STORM-PE: A Prospective, Multicenter, Randomized Controlled Trial Evaluating Anticoagulation Alone vs Anticoagulation plus Mechanical Aspiration with the Indigo® Aspiration System for the Treatment of Intermediate High Risk Acute Pulmonary Embolism

Protocol

CLP 18190.E

Date of Protocol

31 October 2024

Product Name

Indigo® Aspiration System

Sponsor

Penumbra, Inc.
One Penumbra Place
Alameda, CA 94502
USA

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Trial Title:	**STORM-PE: A Prospective, Multicenter, Randomized Controlled Trial Evaluating Anticoagulation Alone vs Anticoagulation plus Mechanical Aspiration with the Indigo® Aspiration System for the Treatment of Intermediate High Risk Acute Pulmonary Embolism**
Trial Registration:	NCT05684796
Trial Objective:	The primary objective of this trial is to evaluate the safety and efficacy of treatment with anticoagulation alone versus anticoagulation and mechanical aspiration thrombectomy with the Indigo Aspiration System for the treatment of intermediate high risk acute pulmonary embolism (PE).
Trial Design:	Post-market, prospective, multi-center, open label, randomized controlled trial that will enroll up to 100 participants at up to 25 enrolling sites globally
Indication:	Per Instructions for Use (IFU)
Patient Population:	Acute intermediate high risk PE patients
Trial Device:	Indigo Aspiration System
Trial Duration:	It is anticipated this trial will take approximately 2 years. All participants will be followed for 90 (± 14 days) days or to outcome (e.g., withdrawal, death), whichever occurs first.
Follow-up:	Participants will undergo follow-up at 48 hours (± 6 hours), discharge, 30 days (± 7 days), and 90 days (± 14 days) post-randomization.
Inclusion Criteria:	1. Age 18-80 years old 2. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less 3. Objectively confirmed acute PE, based on computed tomographic pulmonary angiography (CTPA) imaging showing a filling defect in at least one main or proximal lobar pulmonary artery 4. Classification of intermediate high risk PE as demonstrated by right ventricular dysfunction with RV/LV ratio ≥1.0 on CTPA and elevated cardiac biomarkers, including cardiac troponin, BNP, and/or NT-pro BNP above the upper limit of normal 5. Jugular or femoral access deemed suitable to accommodate pulmonary artery intervention with the Indigo Aspiration System 6. Informed consent is obtained from either the patient or legally authorized representative (LAR)
Exclusion Criteria:	1. Administration of thrombolytic agents or glycoprotein IIb/IIIa receptor antagonist within 30 days prior to baseline imaging 2. Hemodynamic instability with any of the following present: a. Cardiac arrest b. Obstructive shock or persistent hypotension defined as systolic blood pressure (BP) <90 mmHg or an acute drop in systolic BP ≥40 mmHg for

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	>15 min, or requiring vasopressor or inotropic support to achieve a systolic BP ≥90 mmHg 3. Patients on ECMO 4. National Early Warning Score (NEWS) 2 ≥9 5. History, imaging or hemodynamic findings consistent with chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis 6. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, that catheter-based intervention is not appropriate for the patient 7. Allergy, hypersensitivity, or heparin induced thrombocytopenia (HIT) 8. Contraindication or sensitivity to iodinated intravascular contrast that cannot be adequately premedicated 9. <45 mL/min creatinine clearance 10. Severe active infection (e.g., sepsis) requiring treatment at time of enrollment 11. Active bleeding or disorders contraindicating anticoagulant therapy 12. Hemoglobin <10 g/dL 13. Platelets <100,000/μL 14. INR >3 15. Cardiovascular or pulmonary surgery within last 7 days 16. Primary brain or metastatic brain cancer 17. Life expectancy <90 days 18. Pregnancy 19. Intracardiac thrombus (right atrium, right ventricle clot in transit) or thrombus in the inferior vena cava identified on baseline imaging 20. Current participation in another investigational drug or device trial that may confound the results of this trial. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies 21. Other medical, social, or psychological conditions that, in the opinion of the Investigator, precludes the patient from appropriate consent, could limit the patient's ability to participate in the trial, including compliance with follow-up requirements, or that could impact the scientific integrity of the trial
Randomization:	Randomization will be 1:1 to either anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (AC Group) or anticoagulation plus mechanical aspiration thrombectomy with the Indigo Aspiration System (Indigo Group). After a participant is randomized to a trial arm, they will be considered enrolled in the trial. Randomization will be stratified by trial center.
Primary Endpoints:	Change in RV/LV ratio at 48 hours on original therapy as assessed by CTPA

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Secondary Endpoints:	1. Major adverse events (MAEs) within 7 days: a composite of clinical deterioration requiring escalation of care, PE-related mortality, symptomatic recurrent PE, or major bleeding 2. Functional outcome as assessed by the 6-minute walk test (6MWT), New York Heart Association classification (NYHA), post VTE functional status scale (PVFS), modified Medical Research Council Dyspnea Scale (mMRC), and Borg Scale through 90 days 3. Quality of Life (QoL), as assessed by the Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) and EQ-5D-5L through 90 days 4. All-cause mortality within 90 days 5. PE-related mortality within 90 days 6. Symptomatic PE recurrence within 90 days
Primary Statistical Hypothesis:	The trial is designed to test the hypothesis that anticoagulation plus mechanical aspiration thrombectomy is superior to anticoagulation alone with respect to the primary efficacy outcome.
Primary Statistical Test:	The final analysis is a t-test of the change in RV/LV ratios. The primary efficacy endpoint is met if the overall treatment effect is positive at a one-sided alpha of 0.025.
Sample Size Justification:	Assuming a mean change in the RV/LV ratio from baseline to 48 hours of 0.35 in the Indigo Group and 0.10 in the AC Group with a standard deviation of 0.36, the trial needs to enroll 45 patients in each group to have 90% power. To account for approximately 5% attrition, up to 100 participants will be randomized.

1 Introduction and Rationale

1.1 Background and Incidence

Acute high-risk pulmonary embolism (PE), defined by hemodynamic instability from acute PE, and acute intermediate-risk PE, defined by right ventricular strain without hypotension, are common life-threatening conditions that represent the most serious manifestations of venous thromboembolic disease. The physiologic effect of high-risk PE is right ventricular failure, which reduces left ventricular preload and can lead to systemic hypotension and sudden death. Intermediate-risk PE has a lower mortality rate than high-risk PE but has a higher mortality rate and higher rate of clinical deterioration than low-risk PE.

In the United States, an estimated 530,000 cases of symptomatic PE occur annually,[1] and approximately 300,000 people die every year from acute PE.[2] In patients with acute high-risk PE presenting with hemodynamic shock, the mortality rate can exceed 58%,[3] and most of those deaths occur within 1 hour of presentation.[2-4] Acute high-risk PE is believed to be the third most common cause of death among hospitalized patients.[5] The mortality rate of patients with acute intermediate-risk PE has been reported as 3% to 15% and the mortality rate of patients with low-risk PE and normal heart function and treated with anticoagulation is under 1%.[6]

1.2 Treatment of Pulmonary Embolism

Therapeutic anticoagulation is the standard of care first-line treatment; the 2011 American Heart Association (AHA),[7] 2016 American College of Chest Physicians (ACCP),[8] and 2019 European Society of Cardiology (ESC),[9] guidelines all recommend prompt use of anticoagulant therapy (Class Ia, Class 1a, and Grade 1b respectively).[10,11]

Treatment escalation beyond therapeutic anticoagulation is also common practice. The 2019 ESC guidelines recommend systemic thrombolysis for acute-phase treatment of high-risk PE (Class I, Level B),[9] and the 2016 ACCP guidelines (and their 2019 update[12]) recommend systemic thrombolysis for patients with acute PE associated with hypotension and without a high bleeding risk (Grade 2b).[8] Escalating therapy with systemic thrombolysis, which improves short-term and potentially long-term PE-related adverse outcomes, is associated with high incidence of major bleeding. A meta-analysis of 15 trials involving a total of 2057 high-risk and intermediate-risk PE patients found that major hemorrhage (OR 2.91; 95% CI 1.95-4.36) and fatal or intracranial hemorrhage (OR 3.18; 95% CI 1.25-8.11) were significantly more frequent among patients receiving systemic thrombolysis plus anticoagulation than in patients receiving anticoagulation alone.[13] A systematic review and meta-analysis of patients with intermediate-risk PE calculated a lower all-cause mortality rate but a higher major bleeding rate for (mostly systemic) thrombolysis than for anticoagulation alone.[14] Experts agree that further research is needed to tailor treatment protocols and to evaluate long-term outcomes.

Catheter-directed therapy has gained significant interest in recent years; however, few randomized controlled trials have been performed. Catheter-directed therapy encompasses catheter-directed mechanical fragmentation, aspiration of emboli, and direct local infusion of a thrombolytic agent into the clot (local thrombolysis). Accordingly, a variety of devices may be used to treat PE. Mechanical catheter intervention is important for creating an immediate flow channel through the obstruction. For patients that are treated with thrombolytics, mechanical catheter intervention may also expose a greater surface area of thrombus to the locally infused thrombolytic drug. Depending on anticipated bleeding risk,

catheter-directed therapy may be performed with no or low-dose local thrombolytics. The goal of these techniques is to rapidly debulk central thrombus to relieve life-threatening heart strain, immediately improve pulmonary perfusion, and reduce the risk of mortality and clinical deterioration.

Expert guidelines suggest catheter-directed therapy—which includes the Indigo Aspiration System—in certain circumstances.[7-12] For acute PE, the 2019 ESC guidelines state that endovascular treatment should be considered for patients with high-risk PE and failed or contraindicated thrombolysis and for patients with intermediate- or low-risk PE who experience hemodynamic deterioration on anticoagulants (class IIa). Percutaneous mechanical thrombectomy (e.g., aspiration thrombectomy, fragmentation thrombectomy, and rheolytic thrombectomy) procedures were graded in the 2011 AHA guidelines as class IIa and in the 2016 ACCP guidelines as class II.[7,8] The 2019 AHA scientific statement noted that interventional therapies should be strongly considered in patients with PE and hemodynamic instability and that catheter-based embolectomy is an option for intermediate-risk patients with elevated risk for decompensation and bleeding. The 2019 PERT guidelines state that catheter embolectomy should be considered in the following situations: intermediate high risk PE with risk for clinical deterioration based on vital signs, severity of right ventricular (RV) dysfunction, tissue perfusion, or gas exchange, and without absolute contraindication to thrombolysis; high-risk PE with absolute contraindications to systemic thrombolysis; and after failed systemic thrombolysis or failed catheter-directed thrombolysis (CDT).[11] The 2019 update to the 2016 ACCP guidelines suggest catheter-assisted thrombus removal over no such intervention in patients with acute PE associated with hypotension, if those patients also have a high bleeding risk, failed systemic thrombolysis, or shock that is likely to cause death before systemic thrombolysis, and if appropriate expertise and resources are available; however, this was a weak recommendation with low-certainty evidence.[12]

1.3 Prospective Observational Trials on Catheter-Directed Therapy as a Treatment for PE

The PERFECT trial, which enrolled 101 participants, demonstrated that catheter-directed therapy (mechanical or pharmacomechanical thrombectomy, thrombolysis, or both) was associated with a high clinical success rate (defined as stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge) in massive (high-risk) (85.7%) and submassive (intermediate-risk) (97.3%) PE patients.[15] Additionally, there were no major procedure-related complications, major hemorrhages, or hemorrhagic strokes.

The SEATTLE II trial enrolled 150 participants with massive (high-risk) and submassive (intermediate-risk) PE who were treated with ultrasound-assisted catheter-directed thrombolysis (UACDT).[16] Participants received a maximum total dose of 24 mg over 12 hours. The RV/LV ratio at 48 hours post-procedure decreased by 27% or 0.42 and the systolic pulmonary artery pressure decreased by 28% or 14.4 mmHg. However, major bleeding within 30 days occurred in 10% of patients.

The FLARE trial enrolled 106 acute intermediate-risk PE patients who were treated with thrombectomy using the FlowTriever® System - a mechanical thrombectomy device that requires large-bore (20F to 22F) femoral access.[17] The average device time was 57.1 minutes. By 48 hours postprocedure, the RV/LV ratio decreased by 25.1% or 0.38 and 4

patients (3.8%) experienced 6 major adverse events, with 1 patient (1.0%) experiencing major bleeding.

EXTRACT-PE was a prospective, single-arm, multicenter IDE trial designed to evaluate the safety and efficacy of aspiration thrombectomy with the Indigo Aspiration System in 119 patients with submassive (intermediate-risk) acute PE.[18] Median time from device insertion to removal was 37.0 minutes. Median hospital ICU length of stay was 1 day. The mean RV/LV ratio reduction at 48 hours was 27.3% or 0.43 (P <.001). The rate of major adverse events (a composite of device-related death, major bleeding, and device-related serious adverse events) at 48 hours was 1.7%. Within 30 days, the rate of any-cause mortality was 2.5%; device-related SAEs, 1.7%; and symptomatic PE recurrence, 0.0%. The authors concluded that the Indigo Aspiration System was associated with a significant reduction in the RV/LV ratio at 48 hours and appeared safe. Additionally, these results were achieved without intraprocedural thrombolytics in 98.3% of patients. The limitations of this trial were that this trial was not an RCT, lacked a control arm, and was limited to a 30-day follow-up.

1.4 Randomized Trials on Catheter-Directed Therapy as a Treatment for PE

A systematic review and meta-analysis of RCTs comparing treatments for acute PE calculated that the odds of death and PE recurrence were lower for thrombolytic therapy plus heparin than for heparin alone (mortality, OR 0.57, P =.01; PE recurrence, OR 0.51, P =.02).[19] However, the incidence of major and minor hemorrhagic events was higher for thrombolytic therapy plus heparin than for heparin alone (OR 2.90, P <.001). Also, the evidence for each of those conclusions was considered to be low quality or very low quality; when 4 studies were excluded owing to high risk of bias, the advantage of thrombolytic therapy on mortality was weakened (OR 0.66, P =.08). Limited information indicated that thrombolytic therapy may improve hemodynamic and clinical outcomes, pulmonary angiogram assessment, and other clinical parameters and may decrease the incidence of escalation of treatment. The authors concluded that more high-quality, blinded RCTs are required to evaluate therapies for PE.

Owing to the increased risk of bleeding seen with systemic thrombolysis, the ULTIMA trial was performed to investigate the use of ultrasound-assisted catheter-directed thrombolysis (UACDT).[20] Patients were randomized to either UACDT with the EkoSonic Endovascular System (n = 30) or to heparin only (n = 29). Resolution of heart strain was faster for the UACDT group than for the heparin only group. The mean difference in RV/LV ratio from baseline to 24 hours was 0.30 (SD 0.20) in the UACDT group vs 0.03 (SD 0.16) in the heparin only group (P <.001). The rate of minor bleeding problems was higher in the UACDT group (10%) than in the heparin only group (3%), but this difference did not achieve statistical significance (P =.61).

Another RCT compared tissue plasminogen activator (tPA) plus heparin (n = 33) vs placebo plus heparin (n = 33) in normotensive patients with intermediate-risk PE.[21] The mean difference in RV/LV ratio from baseline to 24 hours was 0.31 (SD 0.18) in the tPA plus heparin group vs 0.04 (SD 0.16) in the placebo plus heparin group (P =.001). At 3 months, the rate of minor bleeding events was higher in the tPA plus heparin group (24.2%) than in the placebo plus heparin group (3.0%; P =.027).

1.5 Functional and Quality of Life Outcomes in PE Studies

Most research on prognosis after PE has focused on safety and efficacy outcomes, whereas studies validating functional patient-centric outcomes such as quality of life (QoL), dyspnea, and exercise tolerance are limited. Several functional and QoL measures have been validated in a variety of cardiopulmonary conditions, and the Pulmonary Embolism Quality of Life (PEmb-QoL) Questionnaire has been validated in the PE population. The EQ-5D-5L, EQ visual analog scale (EQ-VAS), New York Heart Association Classification of Heart Failure (NYHA class), 6-minute walk test, and Borg Scale have been evaluated in several cohorts of patients with PE. In particular, a meta-analysis calculated that at a median of 18 months after PE, the mean PEmb-QoL Questionnaire score was 9.1, 33% of patients had NYHA class II to IV symptoms, and the mean 6-minute walk distance was 415 m (95% CI 372-458), which is at the fourth percentile of age- and sex-matched norms.[22]

Several recent studies have reported functional and quality of life outcomes in patients with PE treated with anticoagulants. For instance, Barco et al[23] reported the 1-year results of the PEmb-QoL Questionnaire, EQ-5D-5L, and EQ-VAS for low-risk PE patients treated with rivaroxaban and early discharge followed by continued treatment with rivaroxaban. Nopp et al[24] reported the NYHA class and the results of the 6-minute walk test and Borg scale, before and after a pulmonary rehabilitation program, in PE patients treated with anticoagulation. Danielsbacka et al[25] reported the 1-year results of the 6-minute walk test and Borg scale for acute PE patients treated with anticoagulation.

Less common functional and quality of life outcome measures used in PE studies include the post-VTE functional status scale (PVFS)[26] and the modified Medical Research Council dyspnea scale (mMRC).[27] Both scales have been used to evaluate the effects of pulmonary rehabilitation after PE.[28,29] The mMRC has also been used in 1 study that identified factors influencing length of hospital stay in patients with PE [30] and in another study that evaluated the pathophysiology of dyspnea in patients with PE.[31]

1.6 Trial Rationale

Current guidelines suggest anticoagulation as a first line treatment for PE patients,[7-9] with thrombolytics and catheter-directed therapy reserved for only the most severe cases, in cases with failed or contraindicated thrombolysis, or in cases with hemodynamic instability or deterioration (or risk thereof).[9-12] Previous randomized trials suggest that use of thrombolytics (systemic or catheter directed) with anticoagulation versus anticoagulation alone may improve RV/LV ratio[20,21] or reduce mortality and PE recurrence,[19] but with an increased risk of bleeding.[19,21] Mechanical continuous aspiration thrombectomy without the use of thrombolytics rapidly debulks clot burden in pulmonary vessels, which may reduce RV overload and improve cardiac function without increasing bleeding risk. Data from the single-arm EXTRACT-PE trial suggest that aspiration without thrombolytics can improve RV/LV ratio while maintaining a low bleeding risk.[18] To date, no randomized controlled trials exist that compare anticoagulation alone to anticoagulation plus mechanical continuous aspiration thrombectomy.

The rationale of this randomized trial is to compare the clinical and safety profiles of patients treated with anticoagulation alone to those treated with anticoagulation plus mechanical continuous aspiration thrombectomy with the Indigo Aspiration System.

2 Trial Device (Indigo Aspiration System)

The Indigo Aspiration System (Basic Unique Device Identifier – Device Identifier (UDI-DI): 081454801INDIGOSYSTEMYF) is comprised of several devices:

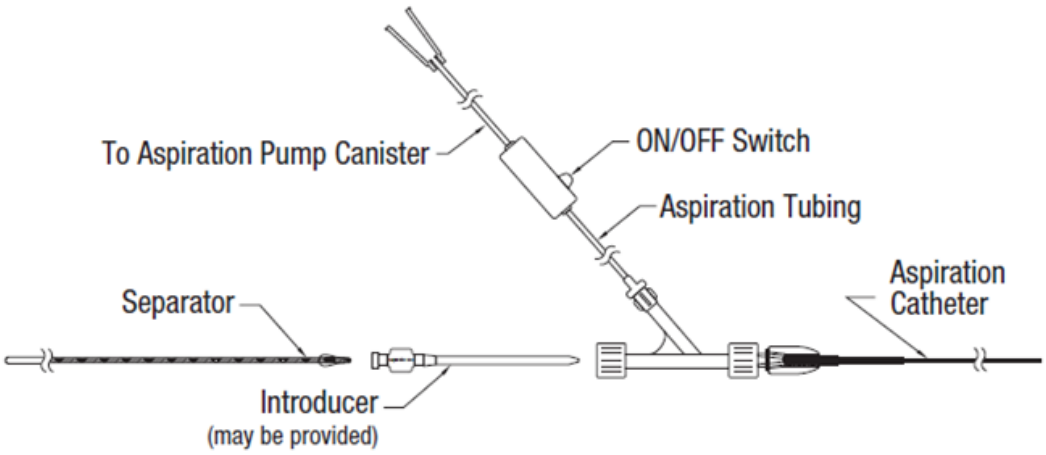
- Indigo Aspiration Catheter
- Penumbra Aspiration Pump
- Indigo Aspiration Pump Canister
- Lightning Aspiration Tubing
- Indigo Separator™

The Indigo Aspiration System is designed to remove thrombus from the vasculature using mechanical aspiration. The Indigo Aspiration Catheter targets aspiration from the pump directly to the thrombus. The Indigo Separator may be used to clear the lumen of the Indigo Aspiration Catheter should it become blocked with thrombus.

The Indigo Aspiration Catheter is introduced through a guide catheter or vascular sheath and into the peripheral vasculature and is guided over a guidewire to the site of the primary occlusion. The Indigo Aspiration Catheter is used with the Penumbra Aspiration Pump to aspirate thrombus from an occluded vessel. As needed, an Indigo Separator may be deployed from the Indigo Aspiration Catheter to assist with thrombus removal. The Indigo Separator is advanced and retracted through the Indigo Aspiration Catheter at the proximal margin of the primary occlusion to facilitate clearing of the thrombus from the Indigo Aspiration Catheter tip. The devices are visible under fluoroscopy. For the aspiration source, the Indigo Aspiration Catheter is used in conjunction with the Penumbra Aspiration Pump, which is connected using the Indigo Aspiration Tubing and the Indigo Aspiration Pump Canister. The Indigo Aspiration Catheter may be provided with a steam shaping mandrel, rotating hemostasis valve, Select Catheter, and introducer. The Indigo Separator may be provided with an introducer and torque device.

The Indigo Aspiration System is FDA cleared for the treatment of PE, has received CE marking, and is commercially available.

Figure 1: Assembled Aspiration System with Indigo Separator



Further detailed description of all the devices listed in this protocol can be found within their respective Instructions for Use (IFU).

2.1 Indigo Aspiration Catheters and Separators

As part of the Indigo Aspiration System, the Indigo Aspiration Catheters and Separators are indicated for the removal of fresh, soft emboli and thrombi from vessels of the peripheral arterial and venous systems, and for the treatment of pulmonary embolism.

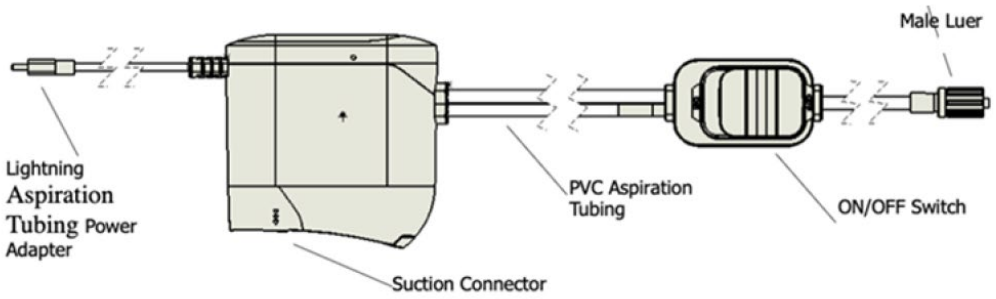
2.2 Lightning Aspiration Tubing

Lightning Aspiration Tubing (Lightning) is a component of the Indigo Aspiration System and is designed to serve as a conduit to assist in thrombus removal and restoration of blood flow in the peripheral vasculature. Lightning facilitates the transfer of vacuum between the Aspiration Catheter and Penumbra Aspiration Pump while providing intermittent or continuous aspiration.

During scenarios when occlusion is detected (e.g., blood clot is engaged with an Indigo Aspiration Catheter), Lightning allows for continuous aspiration through the Indigo Aspiration Tubing. During scenarios when no occlusion is detected, Lightning is designed to minimize aspirated blood volume by converting to intermittent aspiration.

Consistent with the existing Indigo Aspiration Tubing, the operator/physician will be able to maintain manual control of flow via a flow control switch that will completely stop flow when in the “OFF” position.

Figure 2: Lightning Aspiration Tubing



2.3 Penumbra Aspiration Pump

The Penumbra Aspiration Pump is indicated as a vacuum source for Penumbra Aspiration Systems.

3 Risk Analysis

Testing has been completed to ensure that the Indigo Aspiration System does not pose a significant risk. Safety of the Indigo Aspiration System has been demonstrated through pre-clinical testing in both bench-top and in vivo models. A thorough risk analysis was performed in accordance with quality system regulations under 21 CFR 820. Risk management activities performed in accordance with ISO 14971 did not identify any different risks or risk levels compared to other currently marketed devices.

A list of all anticipated adverse events is listed in the Instructions for Use (IFU).

3.1 Risks Related to Aspiration Thrombectomy

In terms of the clinical risk, adverse events that may be associated with the use of the Indigo Aspiration System or with interventional procedures include, but may not be limited to the following:

- allergic reaction and anaphylaxis from contrast media
- acute occlusion
- air embolism
- arrhythmia
- arteriovenous fistula
- cardiac injury
- cardio-respiratory arrest
- death
- device malfunction
- distal embolization
- emboli
- excessive blood loss
- false aneurysm formation
- fibrillation
- hematoma or hemorrhage at access site
- inability to completely remove thrombus
- infection
- hemorrhage
- ischemia
- kidney damage from contrast media
- neurological deficits including stroke
- vessel spasm, thrombosis, dissection, or perforation
- intimal disruption
- myocardial infarction
- emergent surgery
- hypotension
- hemoptysis
- respiratory failure
- thromboembolic events

Risks that may be associated with the Lightning Aspiration tubing include, but may not be limited to the following:

- allergic reaction and anaphylaxis from contrast media
- acute occlusion
- air embolism
- arrhythmia/fibrillation
- arteriovenous fistula
- death
- device malfunction
- distal embolization
- emergent surgery
- false aneurysm formation
- inability to completely remove thrombus or control blood flow
- infection
- ischemia
- kidney damage from contrast media
- myocardial infarction
- neurological deficits including stroke
- respiratory failure
- thromboembolic events
- vascular complications (including vessel spasm, thrombosis, intimal

- hematoma, hemorrhage, or blood loss at access site
- hematoma, hemorrhage, or blood loss
- hypotension

disruption, dissection, or perforation)

4 Trial Overview

Patients with acute PE experience RV dilatation, both anticoagulation and mechanical aspiration thrombectomy are used as treatment strategies to improve RV dilatation. The purpose of this trial is to investigate whether continuous mechanical aspiration thrombectomy with the Indigo Aspiration System is superior to anticoagulation alone in the reversal of RV dilation, with a comparable safety profile.

4.1 Trial Design

This is a post-market, prospective, multicenter, randomized controlled trial (RCT) comparing the use of the Indigo Aspiration System with anticoagulation to anticoagulation alone in patients with acute PE. Anticoagulation will be with LMWH or UFH, determined by institutional standard of care and following the AHA/ESC guidelines. Patients will be enrolled who meet all eligibility criteria, with consent to participate, and who are randomized to one of the trial arms. Patients will be randomly assigned by a central web-based system in a 1:1 manner to either treatment with heparin (AC Group) or treatment with Indigo and heparin (Indigo Group).

Data for each participant will be collected from baseline through final follow-up. Please refer to the Schedule of Assessments (Table 2) for details.

4.2 Trial Objectives

4.2.1 Primary Endpoints

Change in RV/LV ratio at 48 hours on original therapy as assessed by CTPA

4.2.2 Secondary Endpoints

1. Major adverse events (MAEs) within 7 days: a composite of clinical deterioration requiring escalation of care, PE-related mortality, symptomatic recurrent PE, or major bleeding
2. Functional outcome as assessed by the 6-minute walk test (6MWT), New York Heart Association classification (NYHA), post VTE functional status scale (PVFS), modified Medical Research Council Dyspnea Scale (mMRC), and Borg Scale through 90 days
3. Quality of Life (QoL), as assessed by the Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) and EQ-5D-5L through 90 days
4. All-cause mortality within 90 days
5. PE-related mortality within 90 days
6. Symptomatic PE recurrence within 90 days

4.3 Method of Randomization

Randomization will take place using a central Interactive Web Response System (IWRS). Randomization will be a 1:1 ratio to either the AC Group or the Indigo Group. The treatment allocation will be balanced on the basis of the trial center. Once a patient is deemed to meet all eligibility criteria, the Investigator or delegated team member obtains the treatment assignment for the participant.

Once a participant is randomized, the participant is considered enrolled in the trial and that participant must be followed through to 90 days or to participant's trial exit.

5 Trial Population

The patient population will include adult patients with acute PE who are considered intermediate risk.

5.1 Inclusion Criteria

1. Age 18-80 years old
2. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less
3. Objectively confirmed acute PE, based on computed tomographic pulmonary angiography (CTPA) imaging showing a filling defect in at least one main or proximal lobar pulmonary artery
4. Classification of intermediate high risk PE as demonstrated by right ventricular dysfunction with RV/LV ratio ≥1.0 on CTPA and elevated cardiac biomarkers, including cardiac troponin, BNP, and/or NT-pro BNP above the upper limit of normal
5. Jugular or femoral access deemed suitable to accommodate pulmonary artery intervention with the Indigo Aspiration System
6. Informed consent is obtained from either the patient or legally authorized representative (LAR)

5.2 Exclusion Criteria

1. Administration of thrombolytic agents or glycoprotein IIb/IIIa receptor antagonist within 30 days prior to baseline imaging
2. Hemodynamic instability with any of the following present:
    a. Cardiac arrest
    b. Obstructive shock or persistent hypotension defined as systolic blood pressure (BP) <90 mmHg or an acute drop in systolic BP ≥40 mmHg for >15 min, or requiring vasopressor or inotropic support to achieve a systolic BP ≥90 mmHg
3. Patients on ECMO
4. National Early Warning Score (NEWS) 2 ≥9
5. History, imaging or hemodynamic findings consistent with chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis
6. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, that catheter-based intervention is not appropriate for the patient
7. Allergy, hypersensitivity, or heparin induced thrombocytopenia (HIT)

8. Contraindication or sensitivity to iodinated intravascular contrast that cannot be adequately premedicated
9. <45 mL/min creatinine clearance
10. Severe active infection (e.g., sepsis) requiring treatment at time of enrollment
11. Active bleeding or disorders contraindicating anticoagulant therapy
12. Hemoglobin <10 g/dL
13. Platelets <100,000/µL
14. INR >3
15. Cardiovascular or pulmonary surgery within last 7 days
16. Primary brain or metastatic brain cancer
17. Life expectancy <90 days
18. Pregnancy
19. Intracardiac thrombus (right atrium, right ventricle clot in transit) or thrombus in the inferior vena cava identified on baseline imaging
20. Current participation in another investigational drug or device trial that may confound the results of this trial. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies
21. Other medical, social, or psychological conditions that, in the opinion of the Investigator, precludes the patient from appropriate consent, could limit the patient's ability to participate in the trial, including compliance with follow-up requirements, or that could impact the scientific integrity of the trial

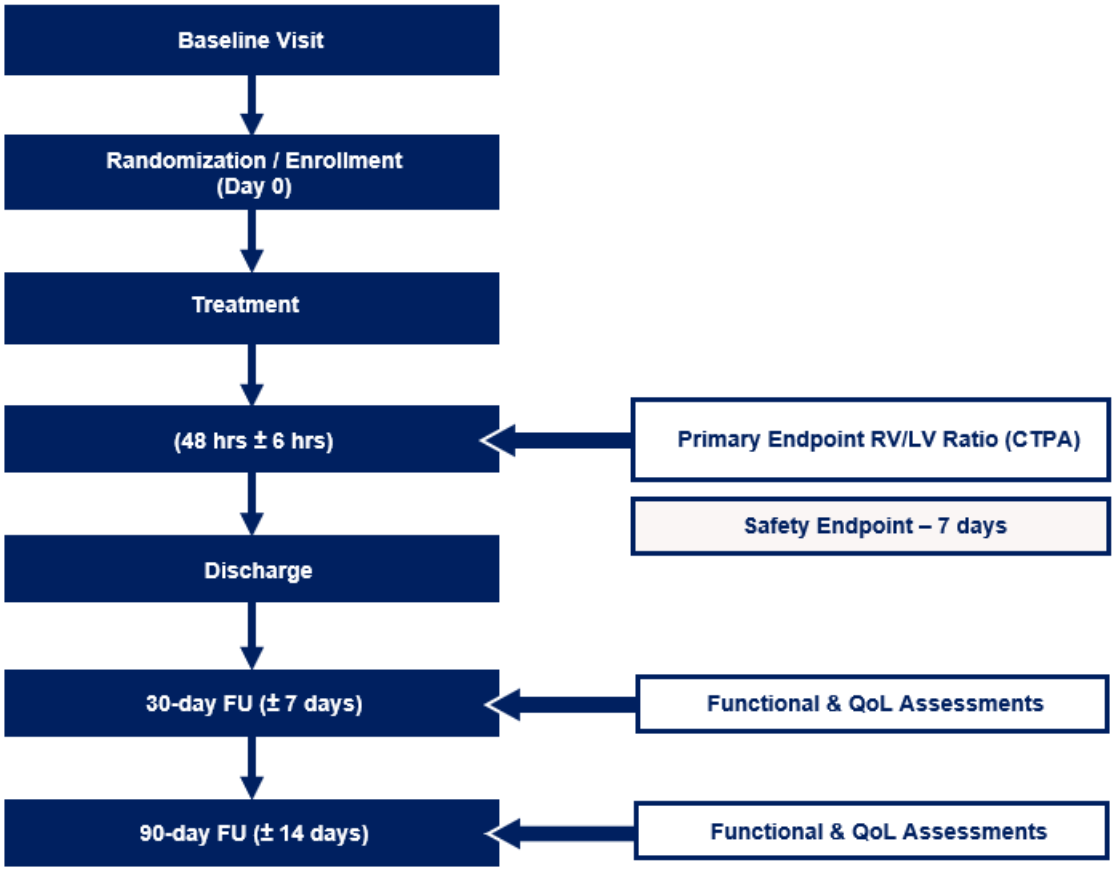
6 Trial Procedures

6.1 Trial Flow

The trial allows for enrollment of up to 100 participants at up to 25 enrolling sites.

Patients presenting with PE should be assessed for eligibility. If a patient is enrolled, they will go through the visits outlined in Figure 3. Baseline assessments that are part of routine care may be carried out prior to enrollment and consent. Trial specific assessments must be conducted after consent.

Figure 3: Trial Flow



6.2 Trial Visits

Participants enrolled in this trial will follow the visit schedule below.

- Baseline
- Treatment
- 48 hours ± 6 hours
- Discharge
- 30 days ± 7 days
- 90 days ± 14 days

6.3 Screening

All sites will keep a screen failure log of all potential trial candidates who are screened and not enrolled or who are screened, consented, and not enrolled. Reason(s) for exclusion will be recorded. Screening information including screen failures will be reported in Electronic Data Capture System (EDC).

Recruitment rates will be tracked over time for each site. The actual recruitment rates will be useful for planning further clinical trials and determining the widespread impact of the therapy.

6.4 Informed Consent

The Investigator or designee will obtain written informed consent from the patient or the patient's representative allowed to provide consent using the current Institutional Review Board (IRB)/Ethics Committee (EC) approved consent form per IRB/EC policy.

The Investigator or designee must obtain informed consent prior to trial related assessments being completed.

All informed consent documents used under this protocol will be consistent with applicable elements of Good Clinical Practice (ICH E6), ISO 14155, Good Clinical Practice (GCP) and 21 CFR 50 Protection of Human Subjects and Medical Device Regulation (MDR) and will be approved by each site's reviewing IRB/EC prior to trial initiation.

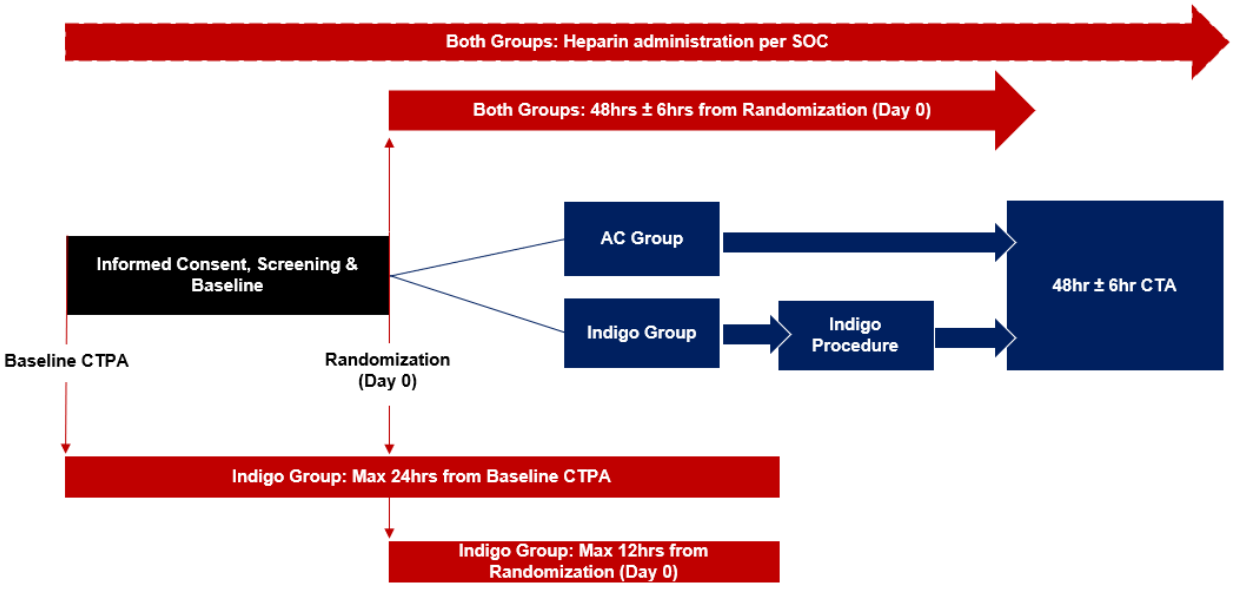
Any modification to the sample informed consent form (ICF) must be approved by the Sponsor and the IRB/EC before use. Each trial site will keep a copy of the ICF approved by IRB/EC and the Sponsor. Informed consent completion will be monitored regularly by the Sponsor.

6.5 Enrollment

A patient is considered enrolled once they or their representative have provided consent, all eligibility criteria have been confirmed, and the participant has been randomized.

Randomization and initiation of treatment must occur within 24 hours of baseline CTPA imaging. Randomization is day 0 for determining follow-up visit dates. Randomization is day 0 for calculating follow-up windows, see Figure 4 below.

Figure 4: Enrollment & Randomization Flow



6.6 Baseline

The following assessments, at a minimum, will be performed:

- Demographics
- Vital signs
- O_2 saturation
- Medical history
- Laboratory assessments (including at a minimum: cardiac troponin and/or BNP/NT-pro BNP, creatinine clearance, Hemoglobin, Platelets, INR)
- Coagulation log
- CTPA
- Echocardiogram (if performed as SOC)
- National Early Warning Score 2 (NEWS2)
    - Determines the degree of illness of a patient by using six physiological findings and one observation. In patients with PE and hospital admission, a NEWS (an earlier version of NEWS2) of 5 of greater was an independent predictor of prolonged hospitalization (OR 3.14, 95% CI 1.2-8.3).[32]
- Modified Medical Research Council (mMRC) Dyspnea Scale
    - A self-rating tool to measure the degree of disability that dyspnea poses on day-to-day activities, on a scale from 0 to 4
- Borg Scale
    - A self-rating tool to measure the participant's perceived dyspnea on a scale of 0-10
- Post-Venous Thromboembolism Functional Status (PVFS)
    - A scale that focuses on relevant aspects of daily life. 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, whether or not as a result of the specific VTE, and to objectively determine the degree of disability.
    - The PVFS scale at baseline will be administered 2 times, first to assess pre-PE functional status and second to assess current functional status during index PE. Historical assessment must be recorded prior to current status assessment.
- NYHA classification
    - Clinician assessment of heart failure symptoms and activity level. Each class in this system describes a patient's symptoms while performing physical activities. At baseline, the assessment should be of pre-index–PE symptoms.
- PEmb-QoL Questionnaire
    - A questionnaire that assesses pulmonary embolism quality of life in the context of pulmonary-specific symptoms. The PEmb-QoL Questionnaire contains six dimensions: 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. At baseline, each participant will be asked to assess quality of life related to their index PE. The assessment should be administered as close to randomization/enrollment as possible and prior to discharge or at 48 hours, whichever occurs first.

- EQ-5D-5L Questionnaire
    - A patient-reported outcome that provides a simple descriptive profile and a single index value for health status through the Visual Analog Score (VAS). 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. At baseline, each participant will be asked to recall symptoms of index PE and assessment should be administered as close to randomization/enrollment as possible and prior to discharge or at 48 hours, whichever occurs first.
- Pregnancy test (if applicable, see details in Table 2)
- Concomitant medications

6.7 Randomization

After all eligibility criteria are confirmed and informed consent has been obtained randomization will occur as described above in section 6.5. Randomization and initiation of treatment must occur within 24 hours of baseline CTPA imaging. Randomization is day 0 for determining follow-up visit dates. Randomized patients who must be excluded from the Indigo procedure due to imaging or hemodynamic criteria will still be followed per protocol through the 90-day visit or early termination, whichever occurs first. The reason for their exclusion will be recorded.

6.8 Treatment

As both the AC and Indigo Groups will receive anticoagulation, UFH or LMWH may be administered prior to randomization. Heparin administration will be determined by the treating physician, institutional standard of care, and will follow the AHA/ESC guidelines.

Initiation of assigned treatment cannot occur >12 hours from randomization or >24 hours from baseline CTPA. Escalation of treatment is described below in section 6.8.2.5.

6.8.1 AC Group

Participants randomized to the AC Group will receive medical management of their index PE with either UFH or LMWH as determined by the treating physician and in accordance with current ESC/AHA guidelines for the treatment of PE.[7,9-11]

At a minimum, the following will be captured:

- Vital signs
- O_2 saturation
- Coagulation log
- Adjunctive treatment(s) for index PE

- Concomitant medications
- Adverse events

6.8.2 Indigo Group

6.8.2.1 Preparation for Treatment

Participants randomized to the Indigo Group will receive medical management of their index PE with either UFH or LMWH as determined by the treating physician and in accordance with current ESC/AHA guidelines for the treatment of PE.[7,9]

All physicians will follow routine site practice guidelines to prepare participants for mechanical thrombectomy with the Indigo Aspiration System.

6.8.2.2 Medication during Intervention

Medications may be administered during the procedure as determined by the attending anesthesiologist and/or interventionalist in accordance with the standard of care at each facility.

6.8.2.3 Devices and Equipment

The following devices/equipment will be used (as described below). Please refer to the device descriptions in Section 2 for complete details. Device use information will be collected in the CRFs, device accountability is not required for this post-market trial.

Table 1: Devices that may be used during the procedure

Device Name	Description / Details
Indigo Aspiration Catheter	The Aspiration Catheter targets aspiration from the pump directly to the thrombus.
Indigo Separator	Size-matched accessory device (optional) for the Aspiration Catheter, intended to clear the distal end of the Aspiration Catheter lumen, should it be blocked with thrombus.
Lightning Aspiration Tubing	Lightning Aspiration Tubing facilitates the transfer of vacuum between the catheter and pump while providing intermittent or continuous aspiration.
Penumbra Aspiration Pump (Penumbra ENGINE Pump)	The aspiration source provides continuous vacuum force.
Indigo Pump Canister and Tubing	The pump canister acts as a collection reservoir for materials aspirated by the Aspiration Catheter. Penumbra ENGINE Pump does not require this additional tubing.

6.8.2.4 Indigo Procedure

The treatment procedure is briefly described below. The Indigo Aspiration System with Lightning Aspiration Tubing must be used frontline for mechanical thrombectomy in the Indigo Group and must be used in accordance with the IFU. All procedures are to be conducted in accordance with routine care at each participating hospital.

It is recommended that an activated clotting time (ACT) is performed during the procedure with a target therapeutic range of 220-300 seconds.

The physician will access the pulmonary artery via venous puncture, perform a diagnostic pulmonary angiogram and measure pulmonary artery pressures. The physician will then use an appropriately sized sheath and introduce the Indigo Aspiration Catheter over an appropriately sized guidewire advancing the catheter to the target vessel. The aspiration catheter will be positioned proximal to the thrombus. The guidewire can then be removed.

The Penumbra Aspiration Pump will then be switched to “ON.” The flow valve on the aspiration tubing will be turned to the “ON” position and aspiration will begin. If needed to clear the lumen of the catheter the appropriate coordinating separator can be advanced through the hemostatic valve. If the Separator is used the physician will advance and retract it to assist with clearing the catheter lumen and aiding in the ingestion of thrombus.

Finally, at the end of the procedure after all treatments have been performed, an angiogram will be performed, and pulmonary artery pressures will be assessed.

If a Penumbra device deficiency occurs prior to or during a procedure, it shall be reported as a complaint to the Sponsor or delegate immediately.

At a minimum, the following will be captured:

- Invasive hemodynamics (pre-procedure, post-Indigo aspiration, final)
- Procedural details (e.g., clot location, treatment location, estimated blood loss)
- Adjunctive treatment(s) for index PE
- Vital signs
- O_2 saturation
- Coagulation log
- Concomitant medications
- Adverse events
- Device deficiencies/observations

6.8.2.5 Escalation of Treatment

Participants should stay in their assigned treatment group. Escalation of treatment beyond the assigned treatment group, including the use of

thrombolytics, during index hospitalization will be considered a protocol deviation for either group if it is done outside of the criteria described below.

Participants that require escalation of treatment for clinical deterioration as defined in Section 17.5 will not require a protocol deviation; however, they will be considered treatment failures. Participants must be assessed for escalation of treatment using the NEWS2 scoring system. Participants who score a 9 or above on the NEWS2 can be considered for escalation of treatment. All efforts should be made to obtain primary endpoint imaging prior to escalation of treatment, unless the participant is too unstable to obtain imaging.

Escalation of treatment is defined as use of at least one of the following:[33]

- infusion of a catecholamine because of persistent arterial hypotension or shock (except for dopamine infused at a rate no more than 5 µg per kilogram of body weight per minute);
- secondary, or "rescue" thrombolysis (for one of the following indications: worsening clinical symptoms, particularly dyspnea, or worsening respiratory failure due to pulmonary embolism; arterial hypotension or shock; and persistent or worsening pulmonary hypertension or right ventricular dysfunction detected by echocardiography or right heart catheterization);
- endotracheal intubation;
- ECMO;
- cardiopulmonary resuscitation;
- emergency surgical embolectomy;
- thrombus fragmentation by catheter;
- mechanical thrombectomy; or
- mechanical aspiration thrombectomy

6.9 48 hours (± 6 hours)

Participants randomized to the Indigo Group should receive the routine post-procedural care for patients who have undergone mechanical thrombectomy for acute PE.
All participants are required to undergo a 48-hour visit, at a minimum, the following will be captured:

- Vital signs
- O_2 saturation
- Coagulation log
- Hemoglobin (if performed as SOC)
- CTPA
- Echocardiogram (if performed as SOC)
- NEWS2

- PEmb-QoL Questionnaire (if not yet assessed; collect only once prior to discharge or at 48 hours, whichever occurs first, as close to randomization/enrollment as possible)
- EQ-5D-5L Questionnaire (if not yet assessed; collect only once prior to discharge or at 48 hours, whichever occurs first, as close to randomization/enrollment as possible)
- Adjunctive treatment(s) for index PE
- Concomitant medications
- Adverse events

6.10 Discharge

The following assessments, at a minimum, will be performed prior to discharge, unless otherwise specified.

- Vital Signs
- O_2 saturation
- Coagulation log
- Hemoglobin (if performed as SOC)
- NEWS2
- mMRC
- Borg Scale
- PVFS Scale
- PEmb-QoL Questionnaire (if not yet assessed; collect only once prior to discharge or at 48 hours, whichever occurs first, as close to randomization/enrollment as possible)
- EQ-5D-5L Questionnaire (if not yet assessed; collect only once prior to discharge or at 48 hours, whichever occurs first, as close to randomization/enrollment as possible)
- Wearable Device dispensing (for participants that qualify and consent to participate)
    - The Garmin Venu® Sq smartwatch, described in more detail in Section 18.9, is a wearable device that measures physical activity, vital signs, and sleep parameters. Physical activity measurements available include steps taken, distance traveled, and intensity minutes. Vital signs measured include HR, RR, and O_2 sat; calculated results include HR variability, resting HR, and maximum HR. Sleep parameters measured include sleep duration, sleep stages (deep, REM, light, and awake); a sleep score, based on sleep duration and quality, is also calculated. Participants will have to meet eligibility criteria outlined in Section 18.9 for and consent to participate during the informed consent process to receive a watch. Once dispensed to the participant, data from the smartwatch will be provided through an application programming interface (API) directly to Sponsor.
- Adjunctive treatment(s) for index PE
- Concomitant medications

- Adverse event review

6.11 30-Day Follow-Up (± 7 days)

The following assessments, at a minimum, will be performed:

- Vital Signs
- O_2 saturation
- Echocardiogram (if performed as SOC)
- mMRC
- Borg Scale
- PVFS Scale
- NYHA
- 6-minute walk test (6MWT)
    - An assessment of distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance. The 6MWT should be completed according to the American Thoracic Society standards.[34]
- PEmb-QoL Questionnaire
- EQ-5D-5L Questionnaire
- Concomitant medications
- Adverse event review

6.12 90-Day Follow-Up (± 14 days)

The following assessments, at a minimum, will be performed:

- Vital Signs
- O_2 saturation
- Echocardiogram (if performed as SOC)
- mMRC
- Borg Scale
- PVFS Scale
- NYHA
- 6MWT: the 6MWT should be completed using the same course used for the 30-day assessment.
- PEmb-QoL Questionnaire
- EQ-5D-5L Questionnaire
- Concomitant medications
- Adverse event review

6.13 Follow-Up Post Trial Completion

Investigators should conduct any follow-up after trial completion in accordance with their routine care.

Table 2: Schedule of Assessments

ACTIVITY	Baseline	Treatment	48 hrs (± 6 hrs)	Discharge	30 Days (± 7 days)	90 Days (± 14 days)
Demographics	X					
Vital Signs	X	X	X	X[10]	X	X
O_2 Saturation	X	X	X	X[10]	X	X
Medical History	X					
Laboratory Assessments	X		X[1]	X[1]		
Coagulation Log	X					
Pregnancy Test[2]	X					
CTPA	X		X			
Echo[3]	X		X		X	X
NEWS2	X		X	X[10]		
mMRC	X			X	X	X
Borg Scale	X			X	X	X
PVFS	X[4]			X	X	X
NYHA	X[5]				X	X
6MWT					X	X
PEmb-QoL	X[6]				X	X
EQ-5D-5L	X[7]				X	X
Wearable device dispensing				X		
Invasive Hemodynamics		X[8]				
Procedural Details		X[8]				
Adjunctive Treatments[9]		X				
Concomitant Medications	X	X	X	X[10]	X	X
Adverse Events		X	X	X	X	X

[1]Hemoglobin collected if performed as part of standard of care/routine care

[2]For women of child-bearing potential, pregnancy can be confirmed using Institutional routine care (e.g., verbal confirmation, written confirmation, serum or urine pregnancy test)

[3]If collected as part of standard of care/routine care

[4]PVFS scale at baseline will be administered 2 times, first to assess pre-PE functional status and second to assess current functional status during index PE. Historical assessment must be recorded prior to current status assessment

[5]Baseline NYHA assessed as historical, prior to index PE

[6]PEmb-QoL questionnaire will assess quality of life related to index PE and should be administered as close to randomization/enrollment as possible and prior to discharge or at 48 hours, whichever occurs first

[7]EQ-5D-5L questionnaire will assess symptoms at time of index PE and should be administered as close to randomization/enrollment as possible and prior to discharge or at 48 hours, whichever occurs first

[8]Applies to Indigo Group only

[9]Requires following protocol procedures for escalation of treatment

[10]If discharge and 48hr visit occur on the same day only one set of values needs to be reported

7 Investigator Responsibilities

7.1 Institutional Review Board/Ethics Committee Approval

Prior to enrolling patients into the trial, the Investigator will ensure that proper IRB/EC approval is obtained in accordance with applicable local state and federal laws and regulations. The IRB/EC shall approve all trial documents as appropriate, including but not limited to the final protocol, amendments to the protocol, IFU, and the informed consent, per 21 CFR 56, MDR, and IRB or applicable EC requirements. The Investigator should keep the IRB/EC informed of any serious adverse events or serious device defects as per their policy.

If the approval to conduct the investigation is withdrawn by the IRB/EC or Regulatory Authority, the party initially notified (e.g., Sponsor, Investigator or designee) will immediately report to other parties. The report will include a complete description of the reason(s) for which approval was withdrawn.

7.2 Informed Consent

The Investigator is responsible for ensuring that a completed ICF is obtained prior to conducting any research-related assessments in accordance with Section 6.4 of this protocol and country and local requirements.

7.3 Adherence to Protocol/Amendments and Applicable Law

The Investigator is responsible for overseeing and ensuring that the trial is conducted according to this protocol and in accordance with the applicable aspects of ISO 14155, 21 CFR 812, 21 CFR 822, MDR, Declaration of Helsinki, along with any conditions imposed by the reviewing IRB/EC, and all other applicable regulations. The Investigator shall approve and adhere to this protocol and to any amendments that arise during the course of the trial. The Investigator is not allowed to deviate from the protocol except to protect the rights, safety, or well-being of human participants under emergency circumstances. Such deviations shall be documented and reported to the Sponsor and IRB/EC in a timely manner and as required by the applicable regulation. No waivers from this protocol will be granted.

The Investigator has overall responsibility of the conduct of this trial, including oversight of all delegated individuals, tasks, and all activities conducted under this protocol. It is the Investigator’s responsibility to ensure that site staff assisting with the trial have the appropriate qualifications, are fully instructed on the trial procedures and will respect trial confidentiality.

7.4 Case Report Form Completion

The Investigator and trial staff shall complete the case report forms (CRFs) associated with this trial. Participant numbers shall be used to identify individual participants in this trial. The CRFs should be a complete and accurate record of participant data collected during the trial according to relevant aspects of ISO 14155, 21 CFR 11, Electronic Records; Electronic Signatures and GCP requirements. It is the Investigator's responsibility to ensure the quality of the data collected and recorded is appropriate and collected in accordance with GCP and all applicable regulations. Data entry will be performed by the trial site(s). Investigators are responsible for completion and timely submission of data to Sponsor.

Every reasonable effort should be made to complete data entry within 7 business days of data collection.

If allowed by the site's Standard Operating Procedures (SOP) or policies, the Investigator and trial staff may enter data directly into the CRFs. In this instance, the CRFs will be considered the primary data source. All sites who wish to enter data directly into the CRFs must document this decision in their Regulatory Binder.

7.5 Image Upload

Images from baseline, 48 hours and 30 and 90 days (if applicable) will be uploaded to an image management system for Core Lab review. Additional images associated with adverse events may be uploaded, if collected as routine care. Required trial images should be uploaded within 14 business days. Instructions for image collection and upload can be found in the Imaging Manual.

Trial staff shall ensure that no images contain any personally identifying information about the participant or trial site (e.g., Physician name, Institution name, participant name, address, insurance number, medical record, etc.).

7.6 Reporting

The Investigator will be responsible for reporting the following:

7.6.1 Adverse Events

Adverse events (AEs) must be assessed and recorded by the Investigator, or designee, on the CRFs and all ongoing events must be monitored throughout the trial. For this trial, endpoint related events, procedure, device or treatment related AEs, all serious adverse events (SAEs) and unanticipated adverse device events (UADEs) will be collected starting at randomization and continuing through 90 days (see section 17.1 for definitions).

Minimum requirements of data to be recorded are the following: adverse event term, event start date, seriousness, relationship to anticoagulation and index PE, action taken, and outcome. For the Indigo Group or participants that received escalation of treatment with the Indigo Aspiration System relationship to procedure and device will be assessed.

To ensure prompt reporting of AEs, all reportable AEs (as well as all related trial data) should be entered into the EDC within 7 business days. Any suspected UADE should be reported immediately upon site awareness by calling the Sponsor. All device-related SAEs should be reported in the EDC within 48 hours of the site staff's first being made aware of the occurrence of the SAE. If the EDC is unavailable, an email can be sent to the Sponsor.

The Investigator must report adverse events to the IRB/EC according to the local reporting requirements. The Investigator is responsible for reporting time frames and complying with local or national requirements. In addition, the Investigator will report to the Sponsor and IRB/EC any device deficiencies that could have led to a SAE, if required by national regulations or by local authorities.

For the purposes of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions are not reportable as AEs unless there is worsening of the condition with an increase in severity or frequency during the trial.

All deaths will be reported regardless of causality. When reporting a death, the primary condition or diagnosis that contributed to the fatal outcome should be reported as an SAE with an outcome of death. Only a single cause of death should be reported in EDC. If the cause of death is unknown, report “unknown cause of death” as an SAE.

Detailed form and narrative reports of the safety endpoint adverse events will be composed.

7.6.2 Evaluation of Adverse Events

General AE and SAE definitions can be found in the Appendix, Section 17.1.

A Clinical Events Committee (CEC) will be used for this trial. A Sponsor Medical Monitor will review the pre-defined categories of adverse events as they are reported during the duration of the trial. Based on the criteria listed in the CEC Charter, the Sponsor Medical Monitor will request pseudonymized and properly redacted copies of medical records with pertinent data to assist in drafting AE written narrative(s) to be forwarded to the CEC for adjudication.

7.6.3 Relationship to the Trial Device

An AE or SAE is considered to be device related when it is reasonable to believe that the event may have been caused by or is related to the trial device performance.

The relationship between the use of the medical device and the occurrence of each AE shall be assessed and categorized. During causality assessment, clinical judgement shall be used and the relevant documents, such as the IFU, the Clinical Protocol and/or the risk Analysis Report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed by these documents. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, or other concurrent illness or risk factors (e.g., comorbidities) shall also be considered. Each (S)AE will be classified according to four different levels of causality. The definitions to be used to assess the relationship are found in Appendix, Section 17.2.

7.6.4 Relationship to Anticoagulation

An AE or SAE is considered to be anticoagulation related when it is reasonable to believe that the event may have been caused by or is related to anticoagulation.

The relationship between the use of the anticoagulation and the occurrence of each AE shall be assessed and categorized. During causality assessment, clinical judgement shall be used. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, or other concurrent illness or risk factors (e.g., comorbidities) shall also be

considered. Each (S)AE will be classified according to four different levels of causality. The definitions to be used to assess the relationship are found in Appendix, Section 17.2.

7.6.5 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety, or performance of the trial device, including malfunction, use error, or inadequacy in information supplied by the manufacturer, shall be documented and reported through the standard commercial process and within the EDC.

Investigators must report all possible device deficiencies with the device(s) observed during the trial. This includes unexpected outcomes or device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention has not be made or c) if circumstances had been less fortunate. Products with suspected device deficiencies should be returned to the Sponsor for investigation.

Device manufacturers are required to report qualifying medical device incidents to the relevant national competent authorities. An incident is defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant or to a serious deterioration in their state of health. A deterioration in state of health is not considered unanticipated if the condition leading to the event was considered in a risk analysis.

7.6.6 Protocol Deviation(s)

Deviations from the protocol identified by the Investigator or Sponsor during monitoring, or through other means should be clearly documented in the CRF and source documents. Every reasonable effort should be made to report protocol deviations within 7 days of identification. For the purposes of this trial deviations being collected include, but are not limited to the following:

- Inclusion/exclusion criteria deviation(s)
- Informed consent deviation(s)
- Incomplete or missing endpoint data
- Out of window endpoint visits or assessments
- Protocol required test/assessments not completed
- Escalation of treatment without clinical deterioration

7.7 Record Retention

The Investigator shall maintain the records associated with this trial for a period of at least two years after either the date on which the investigation is completed or the date that the records are no longer required for supporting a premarket approval/notification submission (if applicable), whichever is later.

The Investigator shall maintain the records associated with this trial in accordance with the local/national regulations. These records may include but are not limited to the following:

- Correspondence with the Sponsor or designee, trial committees, and other Investigators
- Participant source records, including but not limited to ICFs, copies of all completed CRFs, and supporting documents (e.g., laboratory reports and reports of diagnostic tests, medical records, etc.)
- All versions of trial protocol
- Documentation of protocol deviations
- Reports of any serious adverse event or serious device effects
- A copy of all approvals related to the clinical investigation
- Approved, blank, ICF(s)
- Approval/acknowledgment letters from the IRB/EC for all versions of the trial protocol, ICF, and other documents
- Clinical Trial Agreement(s)
- Signed and dated curricula vitae (CVs) for trial personnel
- Medical licenses or equivalent for the Principal Investigator (PI) and participating Sub-Investigators
- Financial disclosures for the PI and participating Sub-Investigators
- Required regulatory documents such as, but not limited to, Delegation of Authority and training logs
- Signed Protocol Signature Page(s)

The Investigator/Institution shall take all necessary measures to prevent accidental or premature destruction of these records.

An electronic trial master file (eTMF) will be used as the master repository for Sponsor regulatory documents.

7.8 Financial Disclosure

Each Investigator shall provide a financial disclosure to Sponsor in accordance with 21 CFR 54. The Investigator shall promptly update this information if any relevant changes occur during the investigation or for 1 year following completion of the trial.

8 Sponsor Responsibilities

Sponsor will ensure that clinical investigation shall not begin until the required approval/favorable opinion from Ethics Committee and regulatory authority has been obtained.

8.1 Training

The Sponsor is responsible for providing training on the protocol, CRF completion, image upload, and randomization as applicable for all trial staff per delegation of authority log or role on trial.

8.2 Investigator List

The Sponsor shall keep a list of the names and addresses of the clinical Investigators for the trial, including the Investigator role.

8.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the trial sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other trial sites as required by the applicable regulation.

8.4 Data Monitoring

The Sponsor is responsible for ensuring that the trial is conducted according to the applicable aspects of the following regulations 21 CFR 812, ISO 14155, and MDR. A list of monitors and respective contact information is maintained in the Sponsor eTMF.
A Sponsor employee or designee will conduct the following site visits per the monitoring plan:

8.4.1 Site Qualification

Conducted to ensure the trial site has the appropriate staff, facilities, and expertise to participate in the trial. Investigator agreement, Investigator CVs and additional information on qualification of Investigators are collected prior to activation. To assess whether Investigator was involved in termination or misconduct, publicly available websites are checked (e.g., FDA Debarment List). Site Qualification can be waived at the discretion of the Sponsor.

8.4.2 Site Initiation

Conducted to train the trial staff on use of the device, trial requirements, and other relevant training.

8.4.3 Interim Monitoring

Conducted by the Sponsor or designee per the monitoring plan, or as needed, to ensure the trial site is operating in compliance with the protocol and local and federal regulations and continues to have the appropriate staff and facilities to conduct trial related activities as indicated in the protocol.

To ensure that Investigators and their staff understand and accept their defined responsibilities, the Sponsor will maintain regular correspondence and perform periodic monitoring visits during the course of the trial to verify the continued acceptability of the facilities, compliance with the trial plan, and maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. Informed consent, CRFs, and complete medical records for all enrolled and screen failed participants will be made available to the Sponsor for review and collection.

For monitoring purpose, the Investigator/Institution shall:

- Provide direct access to the source data throughout the study
- Allow access for investigation-related monitoring visits, audits, IRB/EC review and regulatory inspections
- Allow necessary time to the monitors/auditors/inspectors to answer questions raised during monitoring

8.4.4 Site Close Out

Conducted to ensure all trial, device, regulatory-related activities, and outstanding monitoring action items have been resolved prior to site closure.

8.5 Data Management

CRFs will be used at all trial sites. All trial data will be entered into a commercially available web-based EDC system. Data entry will be performed by the trial site personnel. Investigators are responsible for completion and timely submission of the data to the Sponsor. Every reasonable effort should be made to complete data entry within 7 business days of data collection. The EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Sponsor clinical personnel access project information and trial data centrally via a web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of data listings may be performed, and manual queries created in the EDC system to highlight data discrepancies or inconsistencies for resolution by the trial site. If CRF corrections are necessary, they will be made by the Investigator or an authorized member of the Investigator's staff that is delegated to perform such activity in the EDC system. Questions or problems with submitted data will be addressed via queries in the EDC system, or through direct contact. The Investigator will review the CRFs for completeness and accuracy and provide their electronic signature and date to CRFs as evidence thereof. Any data items that have been changed after initial electronic signature will require reapplication of the electronic signature.

All trial personnel will have an individual username and password to access the clinical trial information based upon each individual’s roles and responsibilities. The EDC system provides role-based user permissions for data entry, data viewing, and reporting.

All initial data entry and data updates, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system.

All CRFs and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, reports, supporting medical records, and ICFs. The source documents will be used during the regular monitoring visits to verify information entered on the CRFs.

9 Ethical Requirements

9.1 Declaration of Helsinki

The trial will be performed in accordance with the Declaration of Helsinki, the ethical principles guiding physicians in medical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions).

9.2 Informed Consent

The Investigator is responsible for ensuring that a signed and dated informed consent is obtained in accordance with Section 6.4 of this protocol, as delegated by the site-specific Delegation of Authority, and according to country and local requirements.

9.3 Participant Data Protection

The Sponsor and the Principal Investigator will uphold the principle of the participant's right to privacy and will comply with applicable privacy laws. Every effort will be made to prevent data breach and protect participant's personal information within all applicable systems.

Each participant will be assigned a unique participant identification number at the time of enrollment. This participant identification number will be retained throughout the trial. All CRFs will be tracked, evaluated, and stored by using only the participant ID number. No personal identifying information will be included on the CRFs.

The ICF will notify participants that representatives of the Sponsor and representatives of government agencies and ethics committees will have access to personal identifying information to ensure that data reported on the CRFs corresponds to the person who signed the consent form and the information contained in the source documentation.

10 Statistical Procedures

10.1 Randomization Schema

Each eligible participant will be randomized in a 1:1 ratio to either anticoagulation with UFH or LMWH (AC Group) or to anticoagulation plus mechanical aspiration thrombectomy with the Indigo Aspiration System (Indigo Group) with a balanced randomization based upon trial center.

10.2 General Statistical Considerations

The efficacy analysis will be conducted in the Intent-to-treat and Per Protocol populations and the safety analysis will be conducted in the Safety population. The specific details of the planned analyses are described completely in the Statistical Analysis Plan (SAP).

All confidence intervals presented will be two-sided. All statistical tests will be two-tailed with a significance level of 0.05. Descriptive statistics will be provided. This includes the number of observations, means and standard deviations for normally distributed variables, medians with interquartile range for non-normally distributed variables, and counts and percentages for discrete variables.

10.3 Sample Size Estimation for the Primary Outcome

The targeted sample size for this trial is 90 randomized participants who have completed their 48-hour follow-up visit. To allow for approximately 5% attrition, enrollment of up to 100 participants will be required.

The sample size estimate is based on estimated ratios of 0.10 in the AC Group and 0.35 in the Indigo Group with standard deviations of 0.36 for the primary efficacy variable. The estimate for the AC Group is based on current literature [20,21,35-37] The standard deviation and mean RV/LV ratio change for the Indigo Group are based on the EXTRACT-PE and Seattle II studies.

To detect a 0.25 difference between groups (0.35 vs. 0.10) in the mean change in RV/LV ratio from baseline to 48 hours at the two-sided alpha level of 5% with a statistical power of 90%, 45 patients per treatment group are needed.

10.4 Control of Systematic Error and Bias

The trial will be conducted under a common protocol for each trial site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in trial execution at each trial site.

For consistency of measurements and to reduce reader bias, a blinded imaging Core Lab will be used for evaluation of baseline, 48-hour, 30-day and 90-day follow-up imaging. In determining patient eligibility for the trial, the Investigator's assessment of baseline imaging will be used. However, to control for intra-observer variability, the imaging Core Lab will determine the imaging results to be used in the data analysis.

The Core Lab will be blinded to treatment assignment for measurement of the RV/LV ratios at baseline and 48 hours. The trial will not be blinded otherwise.

10.5 Missing Data and Imputation Methods

Every effort is to be made to keep all missing data, particularly the 48-hour RV/LV measurements, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly owing to lost to follow-up. Analysis of the distribution of prognostic factors between participants with data and those without data will be reviewed for significance to assess selection bias.

Participants that have escalation of treatment without RV/LV assessment will be imputed for the primary endpoint with a 0 change in RV/LV ratio. This imputed assessment will be utilized in the primary effectiveness analysis.

Sensitivity analysis will be performed. Outlier values will be evaluated for their validity. The analysis may be done both with and without the outlier data to ascertain whether or not the interpretation of the analysis changes.

10.6 Definition of Populations

10.6.1 Screened

Screened patients are all patients considered for participation in the trial, regardless of whether they complete informed consent.

10.6.2 Screen Failure

Screen failure patients are all patients considered for participation in the trial, who failed to meet inclusion criteria or met exclusion criteria. These patients may or may not have signed an ICF. An enrolled participant with an inclusion/exclusion protocol deviation is not a screen failure.

10.6.3 Enrolled (Randomized)

Patients will be considered enrolled based on the criteria described in section 6.5.

10.6.4 Completed

All participants who were enrolled and completed the trial follow-up or were known to have died prior to the follow-up timepoint are considered to have completed. The completed participant metric will be provided for 90-day follow-up.

10.6.5 Early Termination

Early termination participants are all participants who were enrolled but did not complete follow-up and were not known to have died. The early termination participant metric will be provided for 90-day follow-up.

10.7 Definition of Analysis Populations

10.7.1 Intent to Treat Sample

As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent to treat (ITT) principle. Under this principle, the ITT sample includes all participants who are randomized. Each participant will be analyzed according to the treatment group to which they were randomly assigned at the time of randomization. This population is the primary population for all efficacy parameters.

10.7.2 Per Protocol Sample

In addition to the defined ITT analysis sample, a per-protocol (PP) sample is defined as a subset of the ITT sample. The per-protocol sample will include all randomized participants that do not have significant protocol deviations (e.g., eligibility violation) and participants that have received the assigned treatment.

10.8 Interim Analysis

No interim data analysis is planned for publication or presentation.

10.9 Statistical Analysis of Primary Efficacy Endpoint

The primary effectiveness variable is the change in RV/LV ratio at 48 hours on original therapy. The mean change for patients in each group will be calculated. The Core Lab data supersedes the Investigator-reported data in all analyses of assessment scoring.

The primary effectiveness analysis is the change in RV/LV ratio as assessed by CTPA at 48 hours on original therapy.

A t-test at a one-sided alpha of 0.025 will be used to test the null hypothesis that the difference between the Indigo Group and the AC Group in the change in RV/LV ratio at 48 hours is less than or equal to zero (H_0: $RV/LV_{change,\ Indigo} - RV/LV_{change,\ AC} \leq 0$) vs. the alternative hypothesis that the difference between the Indigo Group and the AC Group in the change in RV/LV ratio at 48 hours is greater than zero (H_1: $RV/LV_{change,\ Indigo} - RV/LV_{change,\ AC} > 0$).

10.10 Secondary Statistical Analysis

The secondary endpoints are:

1. Major adverse events (MAEs) within 7 days: a composite of clinical deterioration requiring escalation of care, PE-related mortality, symptomatic recurrent PE, or major bleeding

2. Functional outcome as assessed by the 6-minute walk test (6MWT), New York Heart Association classification (NYHA), post VTE functional status scale (PVFS), modified Medical Research Council Dyspnea Scale (mMRC), and Borg Scale through 90 days
3. Quality of Life (QoL), as assessed by the Pulmonary Embolism Quality of Life (PEmb-QoL) Questionnaire and EQ-5D-5L through 90 days
4. All-cause mortality within 90 days
5. PE-related mortality within 90 days
6. Symptomatic PE recurrence within 90 days

The secondary endpoints will be assessed with descriptive statistics and the associated 95% confidence bound for the difference between groups. The proportion of participants experiencing each secondary endpoint in the Indigo Group and in the AC Group will be calculated. A 95% confidence bound will be constructed for the difference between the Indigo Group and the AC Group in these estimates.

Frequency counts and percentage of participants within each category will be provided for categorical data. Estimates of the treatment differences and their 95% confidence intervals will be calculated.

10.11 Analysis of Adverse Events

All AEs will be summarized by showing the number and percent of participants which report the event. Events will also be reported by relationship to the procedure or device, and/or anticoagulation. Adverse events judged as probably or definitely related to the Indigo Aspiration System will be analyzed as device related. Adverse events judged as probably or definitely related to the index procedure will be analyzed as procedure related. Adverse events judged as probable or definitely related to anticoagulants will be analyzed as anticoagulant related. The CEC data will supersede the Investigator-reported data in all analyses of AEs.

10.12 Baseline Characteristics

Baseline data will be analyzed to assess the comparability of treatment groups. Baseline data including, but not limited to demographics, clinical characteristics, and imaging characteristics will be summarized by using descriptive statistics. Statistical testing will be performed as appropriate.

10.13 Health Economics Information

The trial site will complete CRFs containing healthcare utilization information (e.g., ICU days). This information may be used for analyses to assess overall healthcare costs and resource utilization.

10.14 Final Report

At the end of the trial, a final report will be completed according to the applicable regulations, even if the trial is prematurely terminated. At the conclusion of the trial, a multicenter abstract reporting the results will be prepared and may be presented at a major meeting(s). The final report will be submitted to applicable IRB(s)/EC(s) and regulatory authorities, if required. A multicenter publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience

within the trial is not allowed until the aggregate trial results have been published, unless there is written consent from the Sponsor. All ethical principles and legal requirements will be applied.

11 Trial Committees and Core Labs

11.1 Steering Committee (SC)

The Steering Committee (SC) will be comprised of physicians with participant matter expertise. The SC members will be advisors to the Sponsor regarding trial planning, execution and data presentation, progress of enrollment, participant safety and consideration of new information. Daily trial management is the responsibility of the Sponsor. The SC will oversee dissemination of trial results through appropriate scientific sessions and publications. The SC may recommend additional Investigators, based on enrollment and adherence to the protocol, to participate on a Publication Committee. The Publication Committee will participate in the review and approval of all requests for data analysis and abstract and manuscript preparation and submission.

11.2 Data Safety Monitoring Board (DSMB)

A DSMB will be comprised of members not participating in the trial and will include physicians with participant matter expertise and a statistician. The DSMB will exercise review of the overall safety of the trial and make recommendations to adjustments in the trial protocol, should any be considered necessary for safety or other related reasons.

If at any point, these reviews raise any safety concerns, the DSMB will be empowered to suggest that the trial be placed on hold and request additional analyses of the trial dataset. At the end of each DSMB meeting, this board shall recommend trial (i) continuance according to protocol, (ii) modification of the protocol, or (iii) early trial termination. The DSMB shall base their recommendations on all available evidence and their collective expertise and judgement. Safety stopping rules for the primary safety endpoint will be developed and used to help the DSMB make its safety assessments. Additional details regarding the DSMB structure, frequency of meetings and stopping rules will be included in the Charter.

11.3 Clinical Events Committee (CEC)

The CEC is made up of independent medical doctors who are not participants in the trial. The CEC is responsible for assisting in the development of specific criteria used for the categorization of clinical events and clinical endpoints in the trial.

The CEC will review and adjudicate appropriate clinical events, mainly related to the device and to the trial endpoints. A web-based electronic database will be provided to CEC members for case review and adjudication. The designated Sponsor staff who are responsible for reviewing safety data on an ongoing basis will coordinate collection of information for the event dossier. Additional details related to the CEC are specified in the Charter.

11.4 Imaging Core Lab

The Imaging Core Lab is composed of independent medical doctors who are not participants in the trial. The Core Lab is responsible for assisting in the development of specific criteria used for the categorization of clinical endpoints in the trial. A web-based

electronic database will be provided for Core Lab to review and adjudicate images. Additional details related to the Core Lab are specified in the Core Lab Charter.

The independent imaging Core Lab will review CTPA and Echo images from the baseline, 48-hour, 30 and 90-day follow up visits to determine at minimum RV/LV ratio, reflux into the inferior vena cava (IVC), tricuspid annular plane systolic excursion (TAPSE), left ventricular outflow tract velocity time integral (LVOT VTI), and right ventricular outflow tract velocity time integral (RVOT VTI). An imaging Core Lab Charter will provide procedures for Core Lab review. The Sponsor is responsible for tracking images received and for basic quality review.

12 Trial Administration

12.1 Control Measures for Disruption of Trial

In case of an unforeseen disruption of the trial (e.g., COVID-19, etc.) the Sponsor will conduct an impact assessment and take the following into consideration to protect trial participants and manage trial conduct:

- Electronic informed consent
- Remote and telehealth visits, when feasible
- Remote, centralized monitoring

If product shipment is affected, the risk of product availability to trial participant safety is low as the Indigo Aspiration System is a single-use device and the protocol does not require serial treatments.

If the disruption poses significant risk to trial participants, the Sponsor will evaluate the need for trial suspension or early termination.

12.2 Early Termination/Trial Suspension

The Sponsor may temporarily suspend or prematurely terminate the trial, a site, or an Investigator at any time for the following reasons:

- Suspicion of unacceptable risk to participants or to public health
- If no positive IRB/EC decision is obtained or if the judgement of the IRB/EC is revoked
- If the applicable regulatory body has made an irrevocable objection
- If it transpires that continuation of trial cannot serve any scientific purpose, and this is confirmed by the IRB/EC
- If monitoring or auditing identifies serious or repeated deviations on the part of an Investigator
- Business reasons

In the case of trial suspension or premature termination, the following steps will be taken:

- Sponsor will document reasons for trial suspension or premature termination
- Sponsor will notify all PIs

- Sponsor will ensure that the IRBs/ECs and regulatory authorities are notified in a timely manner
- Sponsor will continue to provide resources to fulfil the obligations from the trial protocol and existing agreements for following up the participants enrolled in the trial
- PI(s) or designee(s) will promptly inform the enrolled participants at their site, if appropriate

If the Sponsor temporarily suspends the trial and wishes to resume it, the following steps will be taken:

- Sponsor will provide and document a rationale for resuming the trial, including corrective actions, if applicable
- Sponsor will inform the PIs
- Sponsor will ensure IRB/ECs are notified. IRB/ECs must provide written approval before the trial is resumed
- Sponsor will notify regulatory authorities (if appropriate)
- PI(s) or designee(s), will inform trial participants as to the reason for resumption

12.3 Stopping the Trial Based on Interim Safety Data

Interim safety data analysis will be performed to monitor participant safety. Additionally, the Sponsor Medical Monitor will review periodic safety reports of all AEs and SAEs. The trial can be temporarily suspended to evaluate any negative safety trends.

12.4 Clinical Trial Termination/Withdrawal

Participants may be terminated or withdrawn from the trial for the following reasons and will not be replaced:

- **Voluntary withdrawal of consent:** a participant voluntarily chooses not to participate further in the trial. All data collected up to the withdrawal of consent will be maintained in the trial database. Withdrawn participants will not have any additional follow-up.
- **Lost to follow-up:** a participant will be considered lost to follow-up when contact is not achieved at the last required follow-up visit window. At a minimum, the effort to obtain follow-up information will include three (3) attempts to make contact via telephone or e-mail and if unsuccessful, then a letter from the Investigator sent via courier or other traceable method will be sent to the participant's last known address. These efforts to obtain follow-up will be recorded in the participant's trial files.
- **Withdrawn by Investigator:** A participant's enrollment in the clinical trial will be terminated if the Investigator believes that this is in the participant's best medical interest or if the participant no longer complies with the clinical trial requirements.

12.5 Missing Visits

Every effort should be made to contact the participant for scheduled follow-up visits. Any trial participant who does not attend a scheduled follow-up visit should be contacted by site

personnel to reschedule. If the missed visit was due to an adverse event, an AE CRF must be completed, and any reporting requirements must be met.

12.6 Protocol Adherence and Amendments

The Principal Investigator(s) must sign the protocol signature page documenting their agreement to conduct the trial in accordance with this protocol and subsequent amendments. Deviations outlined in section 7.6.6 from the protocol must be documented and reported to Sponsor as soon as possible and to the IRB/EC per local guidelines and government regulations.

12.7 Trial Registration

The trial will be registered in a publicly accessible trial database (e.g., clinicaltrials.gov, European Databank on Medical Devices) prior to trial initiation. Results will be made available after completion, in compliance with regulatory timeframes.

13 Publication of Information

All information and data generated in association with this trial will be held in strict confidence and remain the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing this trial and for no other purpose without written consent from the Sponsor.

The results of this trial will be offered for publication. The Investigators and the Sponsor shall collaborate in the writing of the trial to ensure accuracy. All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Sponsor. The Investigator agrees to use this information only in connection with this trial and will not use it for other purposes without written permission from the Sponsor.

The establishment of the clinical investigation report and publication of results shall be carried out in accordance with recognized ethical principles.

14 Contact Information

The address of Penumbra, Inc., who is funding this research, is as follows:

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Key Contacts for the Trial Include:

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16 Appendix I: Acronyms and Abbreviations

Acronyms	Definition
AC	Anticoagulant, anticoagulation
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
API	Application Programming Interface
BP	Blood pressure
CDT	Catheter-directed thrombolysis
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form
CTPA	Computerized tomography pulmonary angiography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
CV	Curriculum Vitae, Curricula Vitae
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EQ-VAS	EQ visual analog scale
EU	European Union
EDC	Electronic Data Capture, Electronic Data Capture System
eTMF	Electronic File Master File
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIT	Heparin Induced Thrombocytopenia
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to treat
IVC	Inferior vena cava

IWRS	Interactive Web Response System
LAR	Legally authorized representative
LMWH	Low molecular weight heparin
LOCF	Last observation carried forward
LV	Left ventricle, left ventricular
LVOT VTI	Left ventricular outflow tract velocity time integral
MAE	Major adverse event
mMRC	Modified Medical Research Council Dyspnea Scale
NEWS2	National Early Warning Score
PE	Pulmonary embolism
PEmb-QoL	Pulmonary Embolism Quality of Life
PP	Per Protocol
PVFS	Post-Venous Thromboembolism Functional Status
QoL	Quality of life
RV	Right ventricle, right ventricular
RVOT VTI	Right ventricular outflow tract velocity time integral
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SC	Steering committee
SOC	Standard of Care
SOP	Standard Operating Procedure
6MWT	6-minute walk test
TAPSE	Tricuspid annular plane systolic excursion
UACDT	Ultrasound-assisted catheter-directed thrombolysis
UADE	Unanticipated Adverse Device Effect
UFH	Unfractionated heparin

17 Appendix II: Definitions

17.1 Adverse Events

- **Adverse Event (AE):** Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the trial device and whether anticipated or unanticipated
- **Adverse Device Effect (ADE):** An adverse event related to the use of the trial medical device(s)
- **Serious Adverse Event (SAE):** An adverse event is serious if the event led to the following:
  - Death
  - Serious deterioration in the health of the participant, users, or other persons that resulted in any of the following:
    - Life-threatening illness or injury
    - Permanent impairment of a body structure or a body function including chronic diseases
    - In patient hospitalization or prolonged hospitalization
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
  - Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

  NOTE: Planned hospitalizations for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE.
- **Serious Adverse Device Effect (SADE):** Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
- **Unanticipated Adverse Device Event (UADE):** An unanticipated adverse device effect is 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 protocol, IFU or risk analysis. Unanticipated adverse device effect also includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

17.2 Relationship to the Device

- **Definite:** The temporal sequence is relevant, and the event abates upon trial device application completion/removal, or reappearance of the event on repeat trial device application.
- **Probable:** The temporal sequence is relevant, or the AE abates upon trial device application completion/removal or the AE cannot be reasonably explained by the participant's condition or comorbidities. The AE is related or most likely associated with the trial device.
- **Possible:** The temporal sequence between the trial device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can

reasonably explain the participant's condition. There is a possibility of a relationship between the AE and the trial device.

- **Unrelated:** The AE is not associated with the device. There is no relation between the AE and the trial device

Similar grading will be used for assessing the relationship to index PE, anticoagulation, and/or index procedure.

17.3 Bleeding

Bleeding will be categorized using the Bleeding Academic Research Consortium Definition for Bleeding standardized endpoint definitions (listed here).[38]

For the purposes of this trial, major bleeding will be defined as meeting BARC Type 3a, 3b, 3c, and Type 5 in line with AHA guidelines. Type 3a will not be considered as a major bleeding event if it is related to an expected drop in hemoglobin due to fluid administration and if transfusion is less than 2 units.

Bleeding Academic Research Consortium Definition for Bleeding	
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	
Type 3a	Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL[1] (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥ 5 g/dL[1] (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision

Type 4: CABG-related bleeding[2]	Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period[3] Chest tube output ≥ 2L within a 24-h period
Type 5: fatal bleeding	
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

[1]Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin)
[2]CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e. within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event
[3]Cell saver products are not counted

17.4 Cardiac Injury

The following events are examples of possible cardiac injury:

- Prolonged Ventricular Arrhythmia requiring intervention
- Cardiac hematoma or cardiac perforation
- Tricuspid or Pulmonic valve damage requiring intervention

17.5 Escalation of Treatment for Clinical Deterioration

Escalation of treatment for clinical deterioration is defined as (modified from Konstantinides et al[33]):

- NEWS2 Score ≥9

AND treated with at least one of the following:

- infusion of a catecholamine because of persistent arterial hypotension/to maintain adequate perfusion and a SBP >90 mmHg or shock (except for dopamine infused at a rate no more than 5 µg per kilogram of body weight per minute);
- secondary, or “rescue” thrombolysis (for one of the following indications: worsening clinical symptoms, particularly dyspnea, or worsening respiratory failure due to pulmonary embolism; arterial hypotension or shock; and persistent or worsening pulmonary hypertension or right ventricular dysfunction detected by echocardiography or right heart catheterization);
- endotracheal intubation;
- ECMO;
- cardiopulmonary resuscitation;
- emergency surgical embolectomy;
- thrombus fragmentation by catheter;
- mechanical thrombectomy;
- mechanical aspiration thrombectomy

17.6 Pulmonary Hypertension[39]

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization.

17.7 Pulmonary Vascular Injury

Pulmonary vascular injury may include the following events occurring in the pulmonary vasculature:

- Dissection
- Pulmonary Hemorrhage
- Intimal Flap
- Perforation
- Rupture

17.8 Recurrent Pulmonary Embolism

Symptomatic new PE objectively confirmed on CTPA, echocardiography, or invasive contrast pulmonary angiography.

17.9 Classification of PE Severity and the Risk of Early (in-hospital or 30 day) Death[9]

Early Mortality Risk		Indicators of Risk			
		Haemodynamic instability[a]	**Clinical parameters of PE severity and/ or comorbidity: PESI class III-V or sPESI ≥ 1**	**RV Dysfunction on TTE or CTPA**	**Elevated cardiac troponin levels**
High		+	(+)[d]	+	(+)[d]
Intermediate	**Intermediate-High**	-	+[e]	+	+
	Intermediate-low	-	+[e]	One (or none) positive	
Low		-	-	-	Assessment optional; if assess, negative

BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.

[a]One of the following clinical presentations: cardiac arrest, obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).

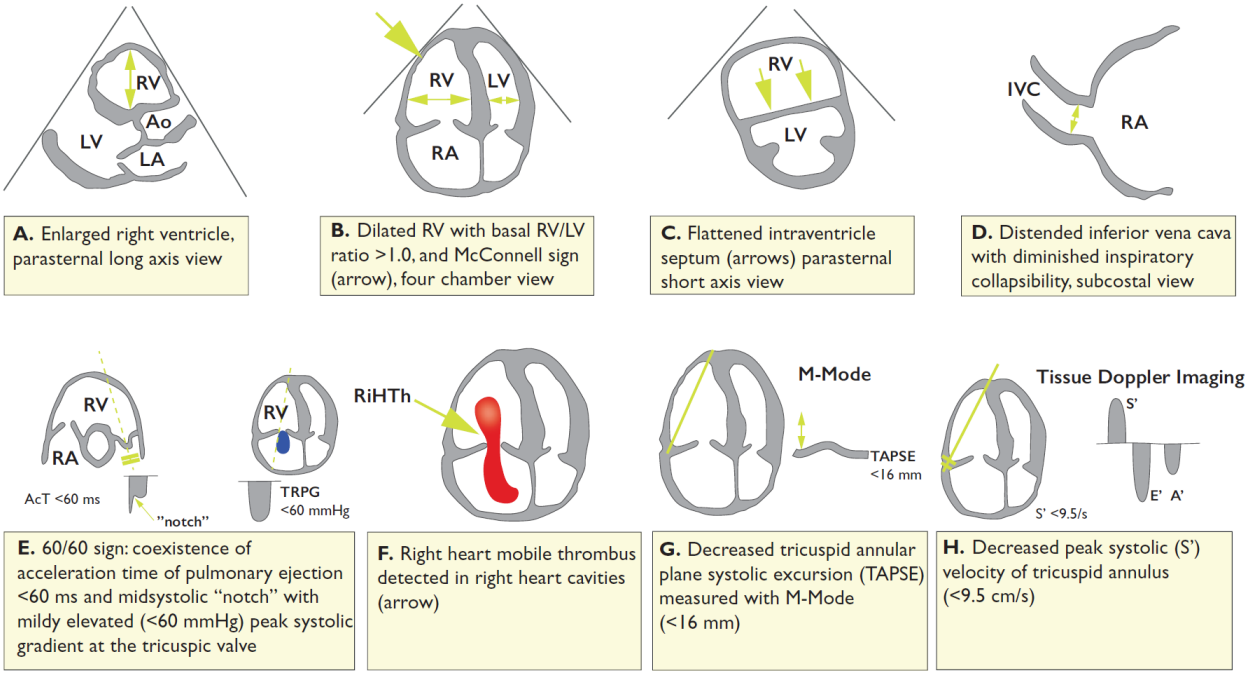
[b]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are graphically presented in Figure 4

[c]Elevation of further laboratory biomarkers, such as NT-proBNP ≥600 ng/L, H-FABP ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomized controlled trials

[d]Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.

[e]Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I – II or an sPESI of 0. Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

Figure 5: Graphical representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload[9]



A. Enlarged right ventricle, parasternal long axis view

B. Dilated RV with basal RV/LV ratio >1.0, and McConnell sign (arrow), four chamber view

C. Flattened intraventricle septum (arrows) parasternal short axis view

D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view

E. 60/60 sign: coexistence of acceleration time of pulmonary ejection <60 ms and midsystolic "notch" with mildy elevated (<60 mmHg) peak systolic gradient at the tricuspic valve

F. Right heart mobile thrombus detected in right heart cavities (arrow)

G. Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<16 mm)

H. Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s)

A' =peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT= right ventricular outflow Doppler acceleration time; Ao= aorta; E' = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC= inferior vena cava; LA= left atrium; LV = left ventricle; RA= right atrium; RiHTh= right heart thrombus (or thrombi); RV = right ventricle/ventricular; S' = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE= tricuspid annular plane systolic excursion; TRPG= tricuspid valve peak systolic gradient.

18 Appendix III: Trial Assessments

18.1 Borg Scale

The Borg scale is a category rating scale used to measure perceived intensities. The numbers are anchored by verbal expressions that are simple and understandable by most people. The Borg scale is used to measure a patient's perceived dyspnea. The Borg scale is a category rating scale used to measure perceived intensities.[40] The numbers are anchored by verbal expressions that are simple and understandable by most people. The Borg scale is used to measure a patient's perceived dyspnea.[41]

The Borg Scale	
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very Severe
8	
9	
10	Very, very severe (maximal)

18.2 PVFS Scale

The post-VTE functional status scale focuses on relevant aspects of daily life during follow-up after VTE.[26] 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 becoming 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.

Post-VTE Functional Status Scale (PVFS)	
PVFS scale grade	**Description**
0 No functional Limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1 Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain or anxiety.
2 Slight functional limitations	Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3 Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain or anxiety.
4 Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D Death	Death occurred before the scheduled assessment.

The scale is ordinal, has 6 steps ranging from 0 (no functional limitations) to 5 (death, D), and covers the entire range of functional outcomes by focusing on limitations in usual duties/activities either at home or at work/trial, as well as changes in lifestyle. The scale grades are intuitive and can easily be grasped by both clinicians and patients.

18.3 mMRC Dyspnea Scale

The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4.[27]

mMRC Dyspnea Scale	
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or I have to stop to catch breath when walking at their own pace on the level
3	Stops for breath after walking about 100 yards or after few minutes on the level
4	Too breathless to leave the house, or breathless when dressing or undressing

18.4 NYHA Classification

The NYHA classification is a system that categorizes a patient's cardiovascular disability according to the degree of symptoms resulting from ordinary or less-than-ordinary activity.[42]

NYHA Classification	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

18.5 6MWT

The 6MWT is a self-paced test that assesses a patient's submaximal level of functional capacity by measuring the distance walked in a period of 6 minutes.[34,43] The 6MWT should be performed along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The walking course must be 30 m in length, the length of the corridor should be marked every 3 m. The use of a treadmill is not recommended as patients are unable to pace themselves on a treadmill.

Prior to starting the test, the patient sits at rest in a chair located near the starting position for at least 10 minutes. The patient then stands and rates their baseline dyspnea and overall fatigue using the Borg scale. The lap counter is set to zero and the timer to 6 minutes. The patient is then instructed to walk at their own pace back and forth as far as possible for 6 minutes (leaning on the wall to rest as needed). During the 6 minutes, the test technician uses an even tone of voice to deliver standard phrases of encouragement and measures each lap with a lap counter while using body language to exaggerate each lap counter click. When 6 minutes have passed, the patient is instructed to stop and rate their post-walk dyspnea and overall fatigue using the Borg scale and the test technician calculates the total distance walked, rounding to the nearest meter.

18.6 NEWS2

NEWS2 is a summary score of six physiological parameters or 'vital signs' (respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, temperature and supplemental oxygen dependency) used to identify patients at risk of early clinical deterioration.[44]

Physiological parameter	3	2	1	Score 0	1	2	3
Respiration rate (per minute)	≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1 (%)	≤91	92-93	94-95	≥96			
SpO_2 Scale 2 (%)	≤83	84-85	86-87	88-92 ≥93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Pulse (per minute)	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

For level of consciousness, score CVPU (new confusion, voice, pain, unresponsive): The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3

or 4 on the GCS (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.[44]

18.7 PEmb-QoL Questionnaire

The Pulmonary Embolism Quality of Life (PEmb-QoL) Questionnaire is a validated tool used to measure QoL after PE.[45] The PEmb-QoL questionnaire was developed based on symptoms reported by patients with severe complaints following PE.[46] It covers 6 broad dimensions: frequency of complaints, intensity of complaints, limitations in activities of daily living, work-related problems, social limitations, and emotional complaints. Higher scores indicate worse outcomes.

18.8 EQ-5D-5L Questionnaire

The EQ-5D-5L is a standardized generic instrument for measuring health-related quality of life.[47] Applicable to a wide range of health conditions and treatments, the questionnaire provides a simple descriptive profile and a single index value for health status.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Each dimension results in a 1-digit number that expresses the level selected. The scores for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The index value, or EQ visual analog scale (VAS), records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

Administration of the EQ-5D-5L over the telephone should be completed using the approved telephone questionnaire.

18.9 Wearable Device Details

Decentralized data from the wearable watch will allow collection of data on a 24/7 basis in a natural setting as participants go through their daily routine at home and work, lending insight into recovery and exercise after PE.

Participants must meet the following eligibility criteria to participate in this portion of the protocol:

1. Meets all eligibility criteria and is enrolled in the STORM-PE trial
2. Consents to participate in wearable device portion of study
3. Participant owns a smartphone with internet connection and is willing to download a mobile application for smartwatch set up and syncing
4. Participant agrees to wear the device 24/7, except when charging, for the duration of the trial

The Sponsor will provide smartwatches to participating sites, in addition to detailed instructions on how to setup the smartwatch for trial purposes. The smartwatch must be setup and provided to participants prior to discharge from their index PE event. Participants will be expected to always wear the smartwatch, except when it is being charged, for the duration of the trial.

The Venu® Sq smartwatch by Garmin© (Figure 6) will be used in the trial. This smartwatch is commercially available but will be provided to participants for no charge.

The Venu Sq incorporates photoplethysmography, global positioning systems (GPS), and accelerometry. Physiological, sleep and activity data will be recorded passively during wear times, without the need for an office visit, further described in Table 3 and Table 4. Participants will need to download a mobile application to ensure data flow to Sponsor.

The watch's battery lasts for up to 6 days without a charge and it stores 200 hours of activity data and will sync through the mobile application. It is recommended that participants open the mobile application to ensure data syncing. Only a participant identifier will be shared with the Sponsor and all data received will de-identified.

Figure 6: Garmin Venu Sq Watch

Table 3: Health Monitoring Features of the Garmin Venu Sq watch

Wrist-based Heart Rate (constant, every second)	X
Daily Resting Heart Rate	X
Respiration rate (24x7)	X
Pulse Ox Blood Oxygen Saturation	X (spot-check, and optionally all-day and in sleep)
Sleep	yes (advanced)

Table 4: Activity Tracking Features of the Garmin Venu Sq Watch

Step counter	X
Distance traveled	X
Intensity minutes	X

STATISTICAL ANALYSIS PLAN

CLP 18190

STORM-PE: A Prospective, Multicenter, Randomized Controlled Trial Evaluating Anticoagulation Alone vs Anticoagulation plus Mechanical Aspiration with the Indigo® Aspiration System for the Treatment of Intermediate High Risk Acute Pulmonary Embolism

Version December 16, 2024

Contents

1 Introduction

The statistical analysis plan (SAP) provides comprehensive details of the statistical analyses that have been outlined in the study protocol. This includes the procedures, methods, and presentation of data analyses. The SAP will be approved prior to database lock.

2 Study Design Overview

This is a post-market, prospective, multicenter, randomized controlled trial (RCT) comparing the safety and efficacy of treatment using the Indigo Aspiration System plus anticoagulation (AC) to AC alone for the treatment of intermediate high-risk acute pulmonary embolism (PE).

Up to 100 adult participants with intermediate high-risk acute PE will be enrolled at up to 25 enrolling sites globally. Each site will be limited to a maximum enrollment of 16 participants (~16% of total enrollment).

Participants will be randomly assigned by a central web-based system in a 1:1 manner to either treatment with heparin (AC Group) or treatment with Indigo and heparin (Indigo Group). Randomization will be stratified by trial center.

The Core Lab will be blinded to treatment assignment for measurement of the RV/LV ratios at baseline and 48 hours. The trial will not be blinded otherwise.

The primary efficacy endpoint is as follows:

> Change in RV/LV ratio at 48 hours on original therapy as assessed by CTPA

The secondary endpoints are as follows:

1. Major adverse events (MAEs) within 7 days: a composite of clinical deterioration requiring escalation of care, PE-related mortality, symptomatic recurrent PE, or major bleeding
2. Functional outcome as assessed by the 6-minute walk test (6MWT), New York Heart Association classification (NYHA), post VTE functional status scale (PVFS), modified Medical Research Council Dyspnea Scale (mMRC), and Borg Scale through 90 days
3. Quality of Life (QoL), as assessed by the Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) and EQ-5D-5L through 90 days
4. All-cause mortality within 90 days

5. PE-related mortality within 90 days
6. Symptomatic PE recurrence within 90 days

3 Sample Size

The sample size will be based on the primary efficacy endpoint. All other endpoints or analyses will be secondary. Assuming a mean change in the RV/LV ratio from baseline to 48 hours of 0.35 in the Indigo Group and 0.10 in the AC Group with a standard deviation of 0.36, the trial needs to enroll 45 participants in each group to have 90% power (Table 1). The targeted sample size for this study is 90 participants treated with Indigo plus anticoagulation or anticoagulation alone. To allow for approximately 5% attrition, enrollment will be up to 100 participants [90 evaluable participants/(1-0.05 attrition rate)=95, rounded up to 100].

Table 1. Primary Endpoint Sample Size Parameters

Alpha	0.05
Sides	2
Estimated Indigo treatment mean	0.35
Estimated AC control mean	0.10
Estimated standard deviation	0.36
Power	90%
Total N	90
Attrition (%)	5%
Total N with attrition	100

3.1 Justification for Sample Size Calculation

A literature search was performed for publications involving a heparin arm for the treatment of PE, guided by Cochrane reviews.[1-7] Overall, the estimated reduction in mean RV/LV ratio from baseline to 24 hours in the AC arm ranged between 0.03 to 0.17 across the articles reviewed. The results are provided in the table below (Table 2). Based on the 48-hour estimates from literature, a point estimate of 0.10 is a reasonable efficacy parameter for the primary outcome in the AC Group.

Table 2. Literature Review for Heparin Anticoagulation

Publication, Lead author and year	**N**	**Mean RV/LV Ratio**				
		Baseline	**24 hrs**	**48 hrs**	**Reduction from Baseline to 24 hrs**	**Estimated Reduction from Baseline to 48 hrs**
Becattini, et al. (2009, Unfractionated Heparin)	28	1.32	1.22	NA	0.10	0.13[1]
Fasullo, et al. (2011, Unfractionated Heparin)	35	1.42	1.25	1.22	0.17	0.20
Kucher, et al. (2014, Unfractionated Heparin)	28	1.20	1.17	NA	0.03	0.06[1]
Mi, et al. (2013, LMWH)	57	1.34	1.30	NA	0.04	0.07[1]
Zhang, et al. (2018, LMWH)	33	1.22	1.17	NA	0.04	0.07[1]
Average (Weighted by N)						**0.10**

[1]Estimated as 0.03 more than the RV/LV ratio reduction from baseline to 24 hours, as Fasullo, et al. (2011) observed a 0.03 greater reduction from 24 to 48 hours and the other references report reductions to 24 hours

A point estimate of 0.35 is used as the efficacy parameter for the primary outcome in the Indigo Group, this is based on the 95% lower confidence limit of the reduction in RV/LV ratio from baseline to 48 hours using Indigo in EXTRACT-PE.[8] The standard deviation is assumed at 0.36 based on the SEATTLE II study.[9]

4 Randomization

Randomization takes place centrally through a commercially available Interactive Web Response System (IWRS). Randomization will occur in a 1:1 ratio to treatment using either the Indigo Aspiration System with AC or AC alone. The treatment allocation will be balanced by trial center.

The IWRS vendor will provide the randomization schedule. Detailed instructions for using the IWRS will be provided to center personnel.

5 Interim Analysis

No interim analyses are planned for the purpose of stopping the study early. No alpha adjustments will be made for the final analysis. Primary endpoint analysis may be performed for purpose of publication of the study results as per Section 6.

6 Primary Endpoint Analysis

The primary endpoint analysis will be performed when all randomized participants have completed primary efficacy endpoint assessment and have, at a minimum, completed 48-hour follow up.

7 Analysis Populations

All primary and secondary efficacy endpoint analyses will be reported for both the intent-to-treat (ITT) population and the per-protocol (PP) population. All safety endpoint analyses will be reported for the ITT population. Subgroup analyses will be reported for the ITT population.

7.1 Definitions

- **Intent to Treat Sample:** As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent to treat (ITT) principle. Under this principle, the ITT sample includes all participants who are randomized. Each participant will be analyzed according to the treatment group to which they were randomly assigned at the time of randomization. This population is the primary population for all efficacy parameters.

- **Per Protocol Sample:** In addition to the defined ITT analysis sample, a per-protocol (PP) sample is defined as a subset of the ITT sample. The per-protocol sample will include all randomized participants that do not have significant protocol deviations (e.g. eligibility violation) and participants that have received the assigned treatment.

8 Baseline Characteristics

8.1 Demographics

Age, sex at birth, ethnicity, and race at a minimum will be summarized by treatment group and overall. Categorical data will be summarized using frequencies and percentages.

8.2 Medical History

Medical history data will be summarized using conditions/diagnoses as captured on the CRF. The number and percentage of participants with a particular condition/diagnosis will be summarized for each treatment group.

8.3 Escalation of Treatment

Frequencies and percentages of participants who experience escalation of treatment will be provided.

9 Participant Disposition

The number of participants for each of the following categories will be summarized.

- Screened participants
- Screen failures
- Enrolled (Randomized) participants
- Participants randomized that did not receive assigned treatment
- Participants completing the study; participants not completing the study
- Participants included in the ITT population
- Participants included in the PP population

9.1 Definitions

- **Screened:** All participants considered for participation in the trial, regardless of whether they complete informed consent.

- **Screen Failure:** All participants considered for participation in the trial, who failed to meet eligibility criteria. These participants may or may not have signed an ICF. An enrolled participant with an inclusion/exclusion protocol deviation is not a screen failure.

- **Enrolled (Randomized):** Participants or their representatives have provided consent, all eligibility criteria have been confirmed, and participants have been randomized.

- **Completed:** All participants who were enrolled and completed the trial follow-up or were known to have died prior to the follow-up timepoint are considered to have completed. The completed participant metric will be provided for 90-day follow-up.

- **Early Termination:** All participants who were enrolled but did not complete follow-up and were not known to have died. The early termination participant metric will be provided for 90-day follow-up.

10 Participant Follow-up

The follow-up will be summarized for each treatment group as well as overall. Participant follow-up is defined for each participant as last follow-up assessment minus randomization date. Follow-up will be summarized with the number of participants, mean, standard deviation, median, IQR, minimum and maximum values. In addition, the number and percentage of participants completing follow-up for the following intervals will be summarized.

- 48 hours ± 6 hours visit
- Discharge
- 30 days ± 7 days visit
- 90 days ± 14 days visit

11 General Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, effectiveness variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median), unless otherwise noted. Frequency counts and percentage of participants within each category will be provided for categorical data. The denominator for all percentages will be the number of participants in that treatment group within the population of interest, unless otherwise noted. All 95% confidence intervals will be two-sided with alpha = 0.05, unless otherwise noted. Continuous variables will be presented with appropriate 95% confidence intervals for the mean and categorical variables will be presented with 95% exact confidence intervals. All p-values presented will be two-sided unless otherwise noted.

Unless otherwise noted, all necessary statistical analysis will be performed using a two-sided hypothesis test at the overall 5% level of significance. P-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be reported as “< 0.0001.” If a p-value is greater than 0.9999 it will be reported as “> 0.9999.”

Statistical tests and models will be applied as appropriate. Grouped analyses will be conducted using Fisher’s exact test or Chi-square test for categorical variables. Wilcoxon rank sum, t-test, Kruskal-Wallis, or ANOVA will be used for univariate continuous analyses. Logistic, Cox, or linear regression will be used for multivariable analyses as appropriate.

Exploratory analyses of the data will be conducted when appropriate. Clinical statisticians at Penumbra will be responsible for performing statistical analyses for this study.

12 Efficacy Analysis

12.1 Primary Efficacy Analysis

The primary effectiveness variable is the change in RV/LV ratio at 48 hours on original therapy. The primary efficacy analysis will be the difference between the baseline and the 48 hours RV/LV diameter ratio. The Core Lab data supersedes the Investigator-reported data in all analyses of assessment scoring. Participants that have escalation of treatment without RV/LV assessment prior to escalation will be imputed for the primary endpoint with a 0 change in RV/LV ratio. This imputed assessment will be utilized in the primary effectiveness analysis. The primary effectiveness endpoint will exclude 48-hour CTA images that are captured less than 10 hours or greater than 80 hours after randomization.

The two-sided 95% confidence interval for the mean difference will be calculated. A t-test at a one-sided alpha of 0.025 will be used to test the null hypothesis that the difference between the Indigo Group and the AC Group in the change in RV/LV ratio at 48 hours is less than or equal to zero (H_0: $RV/LV_{change,\ Indigo} - RV/LV_{change,\ AC} \leq 0$) vs. the alternative hypothesis that the difference between the Indigo Group and the AC Group in the change in RV/LV ratio at 48 hours is greater than zero (H_1: $RV/LV_{change,\ Indigo} - RV/LV_{change,\ AC} > 0$).

The primary efficacy endpoint is met if the one-sided p-value for this t-test is less than 0.025 and the overall treatment effect, $RV/LV_{change,\ Indigo} - RV/LV_{change,\ AC}$, is positive.

As a supplemental analysis, a multivariate stepwise regression model will be run to identify the factors that are significantly associated with the primary effectiveness endpoint. Alpha-to-enter of 0.20 and alpha-to-leave of 0.10 will be used for stepwise selection among these variables. The treatment group will be included in the final, reduced model.

12.2 Secondary Efficacy Analyses

- **Functional outcome as assessed by the 6-minute walk test (6MWT), New York Heart Association classification (NYHA), post VTE functional status scale (PVFS), modified Medical Research Council Dyspnea Scale (mMRC), and Borg Scale through 90 days:** For continuous outcomes, summary statistics will be provided along with the 95% confidence interval for the difference between groups. The change from the baseline

functional outcome measurement (or, for 6MWT distance, the 30-day measurement) will be reported at each subsequent timepoint along with a 95% confidence interval for the difference in this change between groups and a p-value based on the Wilcoxon signed-rank test.

For categorical outcomes, frequencies and percentages will be provided along with the 95% exact confidence interval for the difference between groups. The denominator will include participants who have the assessment completed within the respective analysis window (Table 3). The denominator will exclude participants who have exited the trial before the end of the analysis window without a functional outcome measurement. The change from the baseline functional outcome measurement will be reported at each subsequent timepoint along with a 95% exact confidence interval for the difference in this change between groups and a p-value based on McNemar's exact test or Bowker's symmetry test, as appropriate.

- **Quality of Life (QoL), as assessed by the Pulmonary Embolism Quality of Life (PEmb-QoL) Questionnaire and EQ-5D-5L through 90 days:** Summary statistics for each QoL assessment score (the overall PEmb-QoL score and, for EQ-5D-5L, the Index Score and the Visual Analog Scale) will be provided along with the 95% confidence interval for the difference between groups. In addition, the change from the QoL measurement that is administered as close to randomization/enrollment as possible and prior to discharge or at 48 hour, whichever occurs first, will be reported along with a 95% confidence interval for the difference in this change between groups and a p-value based on the Wilcoxon signed-rank test.

  In addition, for PEmb-QoL, summary statistics, a 95% confidence interval for the difference between groups, and a p-value based on a Wilcoxon rank-sum test, McNemar's exact test or Bowker's symmetry test, as appropriate will be reported for sub-categories in the scale. For EQ-5D-5L, frequency counts and percentages for entries on sub-categories in the scale will be provided along with a 95% exact confidence interval for the difference between groups.

12.3 Handling of Efficacy Multiplicity

As there is a single primary comparison at a single primary endpoint, adjustment of multiplicity is not needed for the primary efficacy analysis. No formal adjustments for multiplicity are planned for secondary efficacy or subgroup analysis.

12.4 Efficacy Subgroup Analysis

To evaluate the impact of baseline conditions, subgroup analyses will be performed for demographics, disease severity, and clinical study center on the primary efficacy endpoint. The subgroups below will be used for these analyses:

- **Age** (≤ 65, or > 65 years)
- **Sex** (male, female)
- **Ethnicity** (Hispanic or Latino, Not Hispanic or Latino)
- **Race** (American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or Other Pacific Islander, Other)
- **Severity of RV dilation** (mild (baseline CTPA RV/LV 1.0 to 1.5), moderate (baseline CTPA RV/LV >1.5 to 1.9), or severe (baseline CTPA RV/LV > 1.9))[3]
- **Concomitant Deep Vein Thrombosis** (DVT and PE, PE alone)
- **Heart rate at baseline** (< 100, ≥ 100)
- **Dyspnea at baseline** (Borg Scale 0 to 3, 4 to 10)
- **sPESI score at baseline** (0, 1+)
- **Systolic PA pressure at pre-procedure (INDIGO group only)** (≤ 70, > 70)
- **Paired imaging modality within the 48-hour analysis visit window** (CTA, echocardiogram)
- **Modified Miller Score at baseline** (Thrombus load: Low (< 12) vs High (≥ 12))
- **Location of clot** (Bilateral, Unilateral)
- **Time from symptom onset to venous puncture (INDIGO group only)** (≤ 72 Hours, > 72 Hours)
- **Type of heparin used** (LWMH, unfractionated)
- **Clinical trial center and primary operator:** See section Pooling Across Centers

The subgroup analysis will be conducted using regression with terms of treatment group, subgroup, and treatment-by-subgroup interaction. The primary statistical inference is the treatment-by-subgroup interaction, which is tested at the significance level of 0.10 unless there are less than five participants in a subgroup. When the treatment-by-subgroup interaction is statistically significant ($p <= 0.10$) for a specific subgroup, the treatment group differences will be evaluated in each stratum of that subgroup. These analyses will be performed on the Intent-To-Treat population.

13 Safety Analysis

13.1 Primary Safety Analysis

All safety endpoints are classified as secondary endpoints.

13.2 Secondary Safety Analysis

The secondary safety endpoints are below. CEC data will supersede investigator-reported data in this analysis. Data on symptomatic recurrent PE and major bleeding are assessed only by the CEC. The analysis will be conducted in the Intent-to-Treat population.

- **Major adverse events (MAEs) within 7 days: A composite of clinical deterioration requiring escalation of care, PE-related mortality, symptomatic recurrent PE, or major bleeding:** The number and percentage of participants who experience one or more of these four events within 7 days will be provided along with the 95% binomial confidence interval for the difference in this percentage between the Indigo Group and the AC Group. The denominator for this analysis will be all enrolled participants. Participant rates will be compared between treatment groups with Fisher's exact test.

- **All-cause mortality within 90 days:** The Kaplan-Meier product-limit method will be the primary method utilized to assess the mortality rate. With the date of randomization set at Day 0, any death occurring on or before 90 calendar days following randomization, will be counted as a death. Participants who are alive past 90 days will be censored at 90 days. If clinical assessment is missing for a participant who has not died, the participant will be censored at the last follow-up date. The time to death will be plotted for overall mortality and mortality by treatment arm with confidence intervals. Kaplan-Meier curves will be compared between treatment arms and assessed for significant differences using the log rank test.

Additionally, the death data will be presented as 90 Day binary deaths. The number and proportion of deaths will be presented with the 95% confidence interval. The denominator will include evaluable participants at 90 days, so that participants who do not complete the study but instead exit the trial alive before 90 days will be excluded from the analysis. Participant rates will be compared between treatment groups with Fisher's exact test.

- **PE-related mortality within 90 days:** The Kaplan-Meier product-limit method will be the primary method utilized to assess the PE-related mortality rate within 90 days. With the date of randomization set at Day 0, any death occurring on or before 90 calendar days following randomization and having death due to an event with a Probable or Definite relationship to the Index Pulmonary Embolism will be counted as a PE-related death. Participants who are alive past 90 days will be censored at 90 days. If clinical assessment is missing for a participant who has not died, the participant will be censored at the last follow-up date. The time to death will be plotted for overall PE-related mortality and PE-related mortality by treatment arm with confidence intervals. Kaplan-Meier curves will be compared between treatment arms and assessed for significant differences using the log rank test.

  Additionally, the PE-related death data will be presented as 90 Day binary PE-related deaths. The number and proportion of PE-related deaths will be presented with the 95% confidence interval. The denominator will include evaluable participants at 90 days, so that participants who do not complete the study but instead exit the trial alive before 90 days will be excluded from the analysis. Participant rates will be compared between treatment groups with Fisher's exact test.

- **Symptomatic PE recurrence within 90 days:** The Kaplan-Meier product-limit method will be the primary method utilized to assess the symptomatic PE recurrence within 90 days. CEC data will supersede investigator-reported data in this evaluation. With the date of randomization set at Day 0, any symptomatic PE recurrence on or before 90 calendar days following randomization, will be counted as symptomatic PE recurrence within 90 days. Participants who have not experienced an event at this visit will be censored at 90 days. If clinical assessment is missing for a participant who has not experienced an event, the participant will be censored at the last follow-up date. The time to event will be plotted for overall mortality and mortality by treatment arm with confidence intervals. Kaplan-Meier curves will be compared between treatment arms and assessed for significant differences using the log rank test.

Additionally, symptomatic PE recurrence within 90 days will be presented as 90 Day binary events. The number and proportion of participants experiencing an event on or before 90 calendar days following randomization, will be presented with the 95% confidence interval. The denominator will include evaluable participants at 90 days, so that participants who do not complete the study but instead exit the trial alive before 90 days will be excluded from the analysis. Participant rates will be compared between treatment groups with Fisher's exact test.

13.3 Analysis of Adverse Events

Adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) and grouped by System Organ Class and Preferred Term. The version of the MedDRA dictionary will be noted in the report. The number and percentage of participants with adverse events (AE) and severe adverse events (SAE) will be summarized.

An AE or SAE will be attributed as related to the device if it was classified as definite or probable relationship. An AE or SAE will be attributed as related to the procedure if it was classified as definite or probable relationship.

Tabulations of adverse events will be presented with descriptive statistics at baseline hospitalization and follow-up visits.

AE incidence rates will be summarized by category and severity of the adverse event. Each participant will be counted only once within a category by using the adverse event with the highest severity within each category.

All information pertaining to adverse events noted during the study will be listed by participant, detailing verbatim given by the investigator, category, date of onset, date of resolution, causality and severity. The onset of adverse events will also be shown relative (in number of days) to the day of treatment.

A tabulation of SAEs will be provided by participant.

AEs and SAEs are defined in the study protocol.

The CEC adjudicated data supersedes the Investigator reported data.

For the tables classified by severity grade, if a participant has multiple occurrences of an AE with the same MedDRA term, the event with the highest severity will be reported.

13.4 Handling of Safety Multiplicity

No formal adjustments for multiplicity are planned for secondary safety or subgroup analysis.

13.5 Safety Subgroup Analysis

Subgroup analyses will be performed for all safety endpoints. The subgroups below will be used for these analyses:

Severity of RV dilation (mild (baseline CTPA RV/LV 1.0 to 1.5), moderate (baseline CTPA RV/LV 1.5 to 1.9), or severe (baseline CTPA RV/LV > 1.9))[3]

- **Concomitant Deep Vein Thrombosis** (DVT and PE, PE alone)
- **sPESI score at baseline** (0, 1+)
- **Location of clot** (Main pulmonary artery, bilateral, branch)
- **Time from symptom onset to venous puncture** (≤ 72 Hours, > 72 Hours)
- **Type of heparin used** (LWMH, unfractionated)

The subgroup analysis will be conducted using regression with terms of treatment group, subgroup, and treatment-by-subgroup interaction. The primary statistical inference is the treatment-by-subgroup interaction, which is tested at the significance level of 0.10 unless there are less than five participants in a subgroup. When the treatment-by-subgroup interaction is statistically significant ($p <= 0.10$) for a specific subgroup, the treatment group differences will be evaluated in each stratum of that subgroup. These analyses will be performed on the Intent-To-Treat population.

14 Pooling Across Centers

The clinical study will be conducted under a common protocol for each investigational center with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational center. Analyses of the primary efficacy endpoint will be presented using data pooled across centers. Appropriate stratified and modeling techniques, including contingency tables, logistic regression, random effects, analysis of variance measures, and proportional hazards regression for time-to-event outcomes will be

used to assess differences between study centers to justify pooling data across centers and to determine differences between individual primary operators (eg, Physician A, Physician B). To avoid the influence that low enrolling sites and operators may have on high enrolling sites and operators, low enrolling sites and operators will be removed from the analysis. This analysis will be conducted in the ITT population.

15 Additional Analyses

To provide insight into recovery and exercise after PE, an additional analysis will be conducted on data from the subset of participants who elect to use the Garmin Venu® Sq smartwatch in the trial. Those participants who wear this device will do so 24/7, except when charging, for the duration of the trial to measure their physical activity, vital signs, and sleep parameters.

At a minimum, the following parameters will be collected and analyzed:

- Distance traveled
- Intensity minutes
- Steps taken
- Heart rate
- Respiration rate
- Oxygen saturation
- Sleep duration
- Sleep efficiency

16 Blinding

The protocol is designed to have open label treatment assignment. The Penumbra, Inc. clinical team, Investigator, site study personnel, and the participant will not be blinded to each participant's randomized treatment group throughout the course of the study. The Core Lab will be blinded to treatment assignment for measurement of the RV/LV ratios at baseline and 48 hours. The Echo (Core Lab) and CTPA (Core Lab) CRFs will be viewable in the Medrio electronic data capture (EDC) system for only the CEC, Clinical Data Manager role, and Core Lab. The trial will not be blinded otherwise.

17 Lost to Follow-Up and Missing Data

For sensitivity purposes, the following additional analyses will be conducted for the primary efficacy endpoint. These analyses will be conducted in the ITT population.

- Analyze only participants with complete data
- The change in RV/LV ratio at 48 hours will be imputed by the worst observed score in the study arm to which the participant is assigned
- The change in RV/LV ratio at 48 hours will be imputed by the best observed score in the study arm to which the participant is assigned
- If needed, additional sensitivity analysis will be performed by multiple imputation. Critical baseline covariates will be used to predict the value of the missing endpoint data. Multiple iterations of the endpoint predictions will be performed (M=25) and the multiple iterations will be pooled to obtain the final estimates of the primary efficacy endpoint.[11]

Participant discontinuation rates prior to the study completion will be tabulated by reason for early termination.

18 Committees

18.1 Clinical Events Committee (CEC)

A CEC will adjudicate adverse events for causality and attribution. The CEC will review and adjudicate appropriate clinical events, mainly related to the device and to the trial endpoints.

18.2 Data Safety Monitoring Board (DSMB)

The DSMB will review the overall safety of the trial.

18.3 Core Laboratory

An independent Core Lab will review the primary efficacy endpoint, the change in RV/LV ratio at 48 hours on original therapy as assessed by CTPA. The Core Lab will provide additional analysis on Echocardiogram images.

19 Changes to Planned Analyses

All changes to the statistical analysis plan (SAP) will be documented in a revised SAP or the Clinical Trial Report.

20 Analysis Conventions

Definition of Analysis Windows: all time points and corresponding time windows are defined based on days from randomization. For the visit-wise secondary efficacy analyses, the time

windows specified in Table 3 describe how secondary efficacy data are assigned to protocol specific visits and corresponding days. Analysis time windows are constructed using the following algorithm:

Determine the follow-up date for each scheduled visit (e.g. 30 day visit equals randomization day + 30).

Determine the analysis window around the follow-up day by adding or subtracting half of the interval between adjacent scheduled visits. The threshold between adjacent scheduled visits is determined by splitting the interval evenly between the visits.

The protocol specified visits and corresponding time windows used in the efficacy and safety analyses are presented in Table 3. To include only post baseline data, the 48-hour analysis visit window starts on the first day after randomization. If more than one assessment is included in a time window, the assessment closest to the scheduled day will be used. If there are two observations equally distant from the scheduled day, the latest one will be used in analysis.

Table 3. Efficacy Analysis Time Windows

Visit Name	**Scheduled Study Day (Target Study Day)**	**Protocol Visit Window**	**Analysis Visit Window (Days Post-Randomization)**	**Example Analysis Visit Window if Discharge Occurs at Day 5**	**Example Analysis Visit Window if Discharge Occurs at Day 20**
Baseline	Randomization day	NA	Randomization day or earlier	Randomization day or earlier	Randomization day or earlier
48 Hours: Primary Efficacy CTA Image Analysis	48 hours after randomization	± 6 hours	10 hours after randomization - 80 hours after randomization	10 hours after randomization - 80 hours after randomization	10 hours after randomization - 80 hours after randomization
48 Hours: Other Analysis	48 hours after randomization	± 6 hours	Day 1 - First day before discharge (limited to Day 1 - Day 3)	Day 1 - Day 3	Day 1 - Day 3
Discharge	Discharge day	NA	Day of discharge up through day 4, whichever occurs earlier (those discharged on or before day 15) to Day of discharge up through day 15, whichever occurs earlier (those discharged after day 15)	Day 4 - Day 5	Day 4 - Day 15
30 Days	30 days after randomization	± 7 days	Day 16 - Day 56	Day 16 - Day 56	Day 16 - Day 56
90 Days	90 days after randomization	± 14 days	Day 57 - Max days after randomization	Day 57 - Max days after randomization	Day 57 - Max days after randomization

21 References

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3. Hennemeyer, C et al. Outcomes of catheter-directed therapy plus anticoagulation versus anticoagulation alone for submassive and massive pulmonary embolism. The American Journal of Medicine. 2019;132(2): 240-246.
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9. Sista, AK, et al. Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. Cardiovascular Interventions. 2021;14(3), 319-329.
10. Piazza G, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II Trial. JACC Cardiovascular interventions. 2015;8(10):1382-1392.
11. Van Buuren, S. (2018). *Flexible imputation of missing data*. CRC Press.

22 SAS Code and Output

The power for a two-group, two-sided test for a single mean difference was calculated using SAS v9.4 (SAS Institute, Cary, NC). The code (Table 4) and output (Table 5) of the SAS PROC POWER procedure are provided for efficacy.

Table 4. Efficacy Power Code

```
proc power;
   twosamplemeans test=diff
   groupmeans = 0.35 | .1
   stddev = .36
   ntotal = .
   power = .8 to .95 by .05;
run;
```

Table 5. Efficacy Power Evaluation

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Indigo Treatment Mean	0.35
AC Control Mean	0.10
Standard Deviation	0.36
Number of Sides	2
Null Difference	0
Alpha	0.05
Indigo Treatment Weight	1
AC Control Weight	1

Computed N Total		
Nominal Power	Actual Power	N Total
0.90	0.903	90