EXTRACT-PE: A Prospective, Multicenter Trial to Evaluate the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism

Protocol
CLP-11373.D

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Device Name
Indigo® Aspiration System

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CLP-11373.D Protocol Synopsis	
Study Title:	**A Prospective, Multicenter Trial to Evaluate the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism**
Study Objective:	The primary objective of this trial is to determine the safety and efficacy of the Indigo® Aspiration System for aspiration mechanical thrombectomy in patients with acute pulmonary embolism (PE).
Study Design:	Prospective, multicenter, single arm design. The planned sample size is up to 150 patients enrolled at up to 25 centers in the US. Acute PE is defined as having clinical signs and symptoms for 14 days or less with an RV/LV ratio of >0.9 on CT angiography and systolic BP ≥90 mmHg. Follow-up is 30 days after initial procedure.
Patient Population:	Patients presenting with symptoms of acute PE and who meet other study entry criteria are eligible for this trial. Enrolled patients will be treated with aspiration thrombectomy by the Indigo® Aspiration System.
Inclusion Criteria:	1. Symptomatic acute PE with duration of 14 days or less. Evidence of PE must be from CTA. 2. Systolic BP ≥90 mmHg with evidence of dilated RV with an RV/LV ratio >0.9 3. Patient is 18 years of age or older
Exclusion Criteria:	1. tPA use within 14 days prior to baseline CTA 2. Systolic BP <90 mmHg for 15 min or the requirement of inotropic support to maintain systolic BP ≥90 mmHg 3. Pulmonary hypertension with peak PA >70 mmHg by right heart catheterization 4. History of severe or chronic pulmonary hypertension 5. FiO_2 requirement >40% or >6 LPM to keep oxygen saturations >90% 6. Hematocrit <28% 7. Platelets <100,000/μL 8. Serum creatinine >1.8 mg/dL 9. INR >3 10. aPTT (or PTT) >50 seconds on no anticoagulation 11. History of heparin-induced thrombocytopenia (HIT) 12. Contraindication to systemic or therapeutic doses of anticoagulants 13. Major trauma < 14 days 14. Presence of intracardiac lead 15. Cardiovascular or pulmonary surgery within last 7 days 16. Cancer which requires active chemotherapy 17. Known serious, uncontrolled sensitivity to radiographic agents

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	18. Life expectancy <90 days 19. Female who is pregnant 20. Intracardiac Thrombus 21. Patients on ECMO 22. Current participation in another investigational study
Primary Endpoints:	• Reduction in RV/LV ratio from baseline to 48 hours assessed by CTA. • Major Adverse Events, a composite of: o Device-related death within 48 hours o Major bleeding within 48 hours o Device-related SAEs within 48 hours ▪ Clinical deterioration ▪ Pulmonary vascular injury ▪ Cardiac injury
Secondary Endpoint:	• Secondary Safety Endpoints: o Device-related death within 48 hours o Major bleeding within 48 hours o Clinical deterioration within 48 hours o Pulmonary vascular injury within 48 hours o Cardiac injury within 48 hours o Any-cause mortality within 30 days o Device-related SAEs within 30 days o Symptomatic PE recurrence within 30 days
Study Rationale:	Use of the Indigo® Aspiration System for mechanical thrombectomy may allow for thrombus removal without the use of thrombolytic drugs with an acceptable device-related serious adverse event rate. Use of tissue-plasminogen activator (tPA) during procedure will not be permitted unless deemed medically necessary by site investigator.
Trial Success/failure Criteria	The lower limit of the 95% confidence interval of the change in RV/LV ratio at 48 hours is >0.20
Clinical Event Committee & Data Safety Monitoring Board	Clinical Events Committee will adjudicate appropriate adverse events for causality and attribution. A Data Safety Monitoring Board will monitor safety during the trial.

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Core Laboratory	An independent Core Lab will review imaging scans.
Duration of the Trial	The trial is anticipated to last 2 years and each patient will be in the trial for approximately 30 days.

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1. INTRODUCTION

1.1 Background

Acute massive pulmonary embolism (PE), defined as hemodynamic instability from acute PE, and acute submassive PE, defined by right ventricular strain without hypotension, are common life-threatening conditions that represent the serious manifestations of venous thromboembolic disease. 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] The mortality rate can exceed 58% in patients with acute massive PE presenting with hemodynamic shock[3], and most of these deaths occur within 1 hour of presentation. [2-4] Acute massive PE is believed to be the third most common cause of death among hospitalized patients.[5]

The physiologic effect of massive PE is right ventricular failure, which reduces left ventricular preload and can lead to systemic hypotension and sudden death. While submassive PE has a lower mortality than massive PE, it is associated with a higher mortality and higher rate of clinical deterioration than low-risk PE. Therapeutic anticoagulation is the standard of care first-line treatment.[6] Treatment escalation beyond therapeutic anticoagulation is also standard practice. Current approved medical therapy for acute massive PE consists of systemic thrombolysis with 100 mg of tPA (Alteplase; Genentech, South San Francisco, California) infused intravenously (IV) over a period of 2 hours.[9] However, there is a known risk of bleeding associated with fibrinolysis. A meta-analysis of 15 trials involving a total of 2057 massive and submassive PE patients found that major hemorrhage (OR: 2.91; 95% CI: 1.95 to 4.36) and fatal or intracranial hemorrhage (OR: 3.18; 95% CI: 1.25 to 8.11) was significantly more frequent among patients receiving thrombolysis.[10] An international registry on massive PE patients who received fibrinolytics and/or inferior vena caval filter placement reported a 90-day mortality rate of 52.4% (95% CI, 43.3% to 62.1%).[11] The study also concluded that thrombolytics did not reduce the 90-day mortality rate.[11] Massive PE treatment may be escalated further to surgical embolectomy and a case series suggests a mortality rate of approximately 40% despite surgical embolectomy.[12]

The optimal treatment strategy for patients with submassive PE is not as clear. Experts agree that further research is needed to tailor treatment protocols and to evaluate long-term outcomes. Several studies have shown higher rates of in-hospital adverse events as well as pulmonary hypertension and poor functional status at follow-up in high risk submassive PE patients given anticoagulants alone.[13-15] Yet, escalating therapy with systemic thrombolytics, while it improves short-term and potentially long-term PE related adverse outcomes, is associated with high incidence of major bleeding. In a meta-analysis of 8 randomized trials investigating submassive PE, major bleeding including intracranial hemorrhage was significantly more common with systemic thrombolytics compared to anticoagulants alone.[13]

For most submassive PE patients, the 2014 European Society of Cardiology (ESC) and 2012 CHEST PE guidelines recommend using anticoagulation alone and rescue systemic thrombolytics if needed.[7,8] The American Heart Association (AHA) guidelines suggest, with only Class IIb/Level of Evidence (LOE) C, systemic thrombolytics for patients with submassive PE with impending hemodynamic collapse.[6] Thus, guidelines acknowledge the questionable

risk-benefit ratio for systemic thrombolysis in the setting of submassive PE.

Given the incomplete efficacy of anticoagulation alone and high bleeding complications of full dose systemic thrombolysis, catheter-directed therapy has garnered significant interest. Medical expert guidelines differ in treatment recommendations for acute PE, but do suggest catheter directed therapy, which could include use of the Indigo Aspiration System, in certain circumstances.[6-8] In patients who are not candidates for or who fail systemic thrombolysis, catheter-directed therapy to achieve rapid central clot debulking can be considered as an alternative treatment option for patients with acute massive PE. While there is more controversy regarding submassive PE therapy, guidelines suggest, that catheter-directed therapy can be considered for the sickest subset of patients with acute submassive PE.[6-8]

Catheter-directed therapy (CDT) encompasses catheter-directed mechanical fragmentation and/or aspiration of emboli and intraclot thrombolytic agent injection if a local drug is infused. Therefore, a variety of devices can be used to treat PE successfully. Depending on anticipated bleeding risk, CDT may be performed with no or low-dose local TPA injection. The goal of these techniques is to rapidly debulk central thrombus to relieve life-threatening heart strain (massive PE), immediately improve pulmonary perfusion, and reduce the risk of mortality and clinical deterioration (submassive PE). Catheter intervention is important not only for creating an immediate flow channel through the obstruction, but also for exposing a greater surface area of thrombus to the locally infused thrombolytic drug. In a meta-analysis of 594 patients with acute massive PE treated with CDT, clinical success was achieved in 86.5% of the cases, with success defined as hemodynamic stabilization, resolution of hypoxia, and survival to hospital discharge.[16] In the same study, 33% of cases were initiated with mechanical treatment alone without local thrombolytic infusion.[16] When injected locally, the required dose of TPA is lower compared with full-dose systemic infusion, potentially reducing the bleeding risk. The ULTIMA trial demonstrated that patients who receive CDT have faster resolution of heart strain than patients treated with anticoagulation alone and equal safety in the 2 arms.[17] The PERFECT registry demonstrated that CDT use was associated with a high clinical success rate in massive and submassive PE patients.[18]

Recently, percutaneous mechanical thrombectomy procedures in this setting were graded in the European guidelines (ESC) as class IIb/LOE C indication, in the American ones as class IIa LOE C (AHA guidelines) and as class II/LOE C indication according to the ACCP guidelines.[6,7] These procedures have been classified as aspiration thrombectomy, fragmentation thrombectomy, and rheolytic thrombectomy.

Interventionalists across the country have been using the CAT6 and 8 aspiration catheters in the setting of submassive and massive PE in a variety of clinical scenarios. The intention of this study is to prospectively study the safety and efficacy of the device in the setting of acute PE.

1.2 Rationale

Currently, it is unknown if catheter aspiration thrombectomy with the Indigo® Aspiration System can safely improve patient outcomes for patients with PE. This is an exploratory

prospective analysis to collect outcomes for patients treated with this novel method of thrombus aspiration.

The primary aim of this study is to assess the Indigo® Aspiration System in patients with PE, which will serve as preliminary data to plan future studies to evaluate this system in this disease state.

1.3 Study Implementation Plan

A sample size of at least 100 evaluable patients is selected for this study. Evaluable patients are defined as those patients who meet eligibility requirements for primary endpoint assessment and who received treatment.

A total population of up to 150 enrolled patients will yield 100 evaluable patients, which provides an adequate level of precision to establish if the Indigo® Aspiration System will provide acceptable performance in decreasing RV dilation.

2. STUDY OBJECTIVES AND STUDY DESIGN

2.1 Primary Objective

The primary objective of the prospective study is to observe the safety and efficacy of the Indigo® Aspiration System for aspiration mechanical thrombectomy in patients with acute pulmonary embolism (PE).

2.2 Study Design

This is a prospective, multicenter, single arm design. Up to 150 patients at up to 25 centers in the United States will be enrolled in order to evaluate 100 patients. Follow-up is 30 days after initial procedure.

3. Study Population, Screening, Recruitment, and Enrollment Procedures

3.1 Patient Population

Patients presenting with symptoms of acute PE, and meeting study entry criteria are eligible for this trial. Enrolled patients will be treated with aspiration thrombectomy by the Indigo® Aspiration System.

3.2 Inclusion Criteria

1. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less. Evidence of PE must be from CTA.
2. Systolic BP ≥90 mmHg with evidence of dilated RV with an RV/LV ratio >0.9
3. Patient is 18 years of age or older

3.3 Exclusion Criteria

1. tPA use within 14 days prior to baseline CTA
2. Systolic BP <90 mmHg for 15 mins or the requirement of inotropic support to maintain systolic BP ≥90 mmHg
3. Pulmonary hypertension with peak PA >70 mmHg by right heart catheterization
4. History of severe or chronic pulmonary hypertension
5. FiO_2 requirement >40% or >6 LPM to keep oxygen saturation >90%
6. Hematocrit <28%
7. Platelets <100,000/μL
8. Serum creatinine >1.8 mg/dL
9. INR >3
10. aPTT (or PTT) >50 seconds on no anticoagulation
11. History of heparin-induced thrombocytopenia (HIT)
12. Contraindication to systemic or therapeutic doses of anticoagulants
13. Major trauma <14 days
14. Presence of intracardiac lead
15. Cardiovascular or pulmonary surgery within last 7 days
16. Cancer requiring active chemotherapy
17. Known serious, uncontrolled sensitivity to radiographic agents
18. Life expectancy <90 days
19. Female who is pregnant
20. Intracardiac Thrombus
21. Patients on ECMO
22. Current participation in another investigational study

3.4 Screening and Enrollment

Patients presenting with signs and symptoms of acute PE will be screened for possible enrollment as a patient into the trial based on Inclusion/Exclusion Criteria ("Entry Criteria") (described in Section 3).

3.4.1 Screen Failures

- Patients who were evaluated and do not meet the Entry Criteria
- Patients who meet the Entry Criteria, but decline to participate in the trial.
- Patients who meet the Entry Criteria, but do not have any component of the study device—Indigo System (described in Section 3.5)—introduced into the body.

The reason for screen failure will be captured in the screening/enrollment section of the database.

3.5 Enrollment Procedure

Consecutive patients presenting with acute PE will be screened for this trial. Those who do not meet study Entry Criteria will not be enrolled with the reason recorded.

A patient is considered enrolled if the patient informed consent form and HIPAA Authorization are signed by either the patient or LAR, and in whom the Indigo System has been introduced into their body.

Any patient enrolled into the trial, but in whom the Indigo System is not able to access a pulmonary embolus is considered an Intent to Treat patient and will be monitored per protocol until the end of required follow-up period of 30 days. Any patient that experiences an adverse event after venous puncture but in whom Indigo is not inserted will be monitored through discharge for safety.

The Indigo Aspiration System usage for this study follows the FDA approved Investigational *Instructions For Use.* Refer to Warnings, Precautions, and Potential Adverse Events in the Investigational Instructions For Use prior to use.

3.5.1 Co-Enrollment Guidelines

Simultaneous participation in other investigational clinical trials is not permitted.

4. Study Treatment

4.1 Study Device

For this Study, the Indigo® Aspiration System is intended for the removal of fresh, soft emboli and thrombi for the treatment of pulmonary embolism. The Aspiration Catheter, Separator™ and Aspiration Tubing are available in multiple configurations. The devices are provided sterile, non-pyrogenic, and intended for single use only. Intended users for this device are physicians who have received appropriate training in interventional techniques.

The Indigo Aspiration System's fundamental mechanism of action is aspiration. Aspiration draws the embolus or thrombus into the catheter to remove the embolus or thrombus from the body.

The Indigo Aspiration System is comprised of several devices:

- Indigo Aspiration Catheter (investigational device)
- Penumbra Aspiration Pump
- Pump Canister/Tubing
- Indigo Aspiration Tubing
- Indigo Separator (investigational device)

The Indigo® Aspiration System is designed to remove thrombus from the vasculature, including the pulmonary artery, using continuous 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 long femoral sheath and 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. For the aspiration source, the Indigo Aspiration Catheter is used in conjunction with the Penumbra Pump Max™ which is connected using the Indigo Aspiration Tubing and the Indigo Pump/Canister Tubing. The Indigo Aspiration Catheter is provided with a rotating hemostasis valve, and a peelable sheath. The Indigo Separator is provided with an introducer and torque device. The devices are visible under fluoroscopy.

Recently Penumbra introduced larger bore aspiration catheters, which are variable stiffness 0.070" and 0.088" single lumen catheters, reinforced by a PTFE lined stainless steel shaft and multi-layer polymers. The aspiration catheters employ multiple layers of polymers that are laminated on top of the stainless steel shaft to achieve a gradual transition in stiffness from the proximal to distal shaft, and are optimized in design for kink resistance, minimum ovalization, and flexibility. The distal segment of the aspiration catheters employ three or more different polymers with radio-opaque characteristics and is hydrophilically coated. The distal segment has also a marker band which is encapsulated. The aspiration catheters are available in multiple length offerings in configurations and shapes. The aspiration catheters are inserted through a guide catheter or sheath. Once in place, the aspiration catheters provide a conduit to remove the thrombus using a compatible Separator™ if required.

5. STUDY PROCEDURE, CLINICAL PROCEDURES, AND LABORATORY EVALUATIONS

5.1 Study Procedure

5.1.1.Sedation and Lytic Use

The sedation whether general anesthesia, local anesthesia or conscious sedation will be determined at the discretion of the Investigative team. The type of sedation and the vascular access time will be captured in the Case Report Form (CRF).

Any use of thrombolytics during the procedure and up to 48-hours post-procedure will be considered a protocol deviation and a treatment failure. The administration of thrombolytics to treat clinical deterioration will not be considered a protocol deviation.

5.1.2 Indigo Aspiration Thrombectomy

The physician will access the pulmonary artery via venous puncture and then perform a diagnostic pulmonary angiogram and measure pulmonary artery pressures. The physician

will perform an exchange and place ≥8Fr sheath from access site to the main pulmonary artery trunk over a 0.035 inch guidewire to minimize trauma to the heart or induction of arrhythmias. The physician will then introduce the Indigo Aspiration Catheter over the 0.035 inch guidewire and place the aspiration catheter proximal to the thrombus. The 0.035 inch guidewire will then be removed and the appropriate coordinating separator will be advanced through the hemostatic valve with the "throw" set 1-2cm distal to the tip of the catheter. The aspiration tubing will be connected to the Y arm of the rotating hemostatic valve.

Next, the physician will gently embed the distal tip of the aspiration catheter into the thrombus. The Penumbra Aspiration Pump will then be switched to "ON" at -20mmHg or greater vacuum. The flow valve on the aspiration tubing will be turned to the 'ON' position and aspiration will begin. The physician will gently advance and retract the Separator to assist with the thrombus removal. If the clot has been ingested, the pump will be switched to "OFF" before disconnecting the Indigo Aspiration Catheter from the Aspiration Tubing. If the clot has not been ingested in the canister, the physician will keep the pump in the "ON" position and will gently remove the Indigo Aspiration Catheter and flush it before doing another aspiration pass. This will be recorded in the corresponding CRF. Finally, at the end of the procedure after all treatments have been performed, an angiogram will be performed and Pulmonary Artery Pressures will be recorded in the CRF.

If a Penumbra device malfunction occurs prior and/or during a procedure, it shall be reported as a complaint to the Sponsor or delegate immediately. A specific device reporting process, as described in Section 6.4, will be followed since the aspiration catheter and separator will be considered investigational.

5.1.3. Adjunctive Treatments

The Sponsor recognizes there may be circumstances for the need to use other techniques to aid the Indigo Aspiration Catheter in recanalizing the targeted vessel.

Adjunctive treatments, will be considered as a protocol deviation unless used to treat clinical deterioration. These adjunctive treatments will be recorded on the CRF.

Any use of adjunctive treatments for the purpose of reducing clot burden in the pulmonary artery (intra-procedure and up to 48 hours post procedure) will be considered a treatment failure.

5.2 Study Visits (see Table 1)

5.2.1 Baseline Visit

- Medical history
- Demographics
- Vital signs
- Hematocrit/FiO_2/Creatinine/ Platelets/INR/Troponin
- CTA

- RV:LV Ratio
- Concomitant Medications
- Pregnancy Test
- Hospital admission date

5.2.2 Procedure (Day Zero)

- Date of procedure
- Vital signs
- Venous puncture for Indigo Procedure
- Pre procedure Pulmonary Artery Pressure
- Post procedure Pulmonary Artery Pressure
- Concomitant Medications
- Device Used
- Time of Indigo Insertion
- Bleeding: Major and Minor
- Adverse Events

5.2.3 48 Hour Post-Procedure (±6 hr)

- Vital signs
- CTA
- RV:LV Ratio
- Concomitant Medications
- Bleeding: Major and Minor
- Adverse Events

5.2.4 Discharge

- Vital signs
- Concomitant Medications
- Bleeding: Major and Minor
- Adverse Events
- Hospital Discharge Date

5.2.5 30 Day Follow-Up (+/-7 days)

- Vital signs
- Concomitant Medications
- PE Recurrence
- Adverse Events
- The "Study Completion Form" CRF will be filled in at the end of the study (even if the patient is lost to follow-up before the 30-day visit, withdrew consent, or expired).

Schedule of Assessments

Table 1 below lists the data to be captured at the various time points in the trial.

	Baseline	Procedure[a]	48 hr Post-Procedure ±6 hours	Discharge	30 Days Follow Up (± 7 Days)[b]
Medical history	X				
Vital signs	X	X	X	X	**X**
Hematocrit/FiO_2/ Creatinine/ Platelets/ INR/Troponin	X				
CTA	X		X		
Pulmonary Artery Pressure (mmHg)		X[d]			
RV:LV Ratio	X		X		
Concomitant Medications[e]	X	X	X	X	X
Device Used		X			
Time of Procedure		X			
Major/Minor Bleeding		X	X	X	
Pregnancy Test[c]	X				
Hospital Stay	X			X	
Adverse Events		X	X	X	X
PE Recurrence					X

[a] *Procedure is defined as day zero*
[b] *30 day follow up begins from procedure*
[c] *Pregnancy test can be from urine or blood test*
[d] *Pulmonary pressures will be obtained pre and post procedure*
[e] *Concomitant medications include: anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study*

5.3 Termination of Patient Participation

All patients have the right to terminate their participation at any point during the study. In addition, Principal Investigators also have the ability to terminate patient participation in the study. Reasons for termination include: completion of study, patient withdrawal, physician-directed patient withdrawal, lost-to-follow-up, and death. A description of the reason for their termination will be documented in the patient's medical file and in the appropriate study Case Report Forms (CRF).

5.4 Lost to Follow-up

Every attempt must be made to have all patients complete the follow-up visit schedule. A patient will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the Principal Investigator must be sent to the patient's last known address. Both telephone and letter contact efforts to obtain follow-up must be documented in both the patient's medical records and on the CRFs.

5.5 Patient Withdrawal

All study patients have the right to withdraw their consent at any time during the study. Whenever possible, the site staff should obtain written documentation from the patient that wishes to withdraw his/her consent for future follow-up visits and contact. If the site staff is unable to obtain written documentation, all information regarding the patient's withdrawal must be recorded in the patient's medical record. In addition, the appropriate CRFs must be completed for the patient and clear documentation of the patient's withdrawal will be in the patient's source documents.

Withdrawal of a patient from the study can occur at the direction of the Principal Investigator or the Sponsor. Reasons for physician-directed patient withdrawal include, but are not exclusive to: the patient has enrolled in another study that conflicts with the evaluation of the primary endpoints, or if the physician deems it in the best interest for the safety or welfare of the patient to withdraw.

6. ADVERSE EVENTS

6.1 Adverse Event Reporting

Safety will be assessed by collecting adverse event data on each patient and will be captured in the CRFs. AE reporting begins with the start of the Indigo procedure (venous puncture) and continues through 30-day follow-up.

All adverse events must be recorded on the CRFs and must be carefully monitored during the entire study. At each evaluation, the Investigator or designee will determine whether any adverse events (AEs) have occurred. In addition, patients should be instructed to contact the Investigator, and/or study coordinator if any significant adverse events occur between study evaluation visits.

Adverse events should be followed up to resolution or stabilization, and if an on-going AE changes in severity, a new AE entry for this event should be recorded. If a mild adverse event changes to a moderate or severe adverse event, the end date for the mild event and the start date for the moderate or severe event should be the same. Additionally, the mild event is considered resolved with the initiation of the moderate or severe event.

Adverse events that are present at the end of a patient's participation in the study should be marked as unresolved at time of study exit on the CRF and the patient should receive post-treatment follow-up as appropriate and standard of care at the institution.

Minimum requirements of data to be recorded are: type of event, duration of adverse event or adverse device effects (start through end), severity, seriousness, action taken, outcome and, if appropriate, causality.

The Investigator will report any serious adverse event or adverse device effect to the Sponsor or its designee as soon as possible from awareness of the event. All serious adverse events or serious device effects must be entered into the database on the Serious Adverse Events form along with an explanation of any medical treatment administered.

An adverse event need not be reported as a serious adverse event if it represents only a relapse or an expected change or progression of the condition that was the cause of treatment without any symptoms and signs other than those present before treatment. This type of event only needs to be reported as an adverse event. The IRB must be informed by the Investigator about serious adverse events or device effects associated with the use of the product, as requested by their local guidelines.

6.2 Definition of Adverse Events

Any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the investigational product (device). This includes a change in a patient's condition or laboratory results that has or could have a deleterious effect on the patient's health or well-being.

For purposes of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions do not need to be reported as an adverse event or a SAE in the CRF unless there is an increase in severity or frequency during the course of the study. If an intervention is planned prior to enrollment and it has been documented in the medical chart then this will not be entered as an AE or a serious adverse event (SAE) in the CRF.

6.3 Definition of Serious Adverse Event (SAE)

An adverse event is serious if the patient outcome was:

a) Death
Report if death was the outcome of an adverse event. The primary cause of death should be reported as the adverse event term.

b) **Life-threatening**
Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

c) Hospitalization (initial or prolonged)
Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

d) Disability or Permanent Damage
Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

e) Required Intervention to Prevent Permanent Impairment or Damage (Devices)
Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

f) Other Serious (Important Medical Events)
Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

6.4 Device Malfunction

A device malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. All device malfunctions must be reported to the Sponsor via the eCRF.

If a device malfunction results in an AE for the patient, then the AE must be reported in a CRF. Device malfunctions that do not result in an adverse event for the patient do not need to be recorded as an AE, as they are not considered an AE.

If a device malfunction occurs with the aspiration catheter and/or separator, contact your Penumbra Clinical representative for the return process. All other Penumbra non-investigational device malfunctions should be reported and returned through the Penumbra commercial representative.

6.5 Unanticipated Adverse Device Effect (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 investigational plan, investigator brochure, or Investigational Instructions For Use. Unanticipated adverse device effect also includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.6 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment

6.7 Relationship to Study Device

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study device:

Unrelated	The event is definitely not associated with device application. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Possible	The temporal sequence between device application and the event is such that the relationship is not unlikely or patient's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the patient's condition.
Definite	The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application (re-challenge).

6.8 Relationship to Study Procedure

The Investigator will use the following definitions to assess the relationship of the adverse event to the study procedure:

Unrelated	The event is definitely not associated with the study procedure. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Possible	The temporal sequence between the study procedure and the event is such that the relationship is not unlikely or patient's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant or the event abates upon study procedure completion or the event cannot be reasonably explained by the patient's condition.
Definite	The temporal sequence is relevant and the event abates upon study procedure completion, or reappearance of the event on repeat interventional procedures (re-challenge).

6.9 Risk/Benefit Assessment

The Indigo® Aspiration System is a FDA-cleared device and part of the current standard of care for clot removal in peripheral arteries and veins.
The risks of intra-arterial thrombectomy/embolectomy are similar to those associated with existing intra-arterial methods of recanalization. These risks include:

- allergic reaction and anaphylaxis from contrast media
- acute occlusion
- air embolism
- arteriovenous fistula
- death
- device malfunction
- distal embolization
- emboli
- false aneurysm formation
- 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
- fibrillation
- hypotension
- respiratory failure
- peripheral embolic events

7. Statistical Considerations

7.1 Study Endpoints

7.1.1 Primary Endpoints

- **Primary Efficacy Endpoint**
  - Change in RV/LV ratio at 48 hours post-procedure. The primary efficacy analysis will be the difference between the baseline and the 48-hour RV/LV diameter ratio. The two-sided 95% confidence interval for the mean difference will be calculated. The Core Laboratory data supersede the investigator-reported data in all analyses of RV/LV diameter.

- **Primary Safety Endpoint**

  The primary safety endpoint is 48 hour major adverse events, a composite of:
  - Device-related death within 48 hours
  - Major bleeding within 48 hours
  - Device-related SAEs within 48 hours, a composite of:
    - Clinical deterioration
    - Pulmonary vascular injury
    - Cardiac injury

  Major bleeding, clinical deterioration, pulmonary vascular injury and cardiac injury are defined in the Study Definitions of Appendix I.

  The data will be analyzed as a binary variable with each patient counted only once. The two-sided 95% confidence interval will be provided for the primary safety rate.

7.1.2 Secondary Endpoints

The secondary safety endpoints will include the following:
- Device-related death within 48 hours
- Major bleeding within 48 hours
- Clinical deterioration within 48 hours
- Pulmonary vascular injury within 48 hours
- Cardiac injury within 48 hours
- Any-cause mortality within 30 days
- Device-related SAEs within 30 days
- Symptomatic recurrence of PE at 30 days

Recurrent pulmonary embolism is defined in the Study Definitions of Appendix I.

The proportion of patients who experience each secondary endpoint will be calculated along with the associated 95% confidence interval.

7.2 Sample Size Justification

Up to 150 patients are to be enrolled in order to provide 100 evaluable patients treated by the Indigo® Aspiration System. Assuming a mean change of 0.42 in the RV/LV ratio from baseline to 48 hours and a standard deviation of 0.36, the expected lower bound of the two-

sided 95% normal distribution confidence interval around the change for a sample size of 100 patients is greater than 0.20.

7.3 Accrual and Follow-up

The trial is anticipated to last 2 years and each patient will be in the trial for 30 days.

7.4 Statistical Analysis

This is a prospective, multicenter, single arm study designed to evaluate the safety and efficacy of the Indigo® Aspiration System for the extraction of clot in patients with acute PE. 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 Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions. The statistical analysis plan will be finalized prior to database lock.

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, mean, median, standard deviation, minimum and maximum for continuous variables and counts and percentages for discrete variables. Results collected at multiple visits will be summarized at each visit for which they are collected as described in Table 1 Schedule of Assessments. Summaries for all measures will include all observed data for each visit.

7.5 Analysis of Adverse Events

All adverse events will be summarized by showing the number and percent of patients reporting the event. Events will also be reported by relationship to the procedure or device. The CEC data supersede the investigator-reported data in all analyses of adverse events. Adverse events judged as probably or definitely related to the Indigo System will be analyzed as device-related.

7.6 Interim Analysis

No interim efficacy analyses are planned for the purpose of stopping the study early. An interim analysis for the purpose of sample size re-estimation will be conducted. Sample size will not be decreased regardless of the results of this evaluation.

7.7 Data Management and Security

All study data will be entered into an electronic data capture (EDC) system provided by a vendor. Standardized electronic Case Report Forms (eCRFs) will be provided for use at all investigational sites. The patients will be identified in the eCRFs with a unique patient identifier. Study personnel will have individual login and password to access the clinical

study information based upon each individual's roles and responsibilities. The application provides hierarchical user permission data entry, viewing, and reporting options. All data entry and data update information, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system. This application is designed to support compliance with the appropriate regulations and guidance for industry.

Data entry will be performed at the investigational sites. Investigators are responsible for completion and timely submission of the data to Penumbra, Inc. Every reasonable effort should be made to complete data entry within (seven) 7 days of data collection. The EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel access project information and study data centrally via a Web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of data listings will be used to identify data discrepancies or inconsistencies. The study site will be queried for clarification concerning eCRF discrepancies or inconsistencies identified. If eCRF corrections are necessary they will be made by the Investigator or an authorized member of the Investigator's staff that is delegated to CRF/EDC Data Entry. Questions or problems with submitted data will be addressed with the Principal Investigator via an electronic querying system, or through direct contact. The Investigator will review the eCRFs for completeness and accuracy and provide his/her electronic signature and date to eCRFs as evidence thereof. Any data items that have been changed will require reapplication of the electronic signature.

All hard copy forms and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, patient report forms, supporting medical records, study worksheet, and informed consent forms. The source documents will be used during the regular monitoring visits to verify information submitted on the eCRFs.

For each enrolled subject, images will be appropriately de-identified, and sent to the imaging Core Lab for evaluation. The Core Lab and CEC reviews will also be entered into the EDC system. Each reviewer will provide his/her electronic signature and date to reviews as evidence thereof. Queries may be issued to the Core Lab or CEC for clarification concerning possible EDC discrepancies or inconsistencies.

8. PATIENT CONSIDERATIONS

8.1 Ethics Review

Investigator will submit this protocol, site-specific informed consent form and HIPAA Authorization, and other requested documents for review and approval to a properly constituted independent Institutional Review Board (IRB) responsible for oversight of the research conducted at the study site.

Subsequent to initial review and approval, the responsible local IRBs will review the protocol at least annually and prior to study termination or completion. Annual progress reports accompanying the protocol provided for each IRB's annual review will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes to research activity, and all unanticipated problems involving risks to patients or others.

All protocol amendments must be submitted to and approved by the relevant IRBs prior to implementing the amendment.

8.2 Informed Consent and HIPAA Authorization

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent and authorization for use of the patient's protected health information from all patients prior to enrollment in the study unless the patient's health condition does not allow informed consent, in which case the local hospital and state procedures will be applied. Such informed consent and authorization will be obtained in accordance with US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25(a,b), CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), and local regulations. In the event a patient is unable to sign the IRB approved informed consent form and the HIPAA authorization, a legally authorized representative (LAR) can sign on behalf of the patient. The original, signed consent and authorization are retained at the site with the site's patient study records, and a copy is provided to the patient.

8.3 Clinical Trial Termination

Penumbra or the appropriate regulators, such as ethics committees, may decide to interrupt or terminate this clinical trial if they believe that this is necessary. Regulators will be informed of the study completion.

8.4 Patient Data Protection

Information about patients will be kept confidential and managed according to the requirements of HIPAA. The patients will be identified in the CRFs with a patient number. All patient study records will be kept securely at the site to prevent unauthorized disclosure of patient information.
The patient must be informed that the data will be stored and analyzed by computer, that local and national regulations for handling of computerized data will be followed, and that only the Investigator and the Sponsor or designee will have access to individual patient data. Furthermore, the patients should be informed about the possibility of inspection of relevant parts of the hospital records by the Sponsor or appropriate regulatory agency.

9. ADMINISTRATIVE CONSIDERATIONS

9.1 Study Activation

All Investigators must submit the following documentation to be considered approved Investigators:

- Signed and dated recent curriculum vitae
- Signed Clinical Trial Agreement
- Complete site qualification process and site initiation

Pending successful submission of all required documents, Penumbra staff will 'activate' the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

9.2 Study Coordination

Study implementation will be directed by this protocol as well as all study related plans. The protocol team will monitor closely and communicate with the study site on a regular basis regarding: rates of accrual, adherence, follow-up and AE incidences.

9.3 Study Monitoring

On-site and/or centralized monitoring will be performed in accordance with the study specific monitoring plan. The Sponsor or its representatives will visit sites to:

- Verify compliance with human subjects requirements and other research regulations and guidelines;
- Assess adherence to the study protocol;
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site Investigators will allow the Sponsor or its representatives to inspect study facilities and documentation (e.g. informed consent forms, clinical and laboratory records, other source documents, Case Report Forms) as well as observe performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of Penumbra, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

9.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval of the Sponsor.

9.4.1 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the IRB.
Principal Investigators and site staff will follow their patients according to this protocol, which meet their routine clinical practices. Nevertheless, deviations during the clinical evaluation may occur and efforts should be made to limit them. Deviations include but are not limited to follow-up visits outside of the routine visit window.
The Investigator is responsible for promptly reporting protocol deviations to their IRB and/or to the Sponsor per IRB policy.
The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and patient safety, and determine if additional reports or actions are required. Additional action may include site re-training, removal of the devices, and/or site termination.

9.5 Investigator's Records

The investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study in compliance with HIPAA and applicable GCP guidelines. In accordance with U.S. regulations, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IDE is discontinued.

All study documents should be uploaded to the Electronic Trial Master File (eTMF) section of the Veeva system. Veeva will be used as the master repository for all site and Sponsor regulatory documents, and all patient source documents with the exception of DICOMs and any records not uploaded to the eTMF (perhaps for confidentiality reasons or due to specific site discretion, as might be suitable for financial contracts). Sites generally do not need to maintain duplicate local files unless otherwise mandated by local institutional requirements.

Study records include administrative documentation – including protocol registration documents and all reports and correspondence relating to the study, as well as documentation related to each participant screened and/or enrolled in the study – including informed consent forms, case report forms, and all other source documentation.

9.6 Imaging

Sites will be required to submit images for sponsor, CEC and Core Lab review. These images should be submitted within 7 days of procedure. Sites will be provided with instructions for how images should be collected and submitted to the sponsor. If the site is unable to provide the images within this timeframe, the appropriate Sponsor contact should be notified. Study staff shall ensure that no images contain PHI as defined by the Health Insurance Portability and Accountability Act of 1996 (Pub.L. 104–191, 110 Stat. 1936, enacted August 21, 1996).

9.7 Device Inventory Requirements

The Investigator shall maintain records pertaining to device inventory. Devices are labeled for clinical investigation and will be managed by the Sponsor as clinical study lots.

The use of each device including device lot number and the date of device use shall be captured in the corresponding patient CRFs and study documents. Each component of the product opened and/or used during the procedure will be recorded in the CRFs.

The Investigator will ensure that, for the purpose of this investigation, only trained physicians who are Sub-Investigators in this study will use the Indigo® Aspiration System.

9.8 Publication of Information

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

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

10. COMMITTEES

10.1 Steering Committee

The Steering Committee (SC) is the main policy and decision-making committee of the study and has final responsibility for the scientific conduct. The specific tasks of the SC are:

- Proper design and conduct of the trial
- Ethical and professional standards of the trial
- Ensuring that the results of the clinical trial and the scientific accomplishments are arrived at in the most efficient manner possible
- Publication policy

The SC will be composed of at least one participating Investigator, and 2 experts in the disease, and might have representatives from the Sponsor.

10.2 Clinical Events Committee

The Clinical Events Committee (CEC) is made up of independent medical doctors who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study, which are based on the protocol. At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC will meet regularly to review and adjudicate appropriate adverse events for causality and attribution.

10.3 Data Safety Monitoring Board

A DSMB will be comprised of 4 members not participating in the trial and will include a statistician and physicians specialized in areas such as Interventional Radiology, Vascular or Thoracic Surgery, Cardiology or Pulmonary Disease. The DSMB will exercise review of the overall safety of the trial, periodically review all adverse events occurring in the trial, and make recommendations to adjustments in the study protocol, should any be considered necessary for safety or other related reasons. Additional details will be specified in the DSMB charter.

10.4 Imaging Core Lab

The independent imaging core lab will review images from baseline to 48 hours post procedure to determine the change in RV/LV ratio. Penumbra is responsible for tracking images received, basic quality review and forwarding applicable results to the CEC.

APPENDIX I
Study Abbreviations and Definitions

Acronyms	Definition
ADAPT	A Direct Aspiration First Pass Technique
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic Acid (aspirin)
CDT	Catheter Directed Therapy
CEC	Clinical Events Committee
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRF	Case Report Form
CSA	Clinical Study Agreement
COV	Close Out Visit
CT Scan	Computed Tomography Scan
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DSA	Digital Subtraction Angiography
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
ENT	Embolization to Uninvolved or New Territories
FDA	Food and Drug Administration
FUP	Follow-Up
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act of 1996
IA	Intra-Arterial
ICH	Intracranial Hemorrhage
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LV	Left Ventricle
LVO	Large Vessel Occlusion
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MR-DWI	Magnetic Resonance – Diffusion Weighted Imaging
mRS	modified Rankin Scale
NCCT	Non-contrast CT
PE	Pulmonary Embolism
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RMV	Routine Monitoring Visit
rt-PA	Recombinant Human Tissue Plasminogen Activator
RV	Right Ventricle
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SC	Steering Committee
SIV	Site Initiation Visit
TIA	Transient Ischemic Attack

UADE	Unanticipated Adverse Device Effect

STUDY DEFINITIONS

ADVERSE EVENT
Any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a patient's condition or laboratory results that has or could have a deleterious effect on the patient's health or well-being.

ADVERSE DEVICE EFFECT
Any adverse event related to the study device (or treatment).

BLEEDING
Loss of blood from the vascular system. Bleeding was classified by the GUSTO[19] (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding criteria:

- **Major bleeding** includes GUSTO Severe/life threatening and Moderate categories:
    - GUSTO Severe:
        - Intracranial Hemorrhage
        - Fatal/life threatening bleeding
        - Resulting in substantial hemodynamic compromise requiring intervention
    - GUSTO Moderate:
        - Requiring blood transfusion but did not result in hemodynamic compromise
- **Minor bleeding** includes GUSTO Mild bleeding:
    - GUSTO Mild bleeding that does not meet above criteria

CARDIAC INJURY
The following events are examples of possible cardiac injury:

- Acute heart failure
- Acute myocardial infarction
- Arrhythmia requiring intervention
- Cardiac hematoma
- Tricuspid or Pulmonic valve damage

CASE REPORT FORM
A record of the data and other information on each patient in the study often abbreviated as CRF.

CLINICAL DETERIORATION
Also referred to hemodynamic collapse[15] is defined as having one of the following:

- need for cardiopulmonary resuscitation, intubation, vasopressors, ECMO/ECLS; or systolic blood pressure (SBP) <90 mm Hg for at least 15 minutes, or

- drop of SBP by at least 40 mm Hg for at least 15 minutes with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL/h or altered mental status); or
- need for catecholamine administration to maintain adequate organ perfusion and a SBP >90 mm Hg (including dopamine at the rate of >5 micrograms/kg per minute).

COMPLICATION (ANGIOGRAPHIC OR CLINICAL)
An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to acute occlusion, air embolism, arteriovenous fistula, death, distal embolization, emboli, false aneurysm formation, hematoma or hemorrhage at access site, infection, intracranial hemorrhage, ischemia, neurological deficits including stroke, vessel spasm, thrombosis, dissection, or perforation. Complications may or may not be related to the investigational product(s).

DEEP VEIN THROMBOSIS
A clot in a vein deep under the skin usually in a leg.

DEVICE MALFUNCTION
Device malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended [21 CFR 803.3(k)]. Performance specifications include all claims made in the labeling for the device.

DISSECTION
Angiographic evidence of a tear in the arterial wall as defined by the occurrence of intramural hematoma.

DISTAL EMBOLIZATION
Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

ECMO
Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support (ECLS), is a means of providing both cardiac and respiratory support to persons whose heart and lungs are unable to provide an adequate amount of gas exchange to sustain life.

EMBOLI
Blood clots or thrombi transported by blood from a distant source.

EMBOLIZATION TO A NEW TERRITORY

An embolic occlusion of an artery affecting an area not supplied by the target vessel (site of primary occlusion).

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)
Decrease in platelet count during or shortly following exposure to heparin.

HYPERTENSION
Persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140mm Hg systolic and 90 mmHg diastolic to as high as 220 mmHg systolic and 110 mmHg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

HYPOTENSION
Sustained Hypotension: Systolic blood pressure less than 80 mmHg lasting more than 30 minutes or requiring intervention (e.g. pacing, intra-aortic balloon pump (IABP), intravenous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.

INTIMAL FLAP
An extension of the vessel wall into the arterial lumen.

INTRACRANIAL HEMORRHAGE
Bleeding in the cranium of the brain.

ISCHEMIA
The deficiency, or a lack of blood flow to an organ resulting in an imbalance between the supply and demand of oxygen (or other nutrients) leading to cell damage or death.

LEUKOPENIA
A leukocyte count of $<3.5 \times 10^9$/liter for more than 3 days.

MAJOR TRAUMA
Limb or life-threatening injury due to blunt force, penetrating injury or burn injury.[20]

NEOINTIMAL HYPERPLASIA
Thickening of the neointima due to intimal cell accumulation.

NEUTROPENIA
A decrease in the number of neutrophilic leukocytes in blood to $<1{,}000$ mm^3

OCCLUSION
The cessation of blood flow in an artery due to the presence of a clot or thrombus.

OCCLUSION LOCATION
Location according to specific artery; a standard code will be provided in the CRF to use for location descriptions.

PERFORATION
The piercing or rupturing of a blood vessel; perforations can be detected or observed angiographically.

PROCEDURAL SERIOUS ADVERSE EVENTS
Serious adverse events that occurred within 24 hours of the procedure.

PULMONARY EMBOLISM
A DVT clot that dislodges from a vein wall and travels to the lungs resulting in complete or partial occlusion of blood supply.

LOW-RISK PULMONARY EMBOLISM[6]
Acute PE in the absence of markers defining massive or submassive PE.

MASSIVE PULMONARY EMBOLISM[6]
Acute PE with presence of one of the following findings:
- Sustained hypotension (systolic BP <90 mm Hg for 15 min or requiring ionotropic support)
- Pulselessness
- Sustained heart rate <40 BPM with signs/symptoms consistent with shock

SUBMASSIVE PULMONARY EMBOLISM[6]
Acute PE with Systolic BP ≥90 mm Hg and RV dysfunction or myocardial necrosis defined by:
- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
- RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT
- Elevation of BNP (>90 pg/mL), or N-terminal pro-BNP (>500 pg/mL)
- EKG changes (new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)
- Elevation of troponin I (>0.4 ng/mL) or troponin T (>0.1 ng/mL)

RECURRENT PULMONARY EMBOLISM
Symptomatic PE objectively confirmed on contrast-enhanced chest CT, ventilation-perfusion lung scan, or invasive contrast pulmonary angiography.

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

- Arterial Venous Fistula
- Dissection
- Hemorrhage
- Intimal flap
- Perforation
- Rupture
- Thromboembolic occlusion resulting in permanent damage i.e. infarction

RIGHT VENTRICLE DYSFUNCTION
Right ventricle dilation (RV to LV ratio >0.9) or wall motion abnormalities (hypokinesis, septal wall deviation).

SERIOUS ADVERSE EVENT (SAE)
An SAE is an AE with a patient outcome that is life-threatening or results in death, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or a birth defect, or intervention required to prevent permanent impairment or damage. An event may also be considered serious if it may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

STROKE
A new focal neurological deficit of presumed vascular origin persisting more than 24 hours and with a neuro-imaging study that does not indicate a different etiology. The 24-hour criterion is excluded if the patient undergoes cerebrovascular surgery or dies during the first 24 hours. It includes patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. It does not include stroke events in cases of blood disorders such as leukemia, and it excludes patients with a history of stroke secondary to trauma.

TARGET OCCLUSION
The occlusion being treated or attempted to be treated during the index procedure.

TARGET VESSEL
The vessel containing a target occlusion.

THROMBUS
Discrete, mobile intraluminal filling with defined borders with or without associated contrast staining; these are classified as either absent or present.

THROMBOCYTOPENIA

A platelet count of <100,000 mm^3

TOTAL OCCLUSIONS
An occlusion with no flow.

TRANSIENT ISCHEMIC ATTACK (TIA)
Brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or Investigational Instructions For Use, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

VASOSPASM
Spasm of a blood vessel, resulting in decrease in lumen diameter. When referring to a vasospasm, the anatomic location should be specified (e.g. peripheral vasospasm or cerebral vasospasm)

Appendix II

Preferred Sheaths

Company	Sheath Name	Valve Type/Tuohy	Length	FR Size	Manufacturer Part Number	Compatibility
Terumo	Pinnacle® Destination® with Tuohy	Tuohy	45 cm, 65 cm, 90 cm	8FR or Larger	54-84506, 54-86506, 54-89006	Yes
Cook®	Flexor® Shuttle® with Tuohy	Tuohy	90 cm	8FR or Larger	KSAW-8.0-38-90-RB, SHTL-HC	Yes

APPENDIX III

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