a shorter delivery duration for the primary efficacy endpoint defined as the reduction in right ventricular–to–left ventricular diameter ratio by computed tomographic angiography (14).

b) **Advance the concept of intermediate-high risk and the PE severity criteria,** to better identify patients who may clinically benefit from thrombolysis. In the PEITHO trial, baseline imaging and laboratory findings, but not clinical parameters (apart from the requirement for hemodynamic 'stability' at presentation), were used as inclusion criteria (1). The combined primary outcome and particularly early mortality rates were low both in the thrombolysis and in the placebo (anticoagulant-only) arm (8). This generates the hypothesis that better identification of 'intermediate-high risk' PE may be necessary to justify early thrombolysis. In a recent post-hoc analysis of the PEITHO trial, baseline clinical variables were identified, which may be used (in addition to RV dysfunction and troponin elevation) as additional criteria to identify patients with an elevated risk of 'imminent' hemodynamic decompensation and an adverse early outcome (1). For the purpose of this post-hoc analysis, the composite clinical outcome was defined as PE-related death, hemodynamic collapse, or non-fatal symptomatic recurrent PE between randomization and day 30. In the placebo arm, the rate of the composite clinical outcome was 20% in patients with at least two clinical criteria of severity, and this was reduced to 7.0% in the thrombolysis arm; this corresponds to a relative risk reduction of 65%. In contrast, in patients who fulfilled none of these clinical criteria, the rate of the composite clinical outcome was only 2.3% in the placebo arm and higher, 3.8%, in the thrombolytic arm. These findings must be regarded as exploratory and hypothesis-generating. However, keeping in mind this limitation, they appear to support the requirement for disease-specific clinical indicators of PE severity at presentation on top of established imaging and biochemical criteria, to be used as inclusion criteria in future trials testing safer reperfusion modalities in intermediate-risk PE.

4.2. *Study Rationale*

The present study has been designed to address the important gaps in clinical evidence by comparing the clinical benefit of the ultrasound-facilitated local delivery of a thrombolytic agent and anticoagulation with those of anticoagulation alone in patients with intermediate-high risk PE at a higher estimated risk of early decompensation based on clinical parameters at presentation.

5. Device Description

5.1. *EkoSonic™ Endovascular Device*

The EkoSonic™ Endovascular device employs ultrasound energy intended for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of PE.

The EkoSonic™ Endovascular System consists of two main components:

1. Single-use sterile device, consisting of an
    a. Intelligent Drug Delivery Catheter (IDDC)
    b. MicroSonic Device (MSD)
2. EkoSonic™ Control Unit (reusable)

The EkoSonic™ device emits ultrasonic energy waves at the treatment zone through the piezoelectric transduction of radiofrequency (RF) energy generated by the control unit based on a preprogrammed acoustic algorithm. The ultrasound emanates radially from the treatment zone into and through blood, thrombus, or tissue surrounding the treatment zone, within the patient's vasculature. The ultrasound acts locally to increase the dispersion of the delivered solution into the treatment region. In addition to generating the prescribed ultrasound energy profile, the system continually monitors RF power output levels and temperature at the treatment zone. The system has safeguard circuits to prevent these parameters from deviating from pre-set normal operating ranges.

The IDDC is 5.4 French with a 106 cm or 135 cm working length. It includes two luer ports for coolant fluid and thrombolytic delivery and an electrical connector for the thermocouples that monitor the catheter system temperature. Radiopaque markers are located approximately 1 cm proximal and 1 cm distal to the treatment zone. The IDDC central lumen is compatible with a 0.035" guidewire, accepts the MSD and delivers coolant during operation. Each EkoSonic™ Device requires its own infusion tubing and infusion pump with coolant of normal saline. Refer to the IFU for specific guidance on coolant infusion rate.

The MSD locks to the luer connector on the central lumen of the IDDC aligning the ultrasound-generating segment to the treatment zone of the IDDC. The device uses multiple ultrasound transducers to emit ultrasound energy radially from the long axis of the catheter system.

The EkoSonic™ Control Unit provides electrical power to the piezoelectric elements in the treatment zone of the Device and monitors operating parameters during operation. The Control Unit also provides the user interface through the front panel display and keypad.

5.1.1. Indication for Use

United States Indications for Use

The EkoSonic™ Endovascular System is indicated for the:

- Ultrasound-facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism.
- Infusion of solutions into the pulmonary arteries.
- Controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.

All therapeutic agents utilized with the EkoSonic™ Endovascular System should be fully prepared according to the instructions for use (IFU) and mixed (concentrated) according to the physician's order.

European Indications for Use

The EkoSonic™ Endovascular System, consisting of the Infusion Catheter and the Ultrasonic Core, is indicated for:

- the treatment of pulmonary embolism in patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean PA pressure ≥ 25 mmHg) or echocardiographic evaluation.
- infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.

All therapeutic agents utilized with the EkoSonic™ Endovascular System should be fully prepared according to the instructions for use and mixed (concentrated) according to the physician's order.

5.2. *Required Medical Equipment*

5.2.1. EkoSonic™ Control Unit



Control Unit PT-3B



Control Unit CU-4.0

The EkoSonic™ Control Unit (CU) consists of a Control Unit and a Connector Interface Cable (CIC). The CU provides electrical energy to the piezoelectric elements in the treatment zone of the MicroSonicDevice and monitors operating parameters during operation via the CIC.

Please refer to the EkoSonic™ Control Unit Instructions for Use for any questions related to the setup, operation, or troubleshooting of the device.

There are two CU models approved for use: PT-3B and CU-4.0. PT-3B allows for one infusion catheter to be connected, while CU-4.0 allows for two to be connected at once. The CU model used will be recorded in the electronic data capture (EDC) system for each patient.

5.2.2. EkoSonic™ Catheters



Please refer to the EkoSonic™ Endovascular Device IFU for any questions related to length, treatment zone, placement, and troubleshooting of the catheters. If technical difficulties are encountered which interfere with proper infusion of either r-tPA or coolant, and issues cannot be resolved through consulting the IFU, the affected catheter device should be exchanged for another catheter. The exchange of the affected catheter and serial number will be recorded in the EDC as a device deficiency. The device will be saved and returned to the Sponsor.

5.3. *Study Medications*

The following medications will be used during this trial. They will be supplied from the local pharmacy and should be prepared according to all local and institutional requirements.

5.3.1. Recombinant Tissue Plasminogen Activator (r-tPA)

The type of thrombolytic drug used in this study is a commercially-available recombinant tissue plasminogen activator (r-tPA) marketed in the participating geographies under various brand names, generic name alteplase, for fibrinolysis of pulmonary embolism by systemic infusion. For this study, alteplase will be procured from local pharmacy supplies. All instructions for reconstitution provided in the manufacturer's package insert and pharmacy procedures should be followed.

In this study, alteplase will be delivered through the EkoSonic™ intelligent drug delivery port to the site of the clot rather than by systemic infusion. The drug will be administered using each facility's standard infusion pumps. See section 10.3.4.1.1 for a description of the doses and duration of alteplase administration.

Activase® (manufactured by Genentech, Inc., San Francisco, CA) and Actilyse® (manufactured by Boehringer Ingelheim Pharmaceuticals, Inc., Ingelheim am Rhein, Germany) are authorized for use by country-specific regulatory agencies in all participating geographies for fibrinolysis of pulmonary embolism. No special labeling or tracking is required for this study.

5.3.2. Anticoagulation

Both the intervention and control arms of the study will receive anticoagulation therapy with low molecular weight heparin (LMWH) and/or unfractionated heparin (UFH). These are both commercially available and will come from the local pharmacy. See section 10.3.4 for a description of the treatment protocols for each arm.

Subjects may be transitioned to any commercially-available oral anticoagulation according to the anticoagulation protocols in section 10.3.4 for both treatment arms of the study. Following current recommendations, the subject should remain on anticoagulation medication a minimum of three months following randomization (6).

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The primary objective of the study is to assess whether ultrasound-facilitated, catheter-directed, thrombolysis and anticoagulation are associated with a significant reduction in the composite outcome of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed recurrence of PE compared to anticoagulation alone within seven days of randomization.

Additional objectives are to contribute further evidence to the existing data on the treatment and outcomes of acute, intermediate-high risk PE and to provide controlled data comparing a catheter-based intervention to the standard of care that is currently recommended in the guidelines.

6.2. *Study Endpoints*

See section 6.2.3 for further clarification of terms.

6.2.1. Primary Endpoint

The primary outcome is a composite of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed recurrence of PE, within seven days of randomization.

6.2.2. Additional Assessments

1. Change in the RV-to-LV diameter ratio as measured by echocardiography between baseline and 48±6 hours
2. PE-related death within 7 days;
3. Cardiorespiratory decompensation within 7 days;
4. Placement on ECMO or mechanical ventilation within 7 days;
5. GUSTO major (moderate and severe) bleeding within 7 days;

6. ISTH major bleeding within 7 days, 30 days, and 6 months;
7. Ischemic or hemorrhagic stroke within 7 days and 30 days;
8. All-cause mortality within 7 days, 30 days, 6 months, and 12 months;
9. Serious adverse events within 30 days;
10. All-cause mortality, cardiorespiratory collapse or recurrence of PE within 30 days;
11. Symptomatic PE recurrence within 30 days and 6 months;
12. Change from baseline in RV dysfunction on echocardiography at 6 months;
13. Duration of hospitalization for the index PE event;
14. Duration of stay at the intensive, intermediate or coronary care unit during hospitalization for the index PE event;
15. Functional status at 30 days, 6 months, and 12 months, including:
    a) WHO functional class (and discharge),
    b) PVFS scale (and discharge),
    c) 6-Minute Walk Test;
16. Quality of life (PEmb-QOL, SF-36, and EQ-5D scales) at 6 months and 12 months;
17. Diagnosis of CTEPH within 12 months;
18. Health economic analysis (length of hospital stay, resource utilization, indirect costs) at 30 days and 12 months (selected sites and countries).

6.2.3. Assessment of Endpoints

Cardiorespiratory collapse or decompensation should fulfill at least one of the following criteria:

a) cardiac arrest or need for CPR at any time between randomization and day 7;

b) signs of shock: new-onset persistent arterial hypotension (SBP below 90 mmHg or SBP drop by at least 40 mm Hg over at least 15 minutes, and despite an adequate volume status; or need for vasopressors to maintain SBP of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time between randomization and day 7;

c) placement on ECMO at any time between randomization and day 7;

d) intubation, or initiation of non-invasive mechanical ventilation at any time between randomization and day 7;

e) National Early Warning Score (NEWS) of 9 or higher, between 24 hours and 7 days after randomization. Note that the score must be confirmed on two consecutive measurements 15 minutes apart.

Recurrent symptomatic PE will be defined by clinical symptoms and objective confirmation by CTPA suggesting recurrent PE (15). There will be no routine surveillance for asymptomatic recurrent venous thromboembolism. Suspected recurrent symptomatic PE will be adjudicated

by the Clinical Events Committee (CEC).

Major bleeding will be adjudicated according to the GUSTO criteria (16):

a) GUSTO severe or life-threatening bleeding: A bleeding episode that leads to hemodynamic compromise requiring emergency intervention (such as replacement of fluid and/or blood products, inotropic support, or surgical treatment), or is life-threatening or fatal.

b) GUSTO moderate bleeding (a bleeding episode requiring blood transfusion(s), but which is not deemed life-threatening and does not lead to hemodynamic compromise requiring emergency fluid replacement, inotropic support, or interventional treatment) (16).

Major bleeding will also be adjudicated according to the ISTH criteria (17):

a) Fatal bleeding and/or

b) Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or

c) Bleeding causing a fall in hemoglobin level of 20 g/L (2 g/dL) or more, or leading to transfusion of two or more units of whole blood or red blood cells

Stroke will be classified as ischemic or hemorrhagic stroke.

CTEPH will be diagnosed by the investigational site according to presence of all of the following criteria (15):

a) At least one mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning after 3 months of adequate therapeutic anticoagulation

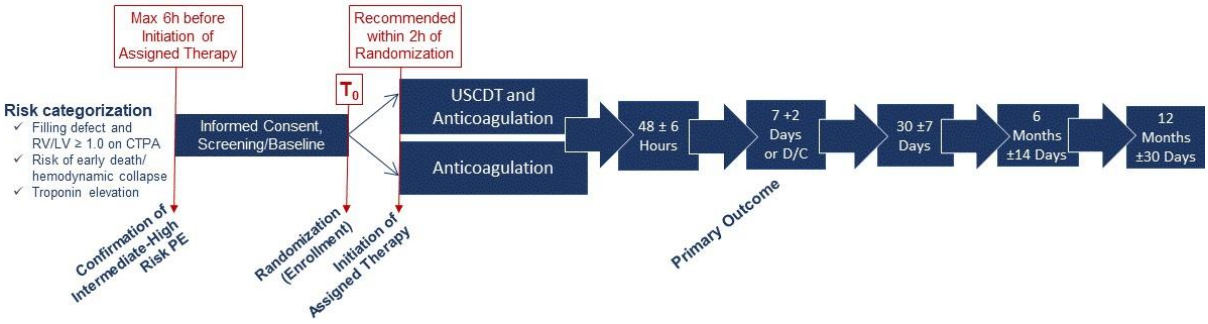
b) Resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg measured by invasive right heart catheterization

c) Pulmonary capillary wedge pressure ≤15 mmHg.

7. Study Design

The trial is a post-market, randomized, controlled, adaptive, open-label, multicenter parallel-group trial with blinded adjudication of the primary composite outcome. Subjects will be randomized 1:1 to treatment with USCDT and anticoagulation or anticoagulation alone. The study is unblinded to Investigators and subjects, but adjudication of the outcome measure and other safety outcomes will be completed by a blinded CEC.

Figure 7.1: **HI-PEITHO Study Design**



7.1. *Scale and Duration*

Initially, 406 subjects are planned to be enrolled at up to 65 sites in the US and Europe. There will be a planned interim analysis after 50% are enrolled, with the potential to enroll up to 544 subjects. The follow up period for each subject is 12 months, so the overall study duration is anticipated to be at least 36 months.

7.2. *Treatment Assignment*

Subjects will be randomized 1:1 to receive either the USCDT intervention with anticoagulation or will be treated with anticoagulation alone. Randomization will be stratified by the following parameters:

- Age: <75 years vs ≥75 years
- RV/LV ratio on CTPA: <1.5 vs ≥1.5

Basic demographic, pseudonymized information about the subject will be entered into the EDC. The research staff will confirm that all eligibility criteria are met. The subject will be assigned a subject ID number and will receive a randomized assignment to the USCDT treatment arm or anticoagulation-only control arm. If they are assigned to receive USCDT, treatment should be initiated as soon as practical, but no later than six (6) hours of confirmation of diagnosis of intermediate-high risk PE. It is strongly recommended that it begins within two hours of randomization.

7.2.1. Test (USCDT) Arm

Assignment to the USCDT arm will include both treatment with the USCDT procedure and treatment with anticoagulation. The USCDT procedure will entail delivery of alteplase using the EkoSonic™ Endovascular System. Alteplase will be delivered using a specified treatment protocol (see section 10.3.4.1.1 for the full protocol). Treatment must be initiated as soon as practical but no more than six (6) hours after confirmation of diagnosis of intermediate-high risk PE. It is strongly recommended that it begins within two (2) hours of randomization.

Assignment to the experimental USCDT arm will also include initiation or continuation of anticoagulation therapy according to a specified treatment protocol. If a subject is already being treated with low molecular weight heparin (LMWH) or unfractionated heparin (UFH),

the treatment protocol for continuation of therapy from the time of randomization is provided. See section 10.3.4.1.2.

7.2.2. Control (Anticoagulation) arm:

Assignment to the anticoagulation-only control arm will include either initiation or continuation of anticoagulation therapy according to a specified treatment protocol (see section 10.3.4.2 for the full protocol). Therapeutic anticoagulation is the current standard of care in the treatment of acute intermediate-high risk PE.

The control arm will not receive an interventional procedure. Note: there are mechanisms in place if a subject requires an escalation in therapy with a documented hemodynamic collapse or decompensation. In the absence of hemodynamic collapse or decompensation, or documentation of such, institution of any PE treatment beyond the therapy to which the subject was randomly assigned will be considered a protocol deviation.

7.3. *Justification for the Study Design*

A randomized study, as opposed to a single-arm study, will give the most robust conclusions and allow causality of treatment benefit to be attributed to the USCDT intervention with anticoagulation.

The interim analysis provides the potential to stop the study early and therefore reduce the likelihood to randomizing further patients to an ineffective treatment. Due to uncertainty in the size of the treatment effect, the ability to increase the sample size at the interim analysis increases the likelihood of demonstrating a statistically significant benefit of the USCDT intervention with anticoagulation.

There are inherent challenges in a randomized, controlled trial in critically ill patients. Investigators in the trial will be responsible for following the protocol and are expected to treat patients according to the randomized treatment assignment in order to collect quality outcomes data from the trial. As the subjects' physicians, they are also responsible for ensuring subject safety and applying appropriate interventions while the patients are under their care. One anticipated challenge will be identifying Investigators who are committed to the equipoise of therapies and who will present treatment options as a study participant to eligible patients. Another anticipated challenge of this trial is the potential for escalation of therapy and/or crossover in subjects assigned to the anticoagulation arm who go on to receive interventions without evidence of meeting the primary endpoint.

Most current guidelines for the management of PE recommend anticoagulation therapy for patients with intermediate-high risk PE, due in part to the elevated bleeding risk associated with treatment with thrombolytics and the absence of level one evidence demonstrating better outcomes with more advanced therapies. With respect to bleeding risk, however, the available research in this population evaluates major bleeding in patients who were treated with full dose, systemic thrombolysis. Several single arm studies have demonstrated a significant reduction in that risk using lower doses of thrombolytic agents (in particular, catheter-directed delivered into the affected PA). Based on these trials, many clinicians treating PE routinely offer catheter-directed thrombolysis for intermediate-high risk PE. In order to understand whether there is benefit to USCDT over anticoagulation alone, a large, randomized, controlled

trial comparing the current standard of care (anticoagulation therapy) to catheter-directed thrombolytic therapy is needed.

8. Subject Selection

8.1. *Study Population and Eligibility*

All patients who present to the emergency department (ED) for evaluation and treatment of PE will be considered for inclusion in the trial. Clinical evaluation and a series of standard of care imaging (e.g., CTPA, echocardiogram) and laboratory tests (e.g., biomarkers) are completed to diagnose patients with PE and classify the PE as intermediate-high risk. Upon confirmation of intermediate-high risk PE, patients will be consented, and the remaining eligibility criteria will be reviewed. Inclusion and exclusion criteria are included, respectively, in Sections 8.2 and 8.3 below.

8.2. *Inclusion Criteria*

Patients who meet all of the following criteria (see Table 8.1: Inclusion Criteria) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Patients will need baseline computed tomographic pulmonary angiography (CTPA) for confirmation of a filling defect in at least one main or proximal lobar PA, as well as a right-to-left-ventricle diameter ratio (RV/LV) of ≥ 1.0. Patients will also need to have a baseline laboratory test for confirmation of elevated serum troponin I or T. A clinician will need to confirm presence of at least two of the clinical criteria of elevated risk in Inclusion Criterion 3.

Table 8.1: Inclusion Criteria

Inclusion Criteria	1) Age 18-80 years, inclusive 2) Objectively confirmed acute PE, based on computed tomography pulmonary angiography (CTPA) showing a filling defect in at least one main or proximal lobar PA 3) Elevated risk of early death/hemodynamic collapse, indicated by at least two of the following new-onset clinical criteria: a) ECG-documented tachycardia with heart rate ≥ 100 beats per minute, not due to hypovolemia, arrhythmia, or sepsis; b) systolic blood pressure (SBP) ≤ 110 mmHg over at least 15 minutes; c) respiratory rate > 20 x min^{-1} or oxygen saturation on pulse oximetry (SpO2) < 90% (or partial arterial oxygen pressure < 60 mmHg) at rest while breathing room air; 4) Right-to-left ventricular (RV/LV) diameter ratio ≥ 1.0 on CTPA 5) Serum troponin I or T levels above the upper limit of normal 6) Signed informed consent.

8.3. *Exclusion Criteria*

Patients who meet any one of the following criteria (see Table 8.2: Exclusion Criteria) cannot be included in this study or will be excluded from this clinical study.

Table 8.2: Exclusion Criteria

Exclusion Criteria	1) Hemodynamic instability*, i.e. at least one of the following present: a) cardiac arrest or need for cardiopulmonary resuscitation; b) need for ECMO, or ECMO initiated before randomization; c) PE-related shock, defined as: (i) SBP < 90 mmHg, or vasopressors required to achieve SBP ≥ 90 mmHg, despite an adequate volume status; and (ii) end-organ hypoperfusion (altered mental status; oliguria/anuria; increased serum lactate); d) isolated persistent hypotension (SBP < 90 mmHg, or a systolic pressure drop by at least 40 mmHg for at least 15 minutes), not caused by new-onset arrhythmia, hypovolemia, or sepsis. * Patients who presented with *temporary* need for fluid resuscitation and/or low-dose catecholamines may be included, provided that they could be stabilized within 2 hours of admission and maintain SBP of ≥ 90 mmHg and adequate organ perfusion without catecholamine infusion. 2) Need for admission to an intensive care unit for a reason other than the index PE episode. Note: Patients who test positive for SARS-CoV-2 can be enrolled where the investigator believes that the pulmonary embolism is the dominant pathology in the patient's clinical presentation and qualifying cardiorespiratory parameters. 3) Temperature above 39°C / 102.2°F 4) Logistical reasons limiting the rapid availability of interventional procedures to treat acute PE (e.g., during the outbreak of an epidemic) 5) Index PE symptom duration > 14 days 6) Active bleeding 7) History of intracranial or intraocular bleeding at any time 8) Stroke or transient ischemic attack within the past 6 months, or previous stroke at any time if associated with permanent disability 9) Central nervous system neoplasm, or metastatic cancer 10) Major neurologic, ophthalmologic, abdominal, cardiac, thoracic, vascular or orthopedic surgery or trauma (including syncope-associated with head strike or skeletal fracture) within the past 3 weeks 11) Platelet count < $100 \times 10^9 \times L^{-1}$ 12) Patients who have received a *once-daily* therapeutic dose of LMWH or a therapeutic dose of fondaparinux within 24 hours prior to randomization 13) Patients who have received one of the direct oral anticoagulants apixaban or rivaroxaban within 12 hours prior to randomization 14) Patients who have received one of the direct oral anticoagulants dabigatran or edoxaban for the index PE episode, as these drugs are not approved for patients who have not received heparin for at least 5 days 15) Administration of a thrombolytic agent or a glycoprotein IIb/IIIa receptor antagonist during the current hospital stay and/or within 30 days, for any reason 16) Chronic treatment with antiplatelet agents other than low-dose acetylsalicylic acid or clopidogrel 75 mg once daily (but not both). Dual antiplatelet therapy is excluded 17) Chronic treatment with a direct oral anticoagulant (apixaban, dabigatran, edoxaban or rivaroxaban)

	18) Chronic treatment with a vitamin K antagonist, or known coagulopathy including severe hepatic dysfunction, with an International Normalized Ratio (INR) > 1.5 19) Pregnancy or lactation 20) Previous inclusion in the study 21) Known hypersensitivity to alteplase, LMWH, UFH, or to any of the excipients 22) Life expectancy less than 6 months

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects will be considered enrolled into the study at the time of randomization. A subject must be eligible and must provide informed consent prior to being randomized. If a subject provides written informed consent, and withdraws consent prior to the time of randomization, the patient will be considered a Screen Failure. This patient will be entered onto the Screening and Enrollment Log and registered within the EDC, but not randomized.

9.2. *Point of Randomization*

Subjects will be computer-randomized 1:1 to either treatment with USCDT combined with anticoagulation or anticoagulation alone. Once a patient has provided written informed consent and eligibility has been confirmed, the subject will be added to the EDC. Basic, pseudoanonomyzed demographic information about the subject, stratification factors and confirmation of eligibility will be entered into the EDC to produce the randomization assignment.

9.3. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow their status/condition outside of the clinical study.

9.4. *Lost to Follow Up*

The follow up period for the study is 12 months after randomization. A subject will be considered lost to follow up if he or she is unable to be contacted by the study staff at the 12-month time point.

Multiple methods of contacting the subject will be collected at enrollment, including phone number, alternate phone number as available, email as available, and address.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule any missed visit within the specified visit window. The site will counsel the subject on the importance of maintaining the visit schedule and will ascertain if the subject wishes to and/or will continue with the study.
- If a subject cannot be rescheduled for the visit to occur within window, they should still be brought in for follow up assessments, as possible, after the window. If the subject is not responsive to attempts to reschedule, the Investigator or designee will attempt to contact the subject in time to schedule the next follow up visit.
- Before a subject is deemed lost to follow up, the Investigator or designee will make every effort to regain contact with the subject (when possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's study file and Study Exit electronic case report form (eCRF). The last date of contact with the subject will be collected. In these cases, there is an opportunity on the Study Exit eCRF to record the last known date the subject can be confirmed alive.

9.5. *End-of-Study Definition*

A study subject is considered to have completed the study if he or she has completed at least one element of the 12-month follow up visit.

The end of the study is defined as completion of the last visit per the Data Collection Schedule in the trial for all enrolled subjects, or classification into one of the following categories at 12 months post-randomization: withdrawn, lost to follow up, or deceased.

10. Study Methods

10.1. *Assessments*

10.1.1. Computed Tomographic Pulmonary Angiography (CTPA)

CTPA is a diagnostic test that uses computed tomographic angiography to obtain an image of the pulmonary arteries and heart. The CTPA is the preferred method for visualizing and measuring the right ventricle (RV) and left ventricle (LV) of the heart.

Following are a few guidelines for measuring RV/LV on CTPA (18, 19):

- RV/LV should be measured at end diastole.
- RV/LV measures on CTPA should be measured using axial transverse images.
- Maximal RV and LV can be measured using different slices of the CT.
- The tricuspid and mitral valve plane should be visualized.
- All measurements should be made perpendicular to the long axis.
- Measurements should be made in the basal third of the ventricle (1 cm below valve plane).
- Papillary muscles and trabeculae should be excluded.
- Measurements should be taken endocardium to endocardium.

10.1.2. Laboratory Tests and Biomarkers

- Biomarkers will be collected at baseline and 48±6 hours post-randomization. Troponin T or I is required to confirm eligibility.
  - *Troponin T or I*: used to detect and evaluate mild to severe heart injury, and to distinguish chest pain that may be due to other causes. Elevations may indicate some degree of damage to the heart. The value must be elevated in accordance with the local laboratory's normal range in order to meet eligibility for the study.
  - *BNP (brain natriuretic peptide)*
  - *Lactate or Lactic Acid*
- Complete Blood Count (CBC) will be collected at baseline and 48±6 hours post-randomization. The lowest reported values will be collected in the case of a bleeding adverse event.
  - *Hemoglobin (Hgb)*
  - *Hematocrit (Hct)*
  - *Platelet count*
- Chemistry will be collected at baseline and 48±6 hours post-randomization.
  - *Renal/Kidney Tests: blood urea nitrogen (BUN), Creatinine*
  - *Hepatic/Liver Tests: alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST)*

10.1.3. Physical Exam, Medical History, and Risk Factors

Data from the routine physical examination of the patient will be documented at Screening (Baseline). The physical exam will include an assessment of all major body systems. Significant findings will be recorded in the subject's Medical History according to the Investigator's clinical judgment. Risk factors may be reviewed within the medical record and may be obtained through patient interview.

10.1.4. Echocardiogram

An echocardiogram (echo) is an ultrasound image of the heart. Transthoracic echocardiographic assessment of the right heart will be performed from the apical 4-chamber, parasternal long-axis and short-axis views, and subcostal views, adhering to the standards recommended by the American Society of Echocardiography and the European Association of Echocardiography (20). All echo images will be collected and uploaded for evaluation by a Core Lab during the study.

The following echocardiographic parameters of RV function and size will be obtained:

Right Ventricle (RV) basal end-diastolic diameter measured endocardium to endocardium of the right ventricle, from the apical 4-chamber view

Left Ventricle (LV) basal end-diastolic diameter measured endocardium to endocardium of the left ventricle, from the apical 4-chamber view

RV/LV ratio of RV to LV. Note: If image quality from the apical view is inadequate, the subcostal view may be utilized for obtaining the RV/LV diameter ratio. If the subcostal view is used for measurement, the same view should be used for subsequent measurements of the same subject.

TAPSE tricuspid annular plane systolic excursion, from the apical 4-chamber view

Flattened ventricular septum/D-sign of the LV from the parasternal short access, presence/absence of a flattened interventricular septum ('D-sign' of the left ventricle)

Tricuspid regurgitation jet velocity from 4-chamber view, using continuous-wave Doppler, in order to estimate systolic RV (and thus PA) pressure

Inferior Vena Cava (IVC) measurement and respirophasic change

- IVC minimum diameter (at end of inspiration) (mm) on subcostal view
- IVC maximum diameter (at end of expiration) (mm) on subcostal view
- IVC collapsibility index (%): $[(IVC_{max} - IVC_{min}) / IVC_{max}] \times 100$ (auto calculated)

10.1.5. NEWS Score

NEWS is a validated, standardized, easy-to-use clinical tool, which determines the degree of illness and mortality risk of a patient and can be used to prompt critical care intervention (21, 22). The score assesses and integrates the following vital parameters: respiratory rate (breaths per minute); oxygen saturation; breathing room air or need for supplemental oxygen; temperature; systolic blood pressure; pulse rate; and level of consciousness. NEWS is recommended by the National Health System in the United Kingdom for initial assessment, serial monitoring, and assessment of patients for triage, but it has also been validated in other countries including the United States (18). See Appendices for a reference NEWS table.

Calculation of the NEWS score will be performed at baseline, 24 hours post randomization, and subsequently every 24 hours through discharge or 7 days post-randomization, whichever comes first. In addition to these predefined times, calculation of the NEWS score should be performed *on an emergency basis* if there is rapid clinical deterioration of the subject any time after the first 24 hours following randomization.

At each planned or emergency measurement, the values of each parameter comprising the NEWS score and the total NEWS score will be entered in the EDC. Precise recording of each individual parameter, and the exact time of measurement, are critical in order to permit adjudication by the independent and blinded CEC.

If at any time a NEWS score of 9 or higher is calculated, the score must be recalculated 15 minutes later to confirm, if it is again 9 or higher, that the primary endpoint is met. This will help to exclude temporary alterations such as a tachycardia run or sudden excitation with hyperventilation.

10.1.6. World Health Organization Functional Class

World Health Organization (WHO) Functional Class assessment is a system for assessing the severity of dyspnea in patients with pulmonary hypertension (30). Subjects will be classified as Class 1-4 at time points throughout their participation in the study. See Appendices B for a table with the categories and descriptions of each category.

10.1.7. 6 Minute Walk Test (6MWT)

The 6MWT measures the distance a patient can walk on a flat surface in a period of 6 minutes (23). A 100 meter distance is measured in a hallway and the patient is asked to walk quickly as many laps as they can over the course of the timed test. The total distance is measured. The patient's baseline vitals and symptoms are compared to their condition at the completion of the test.

10.1.8. Post-Venous Thromboembolism Functional Status (PVFS) Scale

The Post-Venous Thromboembolism (VTE) Functional Status (PVFS) scale focuses on relevant aspects of daily life during follow-up after a venous thromboembolic event (24). The scale is neither intended to solely focus on VTE-associated functional limitations nor to diagnose post-VTE syndrome. In contrast, the scale has been developed to help users become aware of current functional limitations in patients who have suffered a VTE, whether or not as a result of the specific VTE, and to objectively determine the degree of disability (24).

The PVFS scale can be assessed by either medical experts or trained interviewers during a short structured interview or may be self-reported by the subject. For this trial, the PVFS will be completed as a structured interview, which is recommended in clinical trial settings as it is designed to further reduce subjectivity and bias. For the assessment, the interviewer is encouraged to base their assessment on the subject's ability to perform the activity rather than whether the subject performs the activity currently. This prevents overestimation of the severity of symptoms in subjects who have chosen to abandon or who simply never performed certain activities during a VTE diagnosis.

Interviews can be completed in-clinic during office visits, or by phone. The day-7 PVFS will be completed by phone for subjects who have already been discharged from the hospital. In cases in which a subject is unable to return to the clinic for a subsequent follow up visit, the PVFS can also be completed by phone interview.

10.1.9. Pulmonary Embolism Quality of Life (PEmb-QOL)

PEmb-QOL is a questionnaire that assesses post-pulmonary embolism quality of life in the context of pulmonary-specific symptoms. The PEmb-QOL questionnaire contains six dimensions based on the contents of the items: frequency of complaints, limitations in activities of daily living, work-related problems, social limitations, intensity of complaints and emotional complaints. Higher scores indicate worse outcome (25).

Each subject should be given a copy of the questionnaire to complete themself. If there are instances in which the subject cannot return to the clinic for a follow up visit, but they can complete a follow up visit via phone, this questionnaire can be completed by phone interview

or mailed to the subject to be completed at home. If mailed, it should be sent with an addressed return envelope with enough lead time for the subject to complete the questionnaire within the given visit window. The method used to complete the questionnaire will be indicated in the EDC.

10.1.10. Short Form-36 (SF-36)

The SF-36 questionnaire is a generic quality of life measure containing eight health domains (physical functioning, physical role, pain, general health, vitality, social function, emotional role functioning, and mental health) (26). The scoring is on a 0-100 scale, with a higher score indicating better health. Scores are combined into two overall summary scores: physical health summary score and mental health summary score (26).

Each subject should be given a copy of the questionnaire to complete. If there are instances in which the subject cannot return to the clinic for a follow up visit, but can complete a follow up health check via phone, this questionnaire should be mailed to the subject with an addressed return envelope with enough lead time for them to complete it on the day of the follow up phone call.

10.1.11. EQ-5D

The EQ-5D is a patient reported outcome that provides a simple descriptive profile and single index value for health status. The questionnaire consists of 5 questions pertaining to specific health dimensions, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall health status rating scale (27).

Each subject should be given a copy of the questionnaire to complete themself. If there are instances in which the subject cannot return to the clinic for a follow up visit, but they can complete a follow up visit via phone, this questionnaire can be mailed to the subject to be completed at home. If mailed, it should be sent with an addressed return envelope with enough lead time for the subject to complete it within the given visit window. The method used to complete the questionnaire will be indicated in the EDC.

10.1.12. Adverse Events

Specified adverse events and serious adverse events will be reported for this study. At each timepoint, the Investigator or designee will review if the subject has experienced any reportable AEs, and if so, report the event in the EDC. At the 7 day post-randomization time point, they will be prompted to assess for the primary composite endpoint.

Refer to Section 18 for more details on adverse event reporting.

10.1.13. Anticoagulation Medication

For all subjects, anticoagulation therapy (i.e. type, dose/rate, frequency) shall be recorded from the time of hospital presentation through 12-month follow up.

All subjects will be treated with anticoagulant medication [either subcutaneous low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH)] according to the

treatment protocol following randomization. Anticoagulation treatment protocols are provided below in section 10.3.4. Guidelines should be followed for transitioning from parenteral to oral anticoagulation (28).

Based on current guidelines (6), it is recommended that anticoagulant treatment is prescribed at therapeutic doses for a minimum of 3 months and ideally longer. After 3 months, the duration and dose of anticoagulant treatment should be determined by the subject's physician.

At each follow up timepoint, the Investigator or designee will evaluate with the subject whether there have been any changes to prescribed anticoagulation medications.

10.2. *Data Collection Schedule*

The data collection schedule is shown in **Error! Reference source not found.**.

Table 10.1: Data Collection Schedule

Procedure/Assessment	Screening (Baseline)	Enrollment (Randomization)	Index Procedure	48±6 Hours Post-Randomization	Follow-up			
					7+2 Days (or Discharge)[f]	30±7 Days	6 Months ± 14 Days	12 Months ± 30 Days
CTPA	X							
Laboratory tests[a]	X			X				
Informed consent process	X							
Demographics	X							
Transthoracic echocardiogram	X[b]			X		X	X[g]	X
Medical history and risk factors	X[c]							
Confirmation of eligibility		X						
Randomization		X						
Initiation[d] **of assigned therapy [USCDT with anticoagulation or anticoagulation]**			X					
NEWS score	X[b,e]			X[e]	X[e,f]			
Vitals	X			X	X[f]	X	X	
WHO functional class					X[f]	X	X	X
6MWT						X	X	X
PVFS Interview					X	X	X	X
PEmb-QOL							X	X
SF-36							X	X
EQ-5D							X	X
Adverse event assessment		X	X	X	X[f]	X	X	X
Review of anticoagulation medication	X		X	X	X[f]	X	X	X

a) At baseline and 48±6hrs post-randomization, CBC, Chemistry, and Biomarkers will be collected. Troponin I or troponin T is required for eligibility. In the case of a bleeding event, hemoglobin, hematocrit, and platelet count shall be entered in the Bleeding Event form.
b) Baseline may be completed before or after randomization, but must be completed prior to initiation of assigned therapy, i.e. within six (6) hours of confirmation of intermediate-high risk PE.
c) Medical history includes collection of anticoagulation medications since presentation to hospital.
d) Continuation of anticoagulation protocol for subjects who are assigned to anticoagulation and already receiving therapy.
e) NEWS score is collected at baseline, and daily starting at 24 hours post-randomization through 7 days post-randomization
f) When subjects are discharged prior to 7 days post-randomization, indicated assessments shall be performed on day of discharge. At 7 (+2) days post-randomization, a follow-up phone call will be made to the subject to complete the PVFS and review changes to health status.
g) At select sites, where standard of care, up to 100 subjects.

10.3. *Schedule of Events*

10.3.1. Study Candidate Screening

Patients who present for evaluation and treatment of PE shall be serially screened for inclusion in the study. They shall be documented for pre-screening on the Screening and Enrollment Log as they present. Standard of care assessments should be reviewed to assess whether the patient meets criteria for intermediate-high risk PE.

If the patient's condition deteriorates at any time during the screening process such that immediate start of life-saving therapy (such as CPR) becomes necessary, further attempts to complete screening procedures will be abandoned, and the patient will be treated immediately as deemed appropriate by the responsible clinician. The patient will be considered a screen failure.

The following assessments will be performed at Screening (Baseline):

- Computed tomographic pulmonary angiography (CTPA) to confirm eligibility
- Laboratory testing: CBC, Chemistry, and Biomarkers (Troponin I or T required for inclusion)
- Vitals
- Medical history and risk factors (includes anticoagulation medication since presentation to hospital)
- Demographics
- Transthoracic echocardiogram
- NEWS score

10.3.2. Informed Consent

Patients who are enrolled into this study may be treated with anticoagulation or a combination of anticoagulation and a catheter-based intervention. It will be important for patients to understand that both treatment options are approved, commercially-available, and that the best treatment for intermediate-high risk PE is not yet known. During the consenting process, the risks of both treatment options should be presented to the patient, and they should be given adequate time to have their questions answered. Please refer to section 19 of this protocol for all requirements and recommendations related to obtaining informed consent.

Once a patient has been confirmed to meet criteria for intermediate high-risk PE through standard assessments (e.g., CTPA, biomarkers), the Investigator or designee should complete the informed consent process with the patient or legally designated representative.

Informed consent will be obtained prior to performing any study-related procedures or assessments, including study-specific screening and baseline assessments. Patients are not to be placed at additional risk caused by delays in treatment because of difficulties in obtaining informed consent for the research.

10.3.3. Enrollment (Randomization)

Randomization should occur as soon as practical after the Investigator confirms the diagnosis of intermediate-high risk PE as defined by inclusion criteria #2-5. Prior to randomization, the Investigator or designee must also review and confirm the subject meets all other eligibility criteria.

For subjects randomized to receive USCDT, therapy should be initiated no more than six hours of confirmation of diagnosis of intermediate-high risk PE; it is strongly recommended it is initiated within two (2) hours of randomization.

10.3.4. Procedure

10.3.4.1. Experimental (USCDT) Arm

The USCDT procedure must be performed by an appropriately delegated and protocol-trained Investigator. Investigators can be interventional cardiologists, interventional-pulmonologists, radiologists, or vascular, cardiac, or cardiothoracic surgeons, or other vascular specialists credentialed to perform the procedure. The procedure must be performed in a facility with digital angiographic equipment.

The beginning of the intervention, defined as successful venous puncture, must occur no more than six hours in total after confirmation of intermediate-high risk PE as defined above in section 10.3.3. It is strongly recommended the intervention is initiated within two (2) hours of randomization.

The study site personnel should follow standard practices for pre-procedure hydration, and for steroid and histamine antagonist pre-medication for subjects with contrast allergies.

The study physician should review the CTPA, select venous access site(s), and determine whether one or two infusion catheters are required. If bilateral proximal thrombus is present, two infusion catheters should be placed. Each patient requires at least unilateral main left or right PA or lobar arterial clot to qualify, but the PE should be considered for bilateral treatment if there is segmental/lobar or main PA clot on the other side.

Any reportable adverse events following randomization should be documented on the Adverse Event eCRF.

10.3.4.1.1 USCDT Procedure

The procedure should be conducted in accordance with the IFU and local hospital standards.

The infusion time should be 7 hours [total r-tPA dose for 1 catheter, 9 mg (bolus plus infusion); for two catheters, 18 mg (bolus plus infusion)]. NaCl 0.9% at a rate of 35 mL/hour/device will be used as coolant.

Figure 10.1: r-tPA Dose Summary

2 mg bolus/catheter
+ 1 mg/hour/catheter for 7 hours
(total of 9 or 18 mg)

During r-tPA infusion, the physician should reduce the r-tPA dose or stop the infusion altogether if there is evidence of bleeding.

When USCDT is completed, the sheath may be removed at the bedside, but not earlier than 1 hour after the r-tPA infusion is stopped. Hemostasis should be achieved by manual compression. The subject should remain on bedrest for 2 hours after sheath removal, after which he/she may ambulate as tolerated.

10.3.4.1.2 Anticoagulation with USCDT

Ensure all anticoagulation medications are recorded on the Anticoagulation Medication Log throughout and following the procedure.

- *Before the procedure:* The subject will receive LMWH at 1mg/kg twice daily or UFH (at a therapeutic dose according to labeling and established protocols (28)) until the start of the USCDT procedure. Note: If the subject is anticoagulant-naïve at the time of randomization, will be treated with UFH, and will receive the initial dose upon randomization, an intravenous (IV) bolus of 80 U/kg, not to exceed a total of 8,000 U should be given, followed by an infusion at the therapeutic dose, up to the initiation of the procedure.
- *During the procedure:* All subjects will receive an IV UFH infusion throughout the procedure and following for up to four hours, at an infusion rate of 300-600 U/h. The exact infusion rate within this range will be left to the Investigator's discretion and be based, among other things, on the subject's body weight, overall condition, and bleeding risk.
- *Following the procedure:* The subject should be transitioned to full-dose parenteral anticoagulation, either twice-daily LMWH or UFH, no more than four hours after the end of the USCDT procedure (i.e. end of thrombolytic infusion), unless there are documented bleeding concerns.
- *Ongoing Anticoagulation:* Subjects may be transitioned to any commercially-available oral anticoagulant no sooner than 24 hours after the end of the USCDT procedure (i.e. end of thrombolytic infusion). Practical guidelines by scientific societies should be followed for transitioning from parenteral to oral anticoagulation (29).
  - When transitioning from LMWH to a direct oral anticoagulant (DOAC), start the new medication 0–2 hours prior to the next scheduled administration of the initial anticoagulant and then discontinue the initial anticoagulant.
  - When transitioning from UFH to a DOAC, stop the heparin infusion and begin administration of the DOAC at the same time.

  Based on current European Society of Cardiology (ESC) guidelines (6), anticoagulant treatment should be given at therapeutic dose for at least 3 months. After 3 months, the duration and dose of anticoagulant treatment should be determined by the clinician responsible for PE follow up.

10.3.4.2. Control (Anticoagulation) Arm

This is an open-label trial. The control arm will not receive an interventional procedure. Ensure all anticoagulation medications are recorded on the Anticoagulation Medication Log. Any reportable adverse events following randomization should be reported on the Adverse Event eCRF.

10.3.4.2.1 Anticoagulation

If the subject is anticoagulant-naïve, the Investigator may choose to use LMWH or UFH. If the subject has already received LMWH or UFH, therapy with the same anticoagulant should continue. See below for each treatment protocol.

- *Anticoagulation following Randomization:* The subject will receive LMWH at 1mg/kg twice daily or UFH (at a therapeutic dose according to labeling and established protocols (28)).
- *Ongoing Anticoagulation:* The subject may be transitioned to an oral anticoagulation of choice no sooner than 24 hours after initiation of their randomized treatment. Practical guides by scientific societies should be followed for transitioning from parenteral to oral anticoagulation (29).
  - When transitioning from LMWH to a DOAC, start the new medication 0–2 hours prior to the next scheduled administration of the original medication, then discontinue the original anticoagulant.
  - When transitioning from UFH to a DOAC, stop the heparin infusion and begin administration of the DOAC at the same time.

Based on current ESC guidelines (6), anticoagulant treatment should be given at therapeutic dose for at least 3 months. After 3 months, the duration and dose of anticoagulant treatment should be determined by the clinician responsible for PE follow up.

10.3.5. 48 Hours Post-Randomization [±6 Hours]

The following assessments will be performed within 48 ± 6 hours after randomization.

- Transthoracic echocardiogram
- NEWS score (Note: The NEWS score will be collected starting at 24 hours post-randomization, once daily through 7-days post-randomization.)
- Laboratory testing: CBC, Chemistry, and Biomarkers
- Vitals
- Adverse event assessment
- Review of new or changes to anticoagulation medication

10.3.6. 7 Days Post-Randomization (Primary Outcome) [+2 Days]

The following assessments will be performed at 7 days after randomization:

- Vitals
- WHO functional class
- NEWS score (collection of final score)
- PVFS interview
- AE assessment, to include a primary endpoint assessment
- Review of new or changes to anticoagulation medication

If the subject is discharged prior to Day 7, the following assessments shall be completed on the day of discharge: Vitals, WHO functional class, NEWS score, AE assessment, and anticoagulation review. Subject shall be provided the Subject Discharge Card with instructions to seek immediate medical attention if any of the symptoms are experienced. In addition, the Investigator or designee will contact the subject by telephone on Day 7 post-randomization to complete the PVFS interview and an updated AE assessment to assess any changes to the subject's health since discharge, including any of the symptoms listed on the Subject Discharge Card.

The Hospitalization Record should be completed with details of the subject's admission and discharge from the hospital and/or intensive care unit (ICU)

NOTE: Subjects fulfilling any of the primary endpoint criteria for cardiorespiratory collapse or decompensation may undergo rescue reperfusion treatment (such as systemic thrombolysis at any dosage, or percutaneous catheter-directed treatment with or without local thrombolysis) at the Investigator's discretion. In contrast, arbitrary institution of any reperfusion treatment after randomization in the absence (or non-documentation) of any of the listed criteria is strongly discouraged and will be considered a protocol deviation.

10.3.7. 30 Days Post-Randomization [±7 Days]

- Transthoracic echocardiogram
- Vitals
- WHO functional class
- 6MWT
- PVFS interview
- Adverse event assessment
- Review of new or changes to anticoagulation medication

10.3.8. 6 Months Post-Randomization [±14 Days]

- Transthoracic echocardiogram (select sites, where standard of care)
- Vitals
- WHO functional class
- 6MWT
- PVFS interview
- PEmb-QOL
- SF-36
- EQ-5D
- Adverse event assessment
- Review new or changes to anticoagulation medication

10.3.9. 12 Months Post-Randomization [±30 Days]

- Transthoracic echocardiogram
- WHO functional class
- 6MWT
- PVFS interview
- PEmb-QOL
- SF-36
- EQ-5D
- Adverse event assessment
- Review new or changes to anticoagulation medication

10.3.10.Study Completion

Each subject will be followed for 12 months after randomization. At the completion of their participation in the study, a Study Completion eCRF will be completed to indicate their status at the 12-month point (e.g., completed all follow up visits, withdrawn, lost to follow up, deceased).

Reported AEs will be followed until resolved. If there are AEs that are unresolved when a subject's participation in the study has ended, they will be referred to the subject's primary physician for further management.

A subject's data will be considered complete when all data from completed visits have been entered into the EDC, all visits have been monitored centrally, remotely, or on-site, all data issues have been resolved to a satisfactory level, all images have been uploaded into the EDC, images have been read by the core lab, and all reportable AEs have been adjudicated by the Clinical Events Committee.

10.3.11. Strategies for Recruitment and Retention

Subjects will be recruited from patients presenting for emergency evaluation and treatment for pulmonary embolism. Most patients will present through the ED and will be identified by a pulmonary embolism response team (PERT) or by the treating physician once they are diagnosed as having an intermediate-high risk PE. Hospital PERTs (where applicable) and ED staff should be made aware of the key inclusion criteria for the trial so study staff can be notified when potential patients present for screening. Due to the acute nature and emergency status of this patient population, patient recruitment, advertising, and patient referrals are not appropriate. Training materials and other protocol tools will be made available to ED staff and study staff to aid in identification of subjects.

Each subject must complete the informed consent process with an appropriately delegated and trained research staff. Additionally, placement of the EkoSonic™ catheter(s) for subjects randomized to the USCDT treatment arm must be performed by an experienced operator who is appropriately delegated and trained. Each investigational site shall put in place strategies to ensure delegated and trained staff are available to consent and treat (as applicable) study subjects when they present for emergency treatment. Some strategies include but are not limited to: adding research staff trained to the protocol in order to provide coverage for consenting; Investigators delegated to obtain consent and screen for inclusion, and adding interventional staff as sub-Investigators to be delegated and trained to the protocol.

Patients should be serially screened for inclusion as they present to the ED. Patients who present for evaluation and treatment of intermediate-high risk PE will be recorded on the Screening and Enrollment Log. If the patient later chooses not to provide informed consent or is identified as a screen failure, that information will be recorded on the Log. If a site has not enrolled any subjects within the first 6 months, the Sponsor reserves the right to evaluate the site for early closure.

In order to maintain the integrity of the long-term follow up data for this trial, every effort will be made to follow each subject through to their 12-month follow up visit.

- Multiple methods of contact will be collected from each subject at the time of enrollment. In the case of one or more missed visits, research staff will continue to try to contact the subject for scheduling each follow up visit until the 12-month follow up time point.
- Research staff will provide the follow up schedule to each subject and review the importance of them returning for each visit.
- In the case where a subject is not able to return to the site for a follow up visit, research staff will conduct the visit by phone to include a health check to review any new AEs and changes to anticoagulant medication and any assessments that can be completed by phone (e.g., PVFS). Other questionnaires will be mailed to the subject as applicable.

- Compensation for the subject's travel and time will be paid in accordance with local regulations and site policies.

10.4. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.2: Source Documents. Some source documents may be uploaded and redacted within the EDC for remote source document verification and/or adjudication of adverse events.

Table 10.2: Source Documents

Visit	Requirement
Screening (Baseline)	CTPA report to include date/time of assessment and finding; to confirm a filling defect in at least one main or proximal lobar artery, and RV/LV
	Laboratory report
	Clinical assessments since presenting to ED. Necessary to evaluate clinical risk factors for Inclusion Criteria. Should include vitals in review
	Echocardiogram images to include RV/LV*
	Echocardiogram report to include date/time of assessment and findings
Procedure/Intervention	Cath Lab Procedure Report to capture dates/times of placement of device, any AEs, or Device Deficiencies
	Medication Log to include Thrombolytic and Anticoagulation
	Nursing Notes to capture any AEs during therapy
48-Hours Post-Randomization	Laboratory report
	Echocardiogram images to include RV/LV*
	Echocardiogram report to include date/time of assessment and findings
	Nursing and Physician Notes to capture any new AEs.
	Medication Log to review changes to anticoagulation
7-Days Post-Randomization (or Discharge)	PVFS interview
	Nursing and Physician Notes to capture any new AEs.
	Discharge Summary (if applicable)
	Medication Log to review changes to anticoagulation
30-Days Post-Randomization	Echocardiogram images to include RV/LV*
	Echocardiogram report to include date/time of assessment and findings
	Visit summary to capture any new AEs.
	Medication Log to review changes to anticoagulation
	6MWT, PVFS interview
6-Months Post-Randomization	(At select sites) Echocardiogram images to include RV/LV*

Table 10.2: Source Documents

Visit	Requirement
	(At select sites) Echocardiogram report to include date/time of assessment and findings
	Visit summary to capture any new AEs
	Medication Log to review changes to anticoagulation
	6MWT, PVFS interview, PEmb-QOL, SF-36, EQ-5D
12-Months Post-Randomization	Echocardiogram images to include RV/LV*
	Echocardiogram report to include date/time of assessment and findings
	Visit summary to capture any new AEs
	Medication Log to review changes to anticoagulation
	6MWT, PVFS interview, PEmb-QOL, SF-36, EQ-5D
Unscheduled Visit/Adverse Event	Echocardiogram report and image (as applicable), CTPA report and image (as applicable), select hospitalization records

*Will be uploaded for evaluation by the Core Lab.

10.5. *Local laboratory documentation*

This study requires a local laboratory for processing baseline and follow up labs. Appropriate certifications and documentation records are required to be maintained at the site for the laboratory. Copies of certifications and specified local laboratory normal ranges will be requested for Sponsor filing and EDC programming.

11. Statistical Considerations

11.1. *Primary Endpoint*

The primary endpoint is a composite of PE-related mortality, cardiorespiratory decompensation or collapse (as defined below), or non-fatal symptomatic and objectively confirmed recurrence of PE, within seven (7) days of randomization.

Cardiorespiratory collapse or decompensation should fulfill at least one of the following criteria:

a) cardiac arrest or need for CPR at any time between randomization and day 7;

b) signs of shock: new-onset persistent arterial hypotension (SBP below 90 mmHg or SBP drop by at least 40 mmHg over at least 15 minutes, and despite an adequate filling status; or need for vasopressors to maintain SBP of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time between randomization and day 7;

c) placement on ECMO at any time between randomization and day 7;

d) intubation, or initiation of non-invasive mechanical ventilation at any time between randomization and day 7;

e) National Early Warning Score (NEWS) of 9 or higher, between 24 hours and 7 days after randomization, confirmed on consecutive measurements, taken twice.

11.1.1. Hypotheses

The treatment group (i.e. USCDT combined with anticoagulation) will be associated with a significant reduction in the primary outcome compared to the control group (i.e. anticoagulation alone).

The null hypothesis is that the probability of a primary outcome event in the control group (π_c) and in the treatment group (π_t) is identical; the alternative hypothesis is that the probability of an event is lower in the treatment group than in the control group:

$\mathbf{H_0}$: $\pi_t = \pi_c$

$\mathbf{H_1}$: $\pi_t < \pi_c$

11.1.2. Sample Size

The study is designed to detect a 15% versus 5% difference (i.e. odds ratio = 0.298) in the primary endpoint event rate. The expected rate of the primary efficacy endpoint for the control group was derived from the subset of patients in the placebo arm of the PEITHO study who had SBP $\leq$ 110 mmHg and respiratory rate > 20 x min^{-1} at baseline as approximately 15%. Due to uncertainty in the expected event rate in the treatment arm, a sample size re-estimation is planned, which would allow the sample size to increase in order to detect a 15% vs 6% difference in event rates (i.e. odds ratio = 0.362).

A total of 406 patients will yield 90% power to detect the target difference in event rates (i.e. odds ratio = 0.298) with a one-sided alpha of 0.025 using a Pocock alpha spending group sequential design with 1 interim analysis.

If the sample size is increased after the interim analysis, the final analysis will be performed with 544 randomized patients, which will result in 90% power to detect a reduction in the event rate from 15% to 6% (i.e. odds ratio = 0.362) with a final one-sided alpha of 0.01469.

An adjustment to the sample size to take account of patients who will be lost to follow-up is not required since it can be reasonably assumed that all patients will be assessed for the primary endpoint at seven (7) days.

11.1.3. Statistical Methods

Analysis of the primary endpoint will be performed on the Intention-To-Treat (ITT) and Per-Protocol (PP) populations (defined below in section 11.2.1). The primary analysis will be performed on the ITT population.

A Pocock alpha-spending group sequential design will be used with one interim analysis after inclusion of 50% of the patients. Adaption of the trial, including a sample size increase, will be possible based on the results of the interim analysis.

A chi-square test will be used to compare the primary endpoint between the treatment and control groups; the odds ratio and corresponding 95% confidence interval will be presented. A logistic regression, which includes the stratification factors used at randomization as covariates, will be performed as a sensitivity analysis. Multicollinearity will be assessed using the variance inflation factor.

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

Analysis of the primary and secondary assessments will be performed on the ITT and PP populations. The ITT population will comprise all randomized patients who met study eligibility criteria. The PP population will comprise all patients in the ITT population without significant protocol deviations.

Safety analyses, including adverse events and SAEs, will be performed on the treated population, comprising patients in the ITT population who received USCDT (i.e. patients for whom the EkoSonic™ device was activated and r-tPA infusion begun) or who received anticoagulation.

11.2.2. Control of Systematic Error/Bias

Randomization of subjects into the treatment or control group will remove patient selection bias. Blinded review of the primary endpoint data by an independent CEC will remove bias due to the open-label design of the study.

An independent DSMB will review safety data and the results of the interim efficacy analysis. The DSMB will provide their recommendation to the Sponsor to continue the study with the original sample size, to increase the sample size, or to stop the study early, but the actual results of the interim efficacy analysis will not be communicated to the Sponsor (unless the recommendation is to stop the study early) to prevent interim efficacy results impacting the treatment of subsequently randomized patients.

11.2.3. Number of Subjects per Investigative Site

It is anticipated that each site will screen and enroll all eligible and willing participants who present to the investigational site with intermediate-high risk PE over the planned 24-month enrollment period. Sites will not be limited to a number of subjects per site; however, Study Management will track enrollment over the course of the study and enrollment may be suspended at a site at any time if a significant imbalance occurs among sites. If a site has not enrolled any subjects within the first 6 months, the Sponsor reserves the right to evaluate the site for early closure.

11.3. *Data Analyses*

Analysis of additional assessments will be described in the statistical analysis plan (SAP).

11.3.1. Interim Analyses

An **efficacy interim analysis** will be assessed by the independent DSMB after 50% of the expected number of patients (1). The superiority of the treatment group versus the control group will be tested by a chi-square test. If the interim analysis takes place with exactly 50% of the patients, the 1-sided significance level for the interim analysis is $\alpha_1 = 0.01469$, and is $\alpha_2=0.01469$ for the final analysis using Pocock alpha spending. A conditional power of ≤ 15% at the interim analysis could result in the study stopping early for futility. A sample size increase to 544 patients will be considered at the interim analysis following the Promising Zone methodology described in Mehta and Pocock (2), to ensure control of Type I error.

Adaptive design: The following decisions can be made based on which of the zones, defined below, the results of the interim analysis fall into:

- Futility zone: stop for futility if the conditional power is ≤ 15%
- Unfavorable zone: if the conditional power is > 15% and < CP_{min} the study will continue with the original sample size; the value of CP_{min} will be provided in the statistical analysis plan.
- Promising zone: if the conditional power is ≥ CP_{min} and < 90% the sample size will be increased to 544 patients
- Favorable zone: if the conditional power is > 90% the study will continue with the original sample size
- Efficacy: stop for efficacy if the 1-sided p-value is < 0.01469.

11.3.2. Subgroup Analyses

Subgroup analyses to assess the heterogeneity of the treatment (USCDT) effect will be described in the SAP.

11.3.3. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

12. Health Economics Outcomes

A health economics analysis is planned as part of this study. This will take into consideration any differences in survival, complication rates, quality of life, and resource utilization (including length of stay, need for intensive care, and duration of acute care). The EQ-5D and other information collected regarding length of stay and AEs will be used to assess health utilities. Costs associated with the health care utilization measures may be analyzed by region or country.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by the Medidata RAVE EDC System (United States). All changes made to the clinical data will be captured in an electronic audit trail and available for review by the Sponsor or its representative. The associated software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides their electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all closeout activities are completed a request is submitted to have the "Database Locked" or "Decommissioned" and all database access revoked.

13.2. *Data Retention*

The Principal Investigator, designee, or investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the Sponsor must receive written notification of this custodial change. Sites are required to inform the Sponsor in writing where paper or electronic files are maintained in case files are stored off-site and are not readily available.

13.3. *Core Laboratory*

Transthoracic echocardiograms collected at Screening (Baseline), 48 hours, 30 days, 6 months (at select sites) and 12 months post-randomization will be deidentified and uploaded into an image management system to be read by the Core Lab. The Core Lab will access the images

for centralized assessment electronically. Applicable Core Lab data from the images will be entered directly into the EDC on the Core Lab eCRFs.

The option to upload CTPAs and echocardiograms for confirmation of eligibility and adjudication of adverse events will also be available through the image management system.

Further instructions for deidentifying and uploading images will be provided by the Core Lab.

14. Protocol Deviations

An Investigator must not make any changes or intentionally deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the Sponsor and the reviewing Institutional Review Board (IRB), Ethics Committee (EC), or Research Ethics Board (REB), and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and of those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All reportable deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor using the Protocol Deviation eCRF. Sites may also be required to report deviations to the IRB/EC/REB, and the regulatory authority, per local guidelines and national/government regulations.

At a minimum, the following deviations will be reported into the EDC:

- Missing visits or assessments
- Out-of-window visits or assessments
- A subject not consented or for which the consent process is not completed properly
- A subject not meeting eligibility criteria
- A subject not treated according to randomized assignment.

  Note: If a subject meets any of the criteria of the primary endpoint and requires additional therapy, the subject may undergo rescue reperfusion treatment (including systemic thrombolysis at any dosage or percutaneous catheter-directed treatment with or without local thrombolysis) at the Investigator's discretion. The reason for the escalation of therapy will be documented in the eCRFs. However, any reperfusion treatment after randomization, in the absence (or non-documentation) of any of the above criteria, is strongly discouraged and will be considered a protocol deviation.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/EC/REB/Regulatory Authority notification as required, site re-training, or site discontinuation/termination) will be put into place by the Sponsor.

The Sponsor will not approve protocol waivers.

15. Compliance

15.1. *Statement of Compliance*

This clinical investigation is financed by the study Sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the Sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the Investigator. This study will be conducted in accordance with the principles of International Organization for Standardization (ISO) 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the Sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

15.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the principles of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide their qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to Sponsor, per the protocol requirements, all reportable events.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a serious adverse device effect (SADE) and potential/unanticipated serious adverse device effect (USADE) or unanticipated adverse device effect (UADE), if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply Boston Scientific with any additional requested information related to the safety reporting of a particular event.
- Allow the Sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in the clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and

disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, verifying that designees are competent to perform the tasks they have been delegated and performing adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The Principal Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. *Institutional Review Board/ Ethics Committee/ Research Ethics Board*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required. Where possible, the Sponsor or designee will obtain approval from a centralized IRB/EC/REB and provide approval documentation to sites within the applicable region. Approval must also be obtained for the ICF, other materials which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will also be reviewed and approved by the IRB/EC/REB; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the Sponsor. A copy will be maintained in the Investigator Site File as well.

15.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific concerning subjects or their participation in this study will be considered confidential by Boston Scientific and will be kept confidential in accordance with all applicable laws and regulations. Only authorized Boston Scientific personnel and/or a Boston Scientific representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by Boston Scientific for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

15.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the Investigator and other health care providers (collectively HCP) as needed. Support may include HCP training, addressing HCP questions, or providing clarifications to HCP concerning the operation of Boston Scientific equipment/devices.

Boston Scientific personnel may perform certain activities to ensure study quality. These activities may include the following:

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

15.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage for subjects in the study will be obtained by Boston Scientific.

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by Boston Scientific personnel, their designees, and appropriate regulatory authorities.

The Sponsor will put a plan in place to document the specific monitoring requirements. This study will employ risk-based monitoring, with a combination of centralized data review, remote and on-site monitoring visits. A tool will be made available within the EDC for uploading and redacting source records to allow the clinical research monitor to remotely review the records.

The study may also be subject to a quality assurance audit by Boston Scientific or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

17. Potential Risks and Benefits

17.1. *Risks Associated with the Study Intervention*

There are some known risks associated with use of the EkoSonic™ Endovascular Device. The intervention is of no greater risk to subjects who participate in the trial than for patients who would receive the intervention as standard of care. Additional information regarding the intervention can be found in the Instructions for Use.

Some of the potential complications of use of the EkoSonic™ Endovascular Device are:

- Vessel perforation or rupture
- Distal embolization of blood clots
- Vessel spasm
- Hemorrhage
- Hematoma
- Pain and tenderness
- Sepsis/Infection
- Thrombophlebitis
- Tricuspid and pulmonic valve damage
- Pulmonary infarct due to tip migration and spontaneous wedging, air embolism, and/or thromboembolism
- Right bundle branch block and complete heart block
- Hemothorax
- Intimal disruption
- Arterial dissection
- Vascular thrombosis
- Drug reactions
- Allergic reaction to contrast medium
- Arteriovenous fistula
- Thromboembolic episodes
- Amputation
- Pneumothorax
- Perforation of the PA
- Cardiac arrhythmias – most frequently occurring during placement, removal or following displacement into the right ventricle
- Cardiac tamponade

17.2. *Risks associated with Participation in the Clinical Study*

As this study is a post-market study, the additional risk associated with participating in this study is related to the collection of patient data and confidentiality thereof. Follow up assessments (e.g., echocardiogram) are standard of care, but may be collected at different times or more frequently than is typical for a patient not in a clinical trial. Subjects are also asked to complete interviews and questionnaires that are not part of standard care. There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time.

17.3. *Possible Interactions with Concomitant Medical Treatments, if applicable*

The combination of lytics and anticoagulation may increase the risk of bleeding.

17.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying Boston Scientific with all pertinent information required by this protocol.

17.5. *Anticipated Benefits*

Subjects may or may not receive benefits from participating in this study. Medical science and future patients may benefit from the results of this study.

17.6. *Risk to Benefit Rationale, if applicable*

The EkoSonic™ device is commercially approved and has been proven to be suitable for its intended purposes. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of the appropriate Instructions for Use. Evaluation of the risks and benefits that are expected to be associated with the use of the devices demonstrate that when used under the conditions intended, the benefits associated with the use of the devices should outweigh the risks.

18. Safety Reporting

18.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to Boston Scientific any event which occurs in any of following categories:

- All device-related adverse events (AE)

- All procedure-related adverse events
- All device deficiencies (DD)
- Unanticipated adverse device effects (UADE)/unanticipated serious adverse device effects (USADE)
- Serious adverse events (SAE) through 30 days
- Specific events of interest through 12 months post-randomization:
  - All cases of mortality
  - Hemodynamic collapse or decompensation
  - Recurrent PE (symptomatic and objectively confirmed cases)
  - Bleeding events
  - Ischemic or hemorrhagic stroke
  - New diagnosis of CTEPH
- New findings/updates in relation to already reported events

Please note that adverse and serious adverse events are not anticipated to be procedure- or device-related more than 30 days post-randomization.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after randomization, whether prior to, during or after the initiation of therapy, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see Table 18.1: Safety Definitions for AE definitions).

Refer to Instructions for Use or section 17.1 of this protocol for the known risks associated with the commercial device.

18.2. *Escalation of Therapy*

Subjects fulfilling any one of the primary endpoint criteria for cardiorespiratory collapse or decompensation may undergo rescue reperfusion treatment (such as systemic thrombolysis at any dosage, or percutaneous catheter-directed treatment with or without local thrombolysis) at the Investigator's discretion. The reason for the escalation of therapy should be well documented as an AE within the EDC. Reperfusion treatment or additional therapy that is different than the assigned randomized treatment, in the absence (or non-documentation) of an

associated AE, is strongly discouraged, will be considered a protocol deviation and not a primary endpoint.

18.3. *Definitions and Classification*

Adverse event definitions are provided in Table 18.1: Safety Definitions. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18.1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, including chronic diseases, or • in-patient hospitalization or prolongation of existing hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.

Term	Definition
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the device under study.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • ED visit that does not result in in-patient admission Note: although an ED visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief)

Term	Definition
	• pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.

18.4. *Relationship to Device Under Study and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the device(s) under study and study procedure. See criteria in Table 18.2: Criteria for Assessing Relationship of Device Under Study or Procedure to Adverse Event

Table 18.2: Criteria for Assessing Relationship of Device Under Study or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body site, or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the study device or with procedures beyond reasonable doubt when:

Table 18.2: Criteria for Assessing Relationship of Device Under Study or Procedure to Adverse Event

Classification	Description
Ref: MDCG 2020-10/1	- the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

18.5. *Investigator Reporting Requirements*

The communication requirements for reporting to the Sponsor are as shown in **Error! Reference source not found.**.

If it is not possible to report the event in the EDC within the given timelines, the event should be reported using the paper-based Adverse Event or Device Deficiency form located in the site Manual of Operations and submitted to HIPEITHOSafety@bsci.com.

Table 18.3: Communication Requirements for Safety Event Reporting

Event Classification	Communication Method	Communication Timeline (post-market studies) (*EU MDR 2017/745, MDCG 2020-10/1;* MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Reporting required through the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor

Table 18.3: Communication Requirements for Safety Event Reporting

Event Classification	**Communication Method**	**Communication Timeline (post-market studies)** (*EU MDR 2017/745, MDCG 2020-10/1;* MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through 30 days post-randomization.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of Sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of Sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate is considered a reportable event.	Complete the Device Deficiency eCRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE, resolution, assessment of seriousness and relationship to the device.	• Adverse Events: In a timely manner but recommend within 30 business days after becoming aware of the information • Adverse Device Effects: In a timely manner but not later than 30 business days after becoming aware of the information • Reporting required through 12 months post-randomization for ADEs and reportable AEs

Table 18.3: Communication Requirements for Safety Event Reporting

Event Classification	Communication Method	Communication Timeline (post-market studies) (*EU MDR 2017/745, MDCG 2020-10/1;* MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor

18.6. *Boston Scientific Device Deficiencies*

Device deficiencies for the EkoSonic™ Endovascular System will be documented and reported to the Sponsor. If possible, the device(s) under study should be returned to the Sponsor for analysis. Instructions for returning devices are available through the local Boston Scientific sales representative. Device deficiencies should also be documented in the subject's source records and on the Device Deficiency eCRF.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

18.7. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

The Sponsor is responsible for reporting relevant study-wide adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs per local/regional reporting requirements. The Investigator and delegated research staff will determine if an event is reportable to the IRB/EC/REB.

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or their legally designated representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by Boston Scientific or its delegate (e.g. CRO) and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the

investigative site's IRB/EC/REB. Any modification requires acceptance from Boston Scientific prior to use of the form. The ICF must be in a language understandable to the subject and if needed, Boston Scientific will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or their legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as their medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by Boston Scientific to the applicable regulatory authority according to their requirements. Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

20. Committees

20.1. *Safety Monitoring Process*

The Boston Scientific personnel from the Medical Safety and Safety Trial Operations groups review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The Boston Scientific Medical Safety and Safety Trial Operations teams include health care providers with expertise in vascular medicine and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20.2. *Data Safety Monitoring Board*

The independent Data and Safety Monitoring Board (DSMB) is responsible for the review of all safety data. The DSMB will include leading experts in vascular medicine, pulmonology, cardiology, and biostatistics who are not participating in the study and who have no affiliation with Boston Scientific. During the course of the study, the DSMB will review accumulating safety data to monitor the incidence of CEC-adjudicated events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DSMB Charter.

Data will be supplied to the DSMB in coded fashion (e.g., Treatment A, Treatment B). The code to identify which group received which intervention will be provided to the DSMB as described in the DSMB charter. Any DSMB recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality will be submitted in writing to the Executive Committee and Boston Scientific for consideration and final decision. However, if the DSMB at any time determines that a potentially serious risk exists to subjects in this study, the DSMB chairman will immediately notify both the Executive Committee chairman and Boston Scientific.

20.3. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant AEs reported by study investigators. The CEC will be blinded to treatment assignment and review safety event dossiers, which may include copies of subject source documents provided by study sites, for all reported cases of all-cause mortality, cardiorespiratory decompensation or collapse, and objectively confirmed recurrence of PE within seven days of randomization. This review will be for the adjudication of the primary composite endpoint. The CEC will also review event dossiers for safety events as defined in the CEC Charter.

Committee membership may include cardiologists, pulmonologists, vascular medicine specialists, and vascular interventional radiologists, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. CEC responsibilities, qualifications, membership, and committee procedures will be outlined in the CEC Charter.

20.4. *Executive Committee*

An Executive Committee comprised of the study co-Coordinating Investigators and select members of the Steering Committee will meet regularly to oversee the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Executive Committee members may speak directly to Investigators when site-specific issues are identified or questions are raised. They will serve as advisors to Boston Scientific as well as Investigators and research staff. Executive Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission. The Executive Committee may request participation of HI-PEITHO Investigators or Boston Scientific employees as non-voting members on the Committee.

20.5. *Steering Committee*

A Steering Committee (SC) comprised of the Sponsor's Clinical Management, the study co-Coordinating Principal Investigators, and subject matter experts in the treatment of pulmonary embolism and the fields of cardiology, pulmonology, interventional radiology, and biostatistics will be responsible for oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, and decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications.

21. Suspension or Termination

21.1. *Premature Termination of the Study*

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

- A decision on the part of Boston Scientific to suspend or discontinue development/ marketing of the device.
- A decision to stop the study due to futility at the interim analysis.

21.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC/REB Approval*

Any investigator, or associated IRB/EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

21.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations or noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, the IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

22. Study Registration and Results

22.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on the publicly accessible database, clinicaltrials.gov.

22.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, and in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable, in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

22.3. *Publication Policy*

Boston Scientific requires disclosure of its involvement as a Sponsor or financial supporter in any publication or presentation relating to a Boston Scientific study or its results. Boston Scientific may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, Boston Scientific personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- Boston Scientific involvement in the publication preparation and the Boston Scientific Publication Policy should be discussed with the Lead Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

23. Reimbursement and Compensation for Subjects

23.1. *Subject Reimbursement*

Subjects will be compensated for travel and other expenses incurred as a result of participation in the study in accordance with pertinent country laws and regulations and per the study site's policies.

23.2. *Compensation for Subject's Health Injury*

Boston Scientific will maintain an insurance policy to cover the cost of potential health injury for study subjects as required by applicable law.

24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in Table 24.1.

Table 24.1: Abbreviations

Abbreviation/Acronym	Term
6MWT	6 minute walk test
ADE	adverse device effect
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine amino transferase
AST	aspirate amino transferase
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CBC	complete blood count
CEC	Clinical Events Committee
CI	confidence interval
CIC	connector interface cable
CP_{min}	conditional probability of rejecting the null hypothesis at final analysis
CPR	cardiopulmonary resuscitation
CRO	contract research organization
CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomographic pulmonary angiogram
CU	control unit
DD	device deficiency
DOAC	direct oral anticoagulant
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG/EKG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture (system)
EQ-5D	Euro-QOL 5-dimension
ESC	European Society of Cardiology
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries (bleeding scale)
HCP	health care provider
Hct	hematocrit
Hgb	hemoglobin
ICF	informed consent form
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDDC	intelligent drug delivery catheter
IFU	instructions for use
INR	international normalized ratio

Table 24.1: Abbreviations

Abbreviation/Acronym	Term
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISTH	International Society on Thrombosis and Hemostasis (bleeding scale)
ITT	intent to treat
IV	intravenous
IVC	inferior vena cava
LMWH	low molecular weight heparin
LV	left ventricle
MSD	MicroSonic device
NEWS	National Early Warning Score
OR	odds ratio
PE	pulmonary embolism
PEITHO	Pulmonary Embolism International Thrombolysis (study)
PEmb-QOL	Pulmonary Embolism Quality of Life (questionnaire)
PERT	Pulmonary embolism response team
PP	per protocol
REB	Research Ethics Board
PVFS	Post VTE Functional status
RF	Radiofrequency
r-tPA	recombinant tissue-type plasminogen activator
RV	right ventricle
RV/LV	right-to-left-ventricle diameter ratio
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	Steering Committee
SF-36	Short Form 36 (questionnaire)
TAPSE	tricuspid annular plane systolic excursion
UADE	unanticipated adverse device effect
UFH	unfractionated heparin
USADE	unanticipated serious adverse device effect
USCDT	ultrasound-facilitated catheter-directed thrombolysis
VTE	venous thromboembolism
WHO	World Health Organization

24.2. *Definitions*

Terms are defined in Table 24.2.

Table 24.2: Definitions

Term	Definition
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified, (i.e. by a dated signature or by generation through a

Table 24.2: Definitions

Term	Definition
Ref: ISO 14155:2020	validated process), to have the same information including data that describe the context, content, and structure, as the original
Source data *Ref: ISO 14155*	All information in original records, certified copies of original records, of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation. Note 1 to entry: This includes source data partially recorded in an electronic format.
Source document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data.

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26. Appendices

Appendix A

National Early Warning Score (NEWS)

Figure 26.1: NEWS

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Reproduced from: Royal College of Physicians. *National Early Warning Score (NEWS): Standardising the assessment of acute illness severity in the NHS*. Report of a working party. London: RCP, 2012.

Appendix B

World Health Organization Functional Class

Figure 26.2(30): WHO Class

Grade/ functional class	World Health Organization functional class
1	No limitation of physical activity; ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
2	Slight limitation of physical activity, but comfortable at rest; ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
3	Marked limitation of physical activity, but comfortable at rest; less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
4	Inability to carry out any physical activity without symptoms; manifest signs of right heart failure; dyspnoea and/or fatigue may even be present at rest; discomfort is increased by any physical activity