CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the **C**AT RX Aspiration Cath**he**t**e**r in Pa**t**ients with **a** **H**igh Thrombus Burden Acute Coronary Vessel Occlusion

Protocol
CLP-15298.B

Date of Protocol
06 August 2019

Device Name
Indigo® Aspiration System with CAT RX Aspiration Catheter &
Indigo Separator™ 4

Sponsor
Penumbra, Inc.
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CLP-15298 Protocol Synopsis	
Title	**CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion**
Study Objective	The objective of this study is to demonstrate the safety and performance of the Indigo® Aspiration System using the CAT RX Aspiration Catheter in a population presenting with acute high thrombus burden coronary vessel occlusion who are referred for Percutaneous Coronary Intervention (PCI).
Study Design	Post-market, real world, prospective, multi-center study that will enroll up to 400 subjects at up to 25 US sites
Indication	Per Instructions For Use (IFU)
Patient Population	High thrombus burden patients presenting with acute coronary vessel occlusion who are referred for standard of care (SOC) PCI
Study Device	Indigo® Aspiration System with CAT RX Aspiration Catheters and Indigo Separator™ 4
Study Duration	It is anticipated this study will take approximately 2 years. All subjects will be followed for approximately 6 months or to outcome (e.g. withdrawal, death), whichever occurs first
Follow-up	Subjects will undergo follow-up at post-procedure, discharge or 7 days (whichever occurs first), 30 days and 180 days post-procedure
Inclusion Criteria	1. Patient age ≥ 18 years 2. Patient presents to treating facility within 12 hours of symptom onset 3. High thrombus burden at coronary angiography, defined as TIMI thrombus grade 4 or 5 by physician visual estimate after the guidewire crosses the target lesion 4. Frontline treatment with the Indigo® Aspiration System using the CAT RX Aspiration Catheter, prior to standard of care PCI 5. Target lesion is located in a native coronary artery 6. Informed consent is obtained from either patient or legally authorized representative (LAR)
Exclusion Criteria	1. New onset of stroke symptoms and NIHSS > 2, prior to index procedure 2. Treatment with fibrinolytic therapy for index coronary vessel occlusion 3. Life expectancy less than 6 months due to any comorbidities 4. Patient is unwilling or unable to comply with protocol follow up schedule and/or based on the Investigator's judgment the patient is not a good study candidate 5. Participation in another investigational drug or device study that may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies. 6. Patient is pregnant
Primary Endpoints	Composite of cardiovascular (CV) death, recurrent myocardial infarction (MI), cardiogenic shock, or new or worsening New York Heart Association (NYHA) Class IV heart failure within 30 days

CLP-15298 Protocol Synopsis	
Title	**CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion**
Secondary Endpoints	Performance: 1. Final TIMI Flow Grade 2. Final TIMI Thrombus Grade 3. Myocardial Blush Grade 4. Distal Embolization Rate 5. Stent thrombosis within 180 days Safety: 1. Stroke within 30 days 2. Major bleeding within 30 days 3. All-cause mortality within 180 days 4. Cardiovascular (CV) death within 180 days 5. Recurrent MI within 180 days 6. Cardiogenic shock within 180 days 7. Class IV heart failure within 180 days 8. Incidence of device related SAE(s)
Primary Statistical Hypothesis	The null hypothesis is that the difference between the composite primary endpoint rate and the historical control at 30 days is greater than or equal to 10%. The alternative hypothesis is the difference at 30 days is less than 10%.
Primary Statistical Test	The primary effectiveness analysis will be the difference between the composite primary endpoint rate in the study and the historical control PCI rate of 6.1% with a non-inferiority margin of 10%. The primary safety endpoint is met if the upper limit of the 95% confidence interval of the composite primary endpoint rate is less than 16% at a one-sided alpha of 0.025.
Sample Size Justification	The sample size calculations assume that 6.1% (22/360) of the study subjects experience a primary safety event. Based on a binomial analysis with a non-inferiority margin of 10%, a study of 360 enrolled subjects will have greater than 90% power with a one-sided alpha of 0.025. The sample size was adjusted to 400 subjects to account for up to 10% attrition rate.

1. Introduction and Rationale

1.1 Background Information

Acute coronary syndrome (ACS) represents a significant health and economic burden to the United States, accounting for approximately 1.36 million hospitalizations per year.[1] ACS encompasses a spectrum of conditions caused by acute myocardial ischemia and/or infarct that is usually due to a reduction in coronary blood flow. Myocardial infarction (MI) is a severe sub-category of ACS where the ischemia leads to cardiac tissue damage and release of cardiac-specific biomarkers.[1] Myocardial damage in MI is typically precipitated by atherosclerotic plaque disruption and coronary thrombosis formation, leading to reduced or completely eliminated blood flow to the heart.[1-3]

The overall prevalence of MI in the United States (US) in adults ≥ 20 years old is 3.0%.[4] US males in general have a higher prevalence of MI (3.8%) than females (2.3%).[4] MI is among the leading cause of morbidity and mortality in the US.[5] Additionally, it is one of the most expensive, leading to >$12 billion annually in hospitalization costs.[4] These costs are projected to increase by almost 100% between 2013 and 2030.[4] The estimated annual incidence of MI is 605,000 new and 200,000 recurrent attacks. The average age at first MI is 65.6 years for males, and 72.0 years for females.[4] In 2015, MI mortality was 114,023.[4] Of patients >45 years of age who experience a first MI, incidence of recurrent or fatal heart disease within 5 years ranges from 17%-20%.[5]

MI is broken broadly into two categories defined by electrocardiogram (EKG) changes: Non-ST Elevation Myocardial Infarction (NSTEMI), and ST-Elevation Myocardial Infarction (STEMI). NSTEMI is typically the result of a severely narrowed but not completely occluded coronary vessel, while STEMI is typically the result of a completely occluded coronary vessel. Roughly two-thirds of MI patients present with NSTEMI and the rest present with STEMI.[1]

Rapid myocardial perfusion is a main treatment goal in MI.[2,6] First introduced in the 1970s, percutaneous coronary intervention (PCI) has evolved to be one of the main treatment modalities for MI.[1,6-9] In PCI, a guidewire is advanced via arterial access across the stenosis or occlusion site and remains in place until the end of the procedure.[10] A balloon is then passed over the guidewire to the stenosis site, the balloon is then inflated and deflated repeatedly until target artery patency is sufficient. After the balloon is removed, a stent is commonly deployed at the stenosis site to maintain long-term artery patency.[10] Roughly 60% of ACS patients will receive PCI while the remainder will undergo either open surgical coronary artery bypass grafting (CABG) or medical therapy alone.[9] The American Heart Association's guidelines for NSTEMI and STEMI management include recommendations for utilization of PCI as part of the treatment strategy because the benefits of PCI greatly outweigh the risks, and these benefits have been well established by multiple clinical trials and meta-analyses.[7,8,11]

1.2 Development of Percutaneous Coronary Intervention (PCI) with Aspiration Thrombectomy

Despite its success, a major limitation of PCI alone is microvascular obstruction downstream of the infarct-related vessel.[12] In PCI alone, a balloon simply compacts atherothrombotic material against the vessel wall and does not remove it, creating an opportunity for the atherothrombotic material to embolize.[12,13] Increased microvascular obstruction is associated with an increased infarct size, reduced recovery of ventricular function, and increased mortality.[12] Measures of microvascular tissue reperfusion, such as degree of ST-segment resolution, or angiographic myocardial blush grade (MBG), have been shown to predict the rate of death after PCI.[14]

PCI with aspiration thrombectomy has been gaining increased attention as a way to prevent or reduce embolization of atherothrombotic debris caused by PCI.[8] A large meta-analysis of randomized controlled trials (30 studies, 6415 patients) investigating the use of adjunctive devices with PCI compared to PCI alone found that out of the adjunctive therapies studied (aspiration thrombectomy, mechanical thrombectomy, embolic protection devices), only aspiration was beneficial for reducing mortality, while the others either increased mortality or had a neutral effect.[15]

To use aspiration with PCI, the aspiration catheter is navigated to the occlusion site using the same guidewire that is used during conventional PCI. Aspiration is applied while the aspiration catheter is advanced across the target coronary segment to remove atherothrombotic material. Once the aspiration is complete, the catheter is removed, and PCI is performed as per routine protocol.[12]

1.3 Major Clinical Research related to PCI with Aspiration Thrombectomy

The TAPAS trial was a prospective randomized trial of 1071 consecutive PCI-eligible STEMI patients who were treated with either conventional PCI or with manual aspiration thrombectomy prior to PCI.[12] Atherothrombotic material was retrieved in 73% of patients in the aspiration group. Aspiration did not result in a higher rate of intra-procedural complications, none of the complications were thought to be related to the aspiration device, and there were no intraprocedural deaths or strokes.[12] Aspiration prior to PCI resulted in clear improvements in MBG, resolution of ST-segment elevation, and residual ST-segment deviation. The primary endpoint of MBG 0-1 occurred in only 17.1% of patients in the aspiration group compared with 26.3% in the conventional PCI group ($p < 0.001$). These benefits of aspiration were consistently present irrespective of baseline clinical or angiographic characteristics.[12] At 1-year follow-up, the aspiration group had significantly lower rates of cardiac death (3.6% vs 6.7%; HR 1.93; 95% CI 1.11-3.37; $p = 0.020$).[16] These results suggest that manual aspiration prior to PCI does not impact procedural safety, and reduces morbidity and mortality as compared with conventional PCI alone.

Similarly, the EXPIRA trial randomized 175 consecutive PCI-eligible STEMI patients to either conventional PCI or manual aspiration thrombectomy prior to PCI.[17] The primary endpoints were MBG ≥ 2 and rate of ST-segment resolution. Aspiration resulted in

significantly higher rates of MBG ≥2 (88% vs 60%, p = 0.001), ST-segment resolution (64% vs 39%, p = 0.001), and reduced incidence of cardiac death at 9-month follow-up (0% vs 4.6%, p = 0.02). A sub-analysis of 75 patients using contrast enhanced MRI found that the aspiration group had less microvascular obstruction in the acute phase and had significantly reduced infarct sizes at 3 months follow-up. At 2-year follow-up, the aspiration group showed significant reductions in Major Adverse Cardiac Events (MACE; 4.5% vs 13.7%, p = 0.038), and cardiac death (0% vs 6.8%, p = 0.012).[18] These results suggest that manual aspiration prior to routine PCI in STEMI patients prevents thrombus embolization, preserves microvascular integrity, and reduces long term risk of cardiac death and MACE.

The TASTE trial was a large registry-based trial of 7,244 PCI-eligible STEMI patients who were randomized to either manual aspiration thrombectomy followed by PCI, or to conventional PCI.[19] This study did not record findings with respect to myocardial salvage or microvascular obstruction. With respect to safety outcomes, the aspiration group did not have increased rates of stroke or neurologic complications, perforation or tamponade, heart failure, or left ventricular dysfunction. The primary endpoint, all-cause mortality at 30 days, was not significantly different between the groups (2.8% with aspiration vs 3.0% with PCI-only, p = 0.63). At 1-year follow-up, both groups had similar rates of all cause mortality, and rehospitalization for MI.[20] The TASTE trial results suggest that manual aspiration did not impact key safety outcomes, but also did not provide additional benefit over PCI.

The TOTAL trial randomized 10,732 PCI-eligible STEMI patients to manual aspiration prior to PCI or PCI-only.[14] This study showed significant improvements in ST segment resolution and distal embolization with aspiration. But, there was no significant difference with respect to the primary outcome (composite of cardiovascular death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure) both at 180 days (6.9% with aspiration vs 7.0% with PCI-only, p = 0.86) and at 1-year follow-up (8% vs 8%, p = 0.99).[21] Subgroup analysis for patients with higher thrombus burden or patients with initial TIMI flow grade 0-1 also revealed no significant differences. Additionally, there was a small but statistically significant increase in the rate of stroke within 30 days in the manual aspiration group (0.7% vs 0.3%, p = 0.02).[14]

The TATORT-NSTEMI study is currently the only large randomized study that investigated the use of manual aspiration thrombectomy in NSTEMI. Four hundred forty (440) PCI-eligible NSTEMI patients were randomized to either aspiration prior to PCI or to conventional PCI. The primary endpoint of microvascular obstruction was not different between the aspiration group and the PCI-only group (2.0% vs 1.4%, p = 0.17). No difference was found between the groups with respect to infarct size, myocardial salvage index, MBG, TIMI flow grade, MACE at 1-year, functional outcome at 1-year, or quality of life at 1-year.[13,22]

1.4 Study Rationale

Current clinical evidence suggests that manual aspiration thrombectomy is capable of removing atherothrombotic material from target MI lesions. However, the utility of using

aspiration for all PCI-eligible MI patients is mixed. Some studies have found reduction in mortality in patients treated with aspiration prior to PCI,[12,17] others have found neutral mortality benefit.[13,14,19] These variable results may be due to a variety of factors including study design (follow-up time period, time to reperfusion, number of centers included), technological limitations of manual aspiration catheters, or inclusion of all patients regardless of clot burden. Additionally, most prior studies utilized manual aspiration thrombectomy with small volume (e.g. 30-cc) syringes. Compared with power aspiration, manual aspiration suffers from decreased aspiration force as the syringe fills with fluid and requires the operator to exchange syringes. Power aspiration thrombectomy using a continuous aspiration source is an established technique and is commonly used in neurovascular clinical practice for endovascular thrombus removal in acute ischemic stroke patients.[23-27]

The role of aspiration in select cardiac populations, particularly those with high thrombus burden, is still under active debate.[28] By removing thrombus during primary PCI, aspiration thrombectomy may prevent distal embolization, prevent microvascular dysfunction and improve prognosis in patients with acute coronary vessel occlusion. By studying a cohort of subjects with high thrombus burden (TIMI thrombus grade 4 or 5) and treating frontline with the Indigo® Aspiration System that utilizes a dedicated power source capable of delivering continuous aspiration, the CHEETAH study aims to evaluate initial safety and collect performance data on Penumbra's Indigo® Aspiration System with the CAT RX Aspiration Catheter, when used as an adjunctive device prior to standard of care PCI. The results of this study can be used for the planning of future aspiration thrombectomy studies.

2. Device Description

General Description/Overview

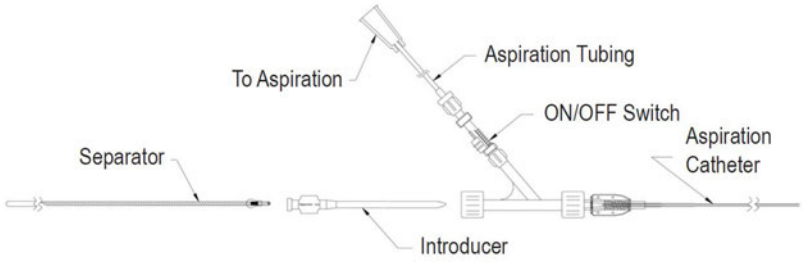
The Indigo® Aspiration System is comprised of several devices:

- Indigo CAT RX Aspiration Catheter
- Indigo Separator™ 4
- Indigo Aspiration Tubing
- Indigo Pump Canister/Tubing
- Penumbra Aspiration Pump

The Indigo® Aspiration System is designed to remove thrombus from the vasculature using continuous aspiration. The Indigo CAT RX Aspiration Catheter (Aspiration Catheter) is a dual lumen rapid exchange catheter that targets aspiration from the Pump directly to the thrombus, removing it via the Indigo Aspiration Tubing and depositing it in the Pump Canister. The Indigo Separator™ 4 (Separator) may be used, if needed, to clear to lumen of the Aspiration Catheter should it become blocked with thrombus. The Aspiration Catheter is introduced through a guide catheter or guiding sheath, over a guidewire, and advanced to the target occlusion site in the coronary vasculature. The Aspiration Catheter is used with the Penumbra Aspiration Pump (Pump) to aspirate thrombus from the occluded vessel. If utilized, the Separator is advanced and retracted through the Aspiration Catheter at the proximal margin of the primary occlusion to facilitate clearing of the thrombus from the Aspiration Catheter tip. For the aspiration source, the Aspiration Catheter is used in

conjunction with the Pump, which is connected using the Aspiration Tubing and the Pump Canister/Tubing. The Aspiration Catheter may be provided with a rotating hemostasis valve and a peelable sheath. The Separator is provided with an introducer and torque device. The Aspiration Catheters and Separators are both visible under fluoroscopy.

Figure 1: Assembled Indigo® Aspiration System with Indigo Separator™ 4



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

2.1 Indigo CAT RX Aspiration Catheter

As part of the Indigo® Aspiration System, the Indigo CAT RX Aspiration Catheter is indicated for removal of fresh, soft emboli and thrombi from vessels in the coronary and peripheral vasculature. The Indigo CAT RX Aspiration Catheter received US Food and Drug Administration (FDA) 510(k) clearance in May 2017 under K163618 and is currently available in the United States.

The Aspiration Catheter is a dual lumen, rapid exchange, intravascular catheter. It is designed and composed of materials common to interventional devices. The distal lumen is polytetrafluoroethylene (PTFE) lined and the shaft is reinforced with both a nitinol round wire and a laser cut stainless steel hypotube. The shaft has variable stiffness with progressively softer polymer extrusion materials moving distally along its length. The distal portion of the shaft is hydrophilically coated for lubricity. The distal tip has a radiopaque platinum/iridium markerband. The Aspiration Catheter is provided sterile for single use and may be packaged in a kit with the Aspiration Tubing. The kit also contains a rotating hemostasis valve (RHV) and an introducer sheath.

2.2 Indigo Separator™ 4

As part of the Indigo® Aspiration System, the Indigo Separator™ 4 is indicated for removal of fresh, soft emboli and thrombi from vessels in the coronary and peripheral vasculature. The Separator is size-matched to the Aspiration Catheter and may be used as needed to clear thrombus from the lumen of the Aspiration Catheter during aspiration. The Separator consists of a stainless steel core wire of variable diameter and variable lengths, a soft tip, and a cone formed from Pebax® with a variable outer diameter (OD) matched to fit the inner diameter (ID) of the Aspiration Catheter. The Separator may be used, if needed, to clear the lumen of the Aspiration Catheter should it become blocked by thrombus. The Separator is provided sterile with a torque device and introducer sheath.

2.3 Indigo Aspiration Tubing

The Aspiration Tubing is indicated to connect the Aspiration Catheter to the Penumbra Aspiration Pump. The Aspiration Tubing has a flow valve which connects directly to the Aspiration Catheter hub or RHV and allows the physician to start and stop the flow of aspiration.

2.4 Penumbra Aspiration Pump

The Penumbra Aspiration Pump is indicated as the aspiration source for the Indigo Aspiration System (Penumbra, Inc., Alameda, CA, USA) for the removal of emboli and thrombi from vessels of the peripheral arterial, venous and coronary vasculature to aid the physician in the removal of tissue and/or fluid during image guided neurosurgery.

The Pump (Pump MAX or Penumbra ENGINE Pump) is an electromechanical device designed to generate negative vacuum pressure as a component of the Penumbra Aspiration Systems. Intended users are physicians who have received appropriate training in surgical procedures and/or interventional techniques for patients who require suction therapy during surgical procedures and/or procedures using interventional techniques. The Penumbra Aspiration Pump is intended for use in operating rooms or interventional catheterizations laboratories and does not come into contact with the patient.

2.5 Indigo Pump Canister and Tubing

A 1000 ml minimum canister with a stemmed lid is designed for use with the Pump. Each canister has a stop-flow filter to prevent excess fluid from entering the Pump Canister Tubing. The patient port on the lid is sized to accept the Suction Connector on the Aspiration Tubing. Graduations are placed on the canister in 50-ml and 100-ml increments. The canister lid is removable.

For the Pump MAX, Pump Canister Tubing is used to connect the Pump to the Pump Canister. This tubing has an inline filter to prevent fluid and contaminants from entering the pump. The tubing lumen remains open under full vacuum. The Penumbra ENGINE Pump does not require this additional tubing. The Suction Connector is securely attached to the Pump Canister lid and Pump via press fit.

3. Risk Analysis

A thorough risk analysis was performed as part of design control requirements of the Quality System Regulation (21 CFR 820).

3.1 Risks Related to PCI and Aspiration Thrombectomy

It is anticipated that the treatment risks associated with the angiographic procedure and any intra-arterial catheterization with the Indigo® Aspiration System devices as part of a PCI procedure are the same as other cleared/approved aspiration catheters based on the same indication, device size, and device profile. 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:

- 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 thromboembolic events

Considerable 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 extensive pre-clinical testing in both bench-top and in vivo models. Critical design characteristics were evaluated to ensure that system components can withstand the rigor of clinical use. A thorough risk analysis was performed as part of design control recommendations of the Quality System Regulation (21 CFR 820). Risk management activities performed in accordance with BS EN ISO 14971:2012 did not identify any different risks or risk levels compared to other currently marketed devices.

A list of all anticipated adverse events is in the IFU for each device.

4. Study Overview

The primary aim of mechanical aspiration thrombectomy using the Indigo® Aspiration System with the CAT RX Aspiration Catheter is to safely achieve removal of clot burden to improve coronary flow and myocardial perfusion in conjunction with PCI. Past studies have focused on manual aspiration techniques, currently no prospective study exists to evaluate mechanical aspiration thrombectomy using the Indigo® Aspiration System with the CAT RX Aspiration Catheter. The purpose of this study is to evaluate the safety and collect performance data on mechanical aspiration thrombectomy using the Indigo® Aspiration System with the CAT RX Aspiration Catheter as a frontline treatment prior to standard of care PCI, in patients presenting with high thrombus burden acute coronary vessel occlusion.

4.1 Study Design

This is a post-market, real world, prospective, multicenter study evaluating the use of the Indigo® Aspiration System with the CAT RX Aspiration Catheter (and Indigo Separator™ 4, if needed) as a frontline adjunctive treatment to standard of care PCI. Patients will be enrolled who meet the inclusion and none of the exclusion criteria, who (or Legally

Authorized Representative (LAR)) consent to participate, and in whom the study device has been inserted.

4.2 Study Objectives/Endpoints

4.2.1 Primary Endpoints

Composite of cardiovascular (CV) death, recurrent MI, cardiogenic shock, or new or worsening NYHA Class IV heart failure within 30 days.

4.2.2 Secondary Endpoints

Performance:

1. Final TIMI Flow Grade
2. Final TIMI Thrombus Grade
3. Myocardial Blush Grade
4. Distal Embolization Rate
5. Stent thrombosis at 180 days

Safety:

1. Stroke within 30 days
2. Major bleeding within 30 days
3. All-cause mortality within 180 days
4. Cardiovascular (CV) death within 180 days
5. Recurrent MI within 180 days
6. Cardiogenic shock within 180 days
7. Class IV heart failure within 180 days
8. Incidence of device related SAE(s)

5. Study Population

5.1 Inclusion Criteria

1. Patient age ≥ 18 years
2. Patient presents to treating facility within 12 hours of symptom onset
3. High thrombus burden at coronary angiography, defined as TIMI thrombus grade 4 or 5 by physician visual estimate after the guidewire crosses the target lesion
4. Frontline treatment with the Indigo® Aspiration System using the CAT RX Aspiration Catheter, prior to standard of care PCI
5. Target lesion is located in a native coronary artery
6. Informed consent is obtained from either patient or legally authorized representative (LAR)

5.2 Exclusion Criteria

1. New onset of stroke symptoms and NIHSS > 2, prior to index procedure
2. Treatment with fibrinolytic therapy for index coronary vessel occlusion
3. Life expectancy less than 6 months due to any comorbidities
4. Patient is unwilling or unable to comply with protocol follow up schedule and/or based on the Investigator's judgement the patient is not a good study candidate
5. Participation in another investigational drug or device study that may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies
6. Patient is pregnant

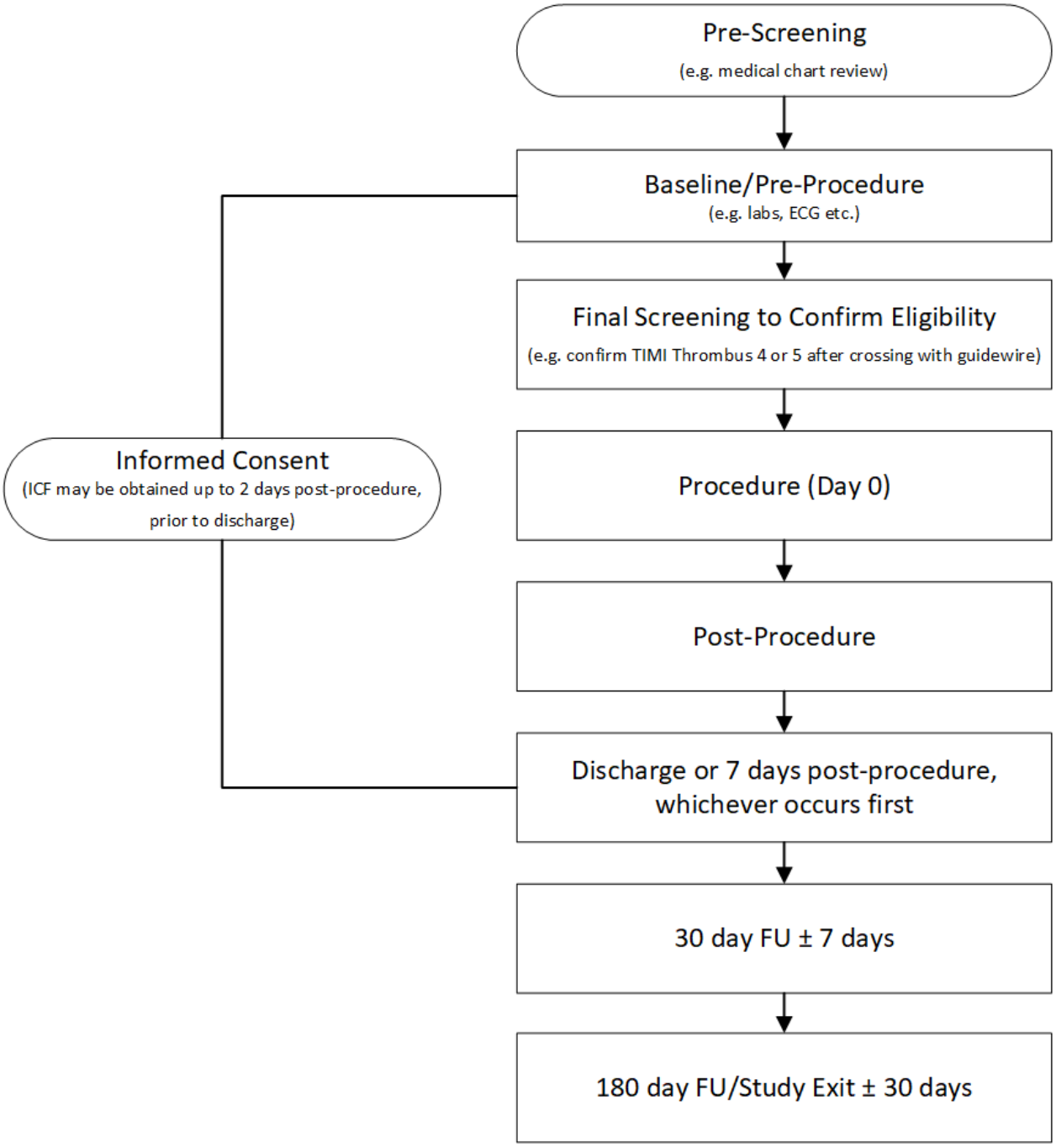
6. Study Procedures

6.1 Overview of Study Flow

To ensure that subjects are considered for enrollment, acute coronary vessel occlusion patients referred for SOC PCI should be assessed for eligibility. All sites will keep a screen failure log of all potential study candidates who are screened and not enrolled or screened, consented, and not enrolled. Reason(s) for exclusion will be recorded. Screening information 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 studies and determining the widespread impact of the therapy.

Figure 2: Study Flow



6.2 Study Visits

Subjects enrolled in this study will follow the visit schedule below.

1. Baseline/Pre-Procedure
2. Procedure (Day 0)
3. Post Procedure
4. Discharge or 7 days, whichever occurs first
5. 30 days ± 7 days
6. 180 days ± 30 days

6.3 Recruitment

The target population are subjects ≥18 years of age who are presenting with an acute coronary vessel occlusion and who are referred for SOC PCI. No study specific screening tests or procedures are required for enrollment in the study. Standard of care evaluations will be used to confirm eligibility.

Potential study participants and/or their legal authorized representative (LAR) will be identified by the study team at each site to obtain consent and determine eligibility. The study allows for enrollment of up to 400 subjects at up to 25 sites in the United States.

6.4 Screening & Enrollment

Enrollment process:

1. Confirm that the subject meets all inclusion and no exclusion criteria.
2. Obtain informed consent from the patient or LAR.
3. A subject will be considered enrolled when all eligibility criteria are met, the subject or LAR has given informed consent and the Indigo CAT RX Aspiration Catheter has been inserted into the subject's body. Subjects who have had a procedure (using the Indigo® Aspiration System with the CAT RX Aspiration Catheter as a frontline adjunctive to PCI) prior to signing informed consent may be consented up to 2 calendar days post-procedure, but prior to initial discharge, and enrolled into the study.
    a. The point of enrollment is defined as the date of informed consent or introduction of the CAT RX Aspiration Catheter, whichever occurs later.
    b. All follow-up visits will be conducted based on date of procedure, regardless of enrollment date.

6.5 Informed Consent

The Investigator or designee will obtain written informed consent from the subject or approved delegate using the current Institutional Review Board (IRB) approved consent form per IRB policy.

All informed consent documents used under this protocol will be consistent with applicable elements of I.S. EN ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good Clinical Practice (GCP) and 21 CFR 50, Protection of Human Subjects, and will be approved by the site's reviewing IRB prior to study initiation.

Any modification to the sample informed consent form made by the study site must be approved by the Sponsor and the IRB before use. Each study site will provide the Sponsor with a copy of the IRB approved consent forms. Informed consent completion will be monitored regularly by the Sponsor.

6.6 Baseline

The following baseline assessments will be performed:

1. Demographics
2. NYHA Classification
3. Killip Classification
4. Canadian Cardiovascular Society (CCS) Classification
5. Vital Signs
6. General and cardiac medical history
7. Cardiac concomitant medications
8. Laboratory assessments (most recent results obtained within 30 days prior to index procedure are permitted as baseline data)
    a. Troponins, BNP, WBC, RBC, Hgb, Hct, Platelets, Ca, CO2, Creatinine, Glucose, K, Na, BUN
    b. Additional SOC labs may be collected, if available
9. Pregnancy test (only required for women of child bearing potential, serum or urine acceptable)
10. 12 lead electrocardiogram (ECG)
11. Echocardiogram (if completed per standard of care, most recent results within 30 days prior to index procedure)

6.7 Index Procedure

The treatment procedure is described below and will involve acute coronary vessel occlusion patients that meet standard of care guidelines for treatment with PCI. The procedure will occur after completion of baseline assessments and pre-procedural imaging. The Indigo® Aspiration System with the CAT RX Aspiration Catheter must be used as a frontline treatment per IFU, prior to PCI.

At a minimum the following information will be collected during Index Procedure:

1. Coronary cineangiography at the following timepoints:
    a. Initial (pre-procedure)
    b. After crossing target lesion with guidewire
    c. After Indigo CAT RX Aspiration is complete

d. After PCI is complete (if additional treatment is not completed after PCI, additional images are not required and after PCI images can be considered final)
e. Final (after all treatment is complete)

2. TIMI Flow Grade
3. TIMI Thrombus Grade (coronary angiogram after crossing the target lesion with the guidewire should demonstrate TIMI thrombus grade 4 or 5 for patient inclusion into the study)
4. Myocardial Blush Grade
5. Target lesion characteristics
6. Procedural details, including key procedural timepoints
7. Adjunctive procedure(s)
8. Cardiac concomitant medications
9. Events of interest/Serious Adverse Events
10. Device Deficiencies/Observations

6.7.1 Preparation for Treatment

All physicians will follow routine site practice guidelines to determine patient eligibility for PCI treatment.

6.7.2 Medication during Intervention

The study recommends the use of optimal medical therapy for patients undergoing PCI per site routine standard of care guidelines. These agents include, but may not be limited to, aspirin, beta blockers, ACE inhibitors, glycoprotein IIb/IIIa, vasodilators, calcium channel blockers, statins, anti-coagulants, and anti-platelet agents.

6.7.3 Devices and Equipment

The following devices/equipment will be used (as described below) in addition to the typical devices used in PCI per site routine standard of care.

Please refer to the device descriptions in Section 2 for complete details.

Table 1: Devices used during the procedure

Device Name	Description/Details
Indigo CAT RX Aspiration Catheter	A dual lumen rapid exchange intravascular aspiration thrombectomy catheter.
Indigo Separator™ 4	Size matched accessory device (optional) for the CAT RX Aspiration Catheter, intended to clear the distal end of the CAT RX Aspiration Catheter lumen, should it be blocked with thrombus.
Indigo Aspiration Tubing	Sterile, appropriately sized tubing that connects the CAT RX Aspiration Catheter to the Penumbra Aspiration Pump
Penumbra Aspiration Pump (Pump MAX and Penumbra ENGINE Pump)	Provides continuous vacuum force
Indigo Pump Canister and Tubing	The pump canister acts as a collection reservoir for materials aspirated by the CAT RX Aspiration Catheter. For Pump MAX, pump tubing is used to connect the pump cannister to the aspiration pump. Penumbra ENGINE Pump does not require this additional tubing.

6.7.4 Index Procedure

With the flow switch in the off position, turn on the Penumbra Aspiration Pump. The Indigo CAT RX Aspiration Catheter is flushed prior to the procedure. After initial angiogram, the lesion will be crossed with a guidewire. The Indigo CAT RX Aspiration Catheter is advanced into the guide sheath/catheter and navigated to the proximal end of the lesion. Upon exiting the distal end of the guide sheath/catheter, the flow switch is turned on and aspiration via the Penumbra Aspiration Pump is applied to the Aspiration Catheter. The Aspiration Catheter may then be advanced across the lesion under continuous aspiration, at the physician's discretion. If flow through the Aspiration Catheter stops during the procedure, remove the Aspiration Catheter from the body under continuous aspiration and flush thoroughly with

saline to clear blockage. The flow switch should not be turned off until the Aspiration Catheter has exited the guide sheath/catheter and the body after performing thrombectomy.

If the Aspiration Catheter does not cross the target lesion, optional pre-dilatation may be performed with a small diameter balloon catheter (≤ 2.00 mm diameter) and then aspiration can be re-attempted. The Separator may be used at physician discretion to clear the lumen of the catheter.

A minimum 6 Fr, 0.070" (1.78mm) ID guide catheter and 0.014" (0.36mm) guidewire should be used with the Aspiration Catheter. The distal OD of the Aspiration Catheter is 0.069" (1.75mm).

After aspiration thrombectomy, PCI should be performed per routine site standard of care.

6.7.5 Post-Procedure

Subjects enrolled in the study should receive the SOC post-procedural care for patients who have undergone PCI.

The following information will be collected post-procedure:

1. Vital Signs
2. Laboratory assessments
3. 12 lead ECG
4. Echocardiogram (if completed as SOC)
5. Cardiac concomitant medications
6. Events of interest/Serious Adverse Events

6.7.6 Discharge (or 7 days, whichever occurs first)

The following information will be collected during discharge (within 1 day prior to discharge or at day 7, whichever occurs first):

1. Vital Signs
2. Laboratory assessments
3. 12 lead ECG
4. Killip Classification
5. CCS Classification
6. Cardiac concomitant medications
7. Events of interest/Serious Adverse Events

6.7.7 30 Day Visit (± 7 days)

The 30-day follow up visit may be conducted either over the phone or in person. Records within the study visit window from an outside Institution may be used to complete the visit. It is recommended that at a minimum, study patients are

contacted via phone by the study site team. The following information will be collected during the 30-day follow up visit:

1. Subject status
2. NYHA Classification
3. Killip Classification (if visit completed in person)
4. CCS Classification
5. Cardiac concomitant medications
6. Events of interest/Serious Adverse Events

6.7.8 180 Day Visit (± 30 days)

The 180-day follow up may be completed over the phone or in person. Records within the study visit window from an outside Institution may be used to complete the visit. It is recommended that at a minimum, study patients are contacted via phone by the study site team. The following information will be collected during the 180-day follow up visit:

1. Subject Status
2. Vital Signs
3. NYHA Classification
4. Killip Classification (if visit is completed in person)
5. CCS Classification
6. 12 Lead ECG
7. Echocardiogram (if completed as SOC – assessment can occur anytime between the 30 day and 180 day follow up windows)
8. Cardiac concomitant medications
9. Events of interest/Serious Adverse Events

Table 2: Schedule of Assessments

ACTIVITY	Baseline/Pre-Procedure	Procedure (Day 0)	Post-Procedure	Discharge or 7-Days (whichever occurs first)	30 days ± 7 days (Phone Call or In Person)	180 days ± 30 days (Phone Call or In Person)
Written Informed Consent	X[1]					
Confirm Eligibility Criteria	X	X[2]				
Demographics	X					
Medical History	X					
Vital Signs	X		X	X		X
Laboratory Assessments	X		X	X		
Pregnancy Test	X[3]					
NYHA Classification	X				X	X
Killip Classification	X			X	X[9]	X[9]
CCS Classification	X			X	X	X
12 Lead ECG	X		X	X		X
Coronary Cineangiography		X[4,5]				
Echocardiogram[6]	X		X		X[7]	
TIMI Flow Grade Score		X[5]				
TIMI Thrombus Grade		X[5]				
Myocardial Blush Grade		X[5]				
Target Lesion Characteristics		X				
Procedure		X				
Adjunctive Procedures		X				
Subject Status					X	X
Cardiac Concomitant Medications	X	X	X	X	X	X
Events of Interest/Serious Adverse Events[8]		X	X	X	X	X

[1] Patients who have had an index procedure with the Indigo® Aspiration System and the CAT RX Aspiration Catheter used frontline (per IFU) as an adjunctive to SOC PCI, prior to informed consent, may be consented up to 2 days post procedure but prior to discharge
[2] TIMI Thrombus Grade 4 or 5 must be confirmed after crossing the target lesion with the guidewire
[3] Only required for women of child bearing potential, urine or serum accepted
[4] Coronary angiography images must be uploaded to image management system for core lab review
[5] Assessment will be required at multiple timepoints within the visit
[6] Data collected if performed as SOC
[7] Follow-up echocardiogram can occur any time within the 30 – 180 day visit follow up windows, per Institutional SOC
[8] Adverse events related to primary and secondary safety endpoints, all device or procedure related events, all Serious Adverse Events (SAE), and all Unanticipated Adverse Device Effects (UADE) will be collected starting at Procedure (Day 0) through final follow-up visit
[9] Assessment to be completed if visit is conducted in person

7. Investigator Responsibilities

7.1 Institutional Review Board

Prior to enrolling patients into the study, the Investigator will ensure that proper Institutional Review Board (IRB) approval is obtained in accordance with applicable local state and federal laws and regulations. The IRB shall approve all study documents as appropriate, including but not limited to the final protocol, amendments to the protocol, subject facing material and the informed consent form.

The Investigator will report to the Sponsor or Sponsor's designee immediately if the approval to conduct the investigation is withdrawn by the IRB. 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 completed informed consent is obtained in accordance with Section 6.5 of this protocol and according to country and local requirements prior to conducting any study-related assessments and prior to enrollment of patients in the study.

7.3 Adherence to Protocol/Amendments and Applicable Law

The Investigator is responsible for overseeing, ensuring that the study is conducted, and completing the study according to this protocol and in accordance with the relevant aspects of I.S. EN ISO 14155:2011, Declaration of Helsinki, along with any conditions imposed by the reviewing IRB and all other applicable regulations. The Investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study.

It is the Investigator's responsibility to ensure that the Institution's staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures, and will respect study confidentiality.

7.4 Case Report Form Completion

The Investigator and study staff shall complete the case report forms (CRFs) associated with this study. Subject numbers shall be used to identify individual participants in this study. The CRFs should be a complete and accurate record of subject data collected during the study according to relevant aspects of I.S. EN 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 investigational site(s). Investigators are responsible for completion and timely submission of data to Penumbra, Inc. Every reasonable effort should be made to complete data entry within 5 (five) business days of data collection.

7.5 Image Upload

Coronary cineangiography will be uploaded to an image management system for Core Lab review. Echocardiogram images and additional images associated with adverse events may

be uploaded, if collected as SOC. Required study images should be uploaded within 5 (five) business days. Instructions for image collection and upload can be found in the Imaging Manual.

Study staff shall ensure that no images contain any personally identifying information about the subject or study site (e.g. Physician name, Institution name, patient name, etc.).

7.6 Reporting

The Investigator will be responsible for reporting the following:

7.6.1 Adverse Events

Adverse events (AE) must be recorded by the Investigator on the CRFs and must be monitored during the study. Primary and secondary safety endpoint events, all device or procedure related events, all Serious Adverse Events (SAE), and all Unanticipated Adverse Device Effects (UADE) will be collected starting at Procedure (Day 0) through final follow-up visit. Minimum requirements of data to be recorded are: event term, event start date, seriousness, action taken, outcome and device-relatedness.

In order to ensure prompt reporting of AEs, all reportable AEs (as well as all related study data) are required to be entered into the EDC in a timely manner. Any suspected UADEs should be reported immediately by calling the Sponsor. All device related SAEs should be reported in the EDC within 72 hours of the site staff first being made aware of the occurrence of the SAE. If the EDC is unavailable, an email can be sent to Penumbra.

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

For the purpose 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 course of the study.

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 a 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 a SAE.

Detailed form and narrative reports will be composed for primary and secondary safety endpoints (at a minimum).

7.6.2 Analysis of Adverse Events

A Medical Monitor will review events related to primary and secondary safety endpoints as they are reported.

In addition to the reporting requirements noted above, pre-defined AE/SAEs as listed in the Independent Medical Reviewer (IMR) Charter will be evaluated by the IMR. Redacted source documents will be collected for events requiring adjudication and for other events where the medical monitor deem necessary.

7.6.3 Relationship to the Study Device

General adverse event and serious adverse event definitions can be found in Section 16 – Appendix I. A (S)AE 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 study device. The following definitions will be used to assess the relationship of the adverse event to the use of study device.

- **Definite:** The temporal sequence is relevant and the event abates upon study device application completion/removal, or reappearance of the event on repeat study device application.

- **Probable:** The temporal sequence is relevant or the AE abates upon study device application completion/removal or the AE cannot be reasonably explained by the subject's condition or comorbidities. The AE is related or most likely associated with the study device.

- **Possible:** The temporal sequence between the study device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the subject's condition. There is a possibility of a relationship between the AE and the study device.

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

Similar grading will be used for assessing the relationship to index procedure/index coronary vessel occlusion.

7.6.4 Device Deficiency

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the study device shall be documented and reported through the standard commercial process and within EDC. Investigators must report all possible device observations associated with the device during the study. This includes unexpected outcomes or device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken; b) intervention has not be made; or, c) if circumstances had been less fortunate.

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 subject 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.

7.6.5 Protocol Deviation(s)

Deviations defined in this protocol will be clearly documented, if identified during monitoring or through other means. For this study, deviations need to be reported for the following categories:

- Inclusion/exclusion criteria deviation(s)
- Major Informed Consent deviation(s)

7.7 Records Retention

The Investigator shall maintain the records associated with this study for a period of at least two years after either the date on which the study is completed or the date that the records are no longer required for supporting a premarket approval/notification submission, whichever is later. An eTMF will be used as the master repository for all site and Sponsor regulatory documents. These records include the following:

- Correspondence with the Sponsor or designee, the Medical Monitor, and other Investigators
- Subject source records, including but not limited to: Informed Consent Forms, copies of all completed CRFs, and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.)
- All versions of study protocol with dates and details of reasons for any deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects
- Instructions For Use
- Reports of any serious adverse event and/or serious adverse device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank, informed consent form
- All approval/acknowledgment letters from the IRB for all versions of the study protocol, ICF and other documents
- Clinical Trial Agreement(s)
- Signed and dated curriculum vitae for all study personnel
- Medical licenses for the Principal Investigator and all participating Sub-Investigators
- Financial disclosure for the Principal Investigator and all participating Sub-Investigators

- All required regulatory documents such as, but not limited to, Delegation of Authority and training logs
- Signed Protocol Signature Page(s)

8. Sponsor Responsibilities

8.1 Training

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

8.2 Investigator List

The Sponsor shall keep a list of the names and addresses of the clinical Investigators for the study.

8.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the Investigational Sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other Investigational Sites as necessary.

8.4 Data Monitoring

Penumbra is responsible for ensuring that the study is conducted according to relevant aspects of appropriate regulations (21 CFR 812, I.S. EN ISO 14155). A Penumbra employee or designate will conduct the following site visits:

8.4.1 Site Qualification Visit

Conducted to ensure the Investigational Site has the appropriate staff, facilities, and expertise to participate in the study. Site Qualification can be waived under certain circumstances.

8.4.2 Site Initiation Visit

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

8.4.3 Interim Monitoring Visit(s)

Conducted as needed to ensure the investigational site is operating in compliance with this protocol, continues to have the appropriate staff and facilities, and is correctly completing the CRFs.

To ensure that Investigators and their staff understand and accept their defined responsibilities the Sponsor will maintain regular correspondence and perform periodic site visits during the course of the study where they will verify the continued acceptability of the facilities, compliance with the investigational 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 medical records for all enrolled and screen failed subjects will be made available to the Sponsor for review and collection.

8.4.4 Site Close Out Visit

Conducted to ensure all study and regulatory-related activities have been completed prior to site closure.

8.5 Data Management

CRFs will be used at all investigational sites. All study data will be entered into commercially available web-based EDC. Data entry will be performed by the study site personnel. The EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel will 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 may be used to identify data discrepancies or inconsistencies. The study site may be queried for clarification concerning CRF discrepancies or inconsistencies identified. 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 complete data entry (e.g. CRF/EDC). 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 CRFs for completeness and accuracy and provide his/her electronic signature and date to CRFs as evidence thereof. Any data items that have been changed will require reapplication of the electronic signature.

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.

All CRFs and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including but not limited to laboratory results, reports, supporting medical records, and Informed Consent Forms. 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 study will be performed in accordance with the applicable aspects of I.S. EN ISO 14155:2011, recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), ICH and US FDA GCP guidelines.

It is the responsibility of the Investigator to obtain approval of the study protocol from the Institutional Review Board (IRB) and to keep the IRB informed of any serious adverse event, serious adverse device effects, and amendments to the protocol. All correspondence with the IRB should be filed by the Investigator and copies sent to the Sponsor or its designee.

9.2 Informed Consent

The Investigator is responsible for ensuring that a completed informed consent is obtained in accordance with Section 6.5 of this protocol, as delegated by the site-specific Delegation of Authority, and according to country and local requirements.

9.3 Subject Data Protection

Each subject will be assigned a unique subject identification number at the time of enrollment. This subject identification number will be retained throughout the study. Study sites will keep a log that notes the subject's name and corresponding subject identification number. All CRFs will be tracked, evaluated, and stored using only the subject ID number. No personal identifying information will be included on the CRFs.

The informed consent form will notify subjects that study monitors, Sponsor's representatives, auditors, 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 General Statistical Considerations

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, inter-quartile range, minimum

and maximum for continuous variables and counts and percentages for discrete variables. Analyses will be conducted using SAS (SAS Institute, Cary, NC). The specific details of the planned analyses are described completely in the statistical analysis plan.

10.2 Sample Size Estimation for the Primary Outcome

The sample size calculations assume that 6.1% (22/360) of the study subjects experience a primary safety event as compared to 6.1% (272/4454) of the TOTAL trial high thrombus burden subset.[29] Based on a binomial analysis with a non-inferiority margin of 10%, a study of 360 Indigo System subjects will have 99% power with a one-sided alpha of 0.025. The sample size was adjusted to 400 subjects to account for up to 10% attrition rate.

10.3 Control of Systematic Error and Bias

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

10.4 Missing Data and Imputation Methods

Every effort will be made to keep all missing data, particularly the 30-day outcomes, to a minimum. Some data may be missing, mainly due to lost-to-follow-up (LTFU) subjects. The primary analysis will be data as observed. Sensitivity analysis will be performed.

10.5 Definition of Populations

10.5.1 Screened

Screened patients are all patients considered for participation in the study, whether or not they sign informed consent.

10.5.2 Screen Failure

Screen failure patient are all patients considered for participation in the study, who failed to meet inclusion criteria or met exclusion criteria. Patients can be screen failed based on general or imaging criteria. These patients may or may not have signed an informed consent form.

10.5.3 Enrolled

An eligible patient is considered enrolled when the Indigo CAT RX Aspiration Catheter enters the body and informed consent is obtained (whichever is later).

10.5.4 Completed

Completed subjects are all subjects who were enrolled and completed the study follow-up or were known to have died prior to the follow-up timepoint are

considered completed. The completed subject metric will be provided for 180-day follow-up.

10.5.5 Early Termination

Early termination subjects are all subjects who were enrolled but did not complete follow-up and were not known to have died. The early termination subject metric will be provided for 180-day follow-up.

10.6 Definition of Analysis Populations

10.6.1 Intent to Treat Sample

As the primary analysis, all performance and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the ITT sample includes all subjects who are enrolled. This population is the primary analysis population.

10.7 Interim Analysis

No interim analyses are planned for the purpose of terminating the study for a positive result. No adjustments will be made to the confidence bounds for the final analysis.

10.8 Statistical Analysis of Primary Endpoint

The primary endpoint is the 30-day composite endpoint. The primary effectiveness analysis will be the difference between the study group and the historical control rate of 6% observed in the TOTAL trial high thrombus burden subset.

The null hypothesis is that the difference between the composite endpoint rate and the historical control at 30 days is greater than or equal to 10%. The alternative hypothesis is the difference at 30 days is less than 10%. Formally, the null and alternative hypotheses to be tested are as follows:

$$H_0: \ P_{study} - 0.06 \geq 0.10$$

$$H_A: \ P_{study} - 0.06 < 0.10$$

Where P_{study} is the proportion of patient experiencing a composite endpoint event at 30-day follow-up visit.

Statistical analysis of the primary endpoint will be conducted using a binomial comparison to test the one-sided null hypothesis that the difference in proportions is less than or equal to 0.10.

The primary safety endpoint is met if the upper limit of the 95% confidence interval of the composite primary endpoint rate is less than 16% at a one-sided alpha of 0.025. The primary analysis will be unadjusted.

10.9 Secondary Statistical Analysis

The secondary performance and safety endpoints will be assessed via proportions based on the endpoint criteria and 95% confidence intervals will be presented. The Imaging Core Lab data supersede the investigator-reported data in all analyses of imaging-based endpoints. Survival estimates will also be utilized to evaluate the time-to-event using Kaplan-Meier methodology for events through 180 days. With the date of procedure set at day 0, any event occurring on or before day 180 will be included.

10.10 Analysis of Adverse Events

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

10.11 Baseline Characteristics

Baseline data including, but not limited to, demographics, clinical characteristics, and angiographic characteristics will be summarized using descriptive statistics.

10.12 Pooling Across Centers

Analyses will be presented by treatment group using data pooled across sites. Adjusted analysis using key baseline variables and the study site will be used to assess any potential site effects. This analysis will be performed on the intent-to-treat population.

10.13 Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the study, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the study is not allowed until the aggregate study results have been published, unless there is written consent from the Sponsor.

11. Study Committees and Core Labs

11.2 Independent Medical Reviewer

The Independent Medical Reviewer (IMR) will be an independent medical doctor(s) who does not participate in the study. There may be more than one IMR. The IMR is responsible for assisting in the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study.

The IMR will review and adjudicate appropriate clinical events, mainly related to the device and study endpoints. A web-based electronic database will be provided to the IMR

for case review and adjudication. The designated Penumbra 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 IMR are specified in the IMR Charter.

11.3 Imaging Core Lab

The Imaging Core Lab is composed of independent medical doctor(s) who are not participants in the study. The Imaging Core Lab is responsible for assisting in the development of specific criteria used for the categorization of clinical endpoints in the study. A web-based electronic database will be provided for the Imaging Core Lab to review and adjudicate images. Additional details related to the core lab are specified in the Imaging Core Lab Charter.

12. Study Administration

12.1 Stopping the Study Based on Interim Safety Data

The IMR will receive periodic safety reports of all AEs and SAEs. This study can be temporarily suspended or stopped to evaluate any negative safety trends.

12.2 Clinical Study Termination/Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- **Voluntary withdrawal of consent:** meaning that a subject voluntarily chooses not to participate further in the study. All data collected up to the withdrawal of consent will be maintained in the study database. Withdrawn subjects will not have any additional follow-up and will not be replaced.

- **Lost to follow-up:** a subject 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 subject's last known address. These efforts to obtain follow-up will be recorded in the subject's study files.

- **Withdrawn by Investigator:** Subjects may be withdrawn at the Investigator's discretion if within their best interest. A subject's participation in the clinical study will be terminated if the Investigator believes that this is in the subject's best medical interest or if the subject no longer complies with the clinical study requirements.

The sponsor may temporarily suspend or prematurely terminate the study at any time for the following reasons:

- Suspicion of risk to subjects

- If no positive IRB decision is obtained or if the judgement of the IRB is revoked
- If the applicable regulatory body has made an irrevocable objection
- If it transpires that continuation of study cannot serve any scientific purpose, and this is confirmed by the IRB
- Business reasons

The Sponsor will document reasons for study suspension or premature termination and notify the PIs. The Sponsor will ensure that the IRB and regulatory authorities are notified in a timely manner.

The Sponsor will continue to provide resources to fulfill the obligations from the study protocol and existing agreements for following up the subjects enrolled in the study.

The Principal Investigators will promptly inform the enrolled subjects at his/her site, if appropriate.

If the Sponsor temporarily suspends the study and wishes to resume it, the Sponsor will inform the PIs, IRB, and (if appropriate) regulatory authorities. The Sponsor will provide a rationale for resuming the study. IRB must provide written approval before the study is resumed.

12.3 Missing Visits

Every effort should be made to bring subject in to scheduled follow-up visits, within the visit window specified in the protocol. Any study subject 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 met.

12.4 Protocol Adherence and Amendments

Prior to beginning the study, the Principal Investigator must sign the protocol signature page documenting his/her agreement to conduct the study in accordance with this protocol. An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Deviations from the protocol as defined in Section 7.6.5 must be documented and reported to Penumbra as soon as possible, and to the IRB per local guidelines and government regulations.

12.5 Study Registration

The study will be registered in a publicly accessible study database (e.g., clinicaltrials.gov) prior to study initiation.

13. Publication of Information

All information and data generated in association with this study 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 study and for no other purpose without written consent from the Sponsor.

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 test 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.

14. Contact Information

The address of Penumbra Incorporated is:

Penumbra, Inc.
One Penumbra Place
Alameda, CA 94502
Tel. (510) 748-3200
Fax (510) 814-8305

Key contacts for the study include:

[redacted]	Clinical Study Manager	[redacted]
[redacted]	Director of Medical Affairs	[redacted]

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16. Appendix I – Definitions

16.1 Adverse Event Definitions

Adverse Event (AE): Any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the study 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.

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device.

Serious Adverse Event (SAE):

A SAE is an adverse event that:

- Led to death
- Led to a serious deterioration in the health of the patient that:
  - Resulted in life-threatening illness or injury
  - Resulted in chronic disease
  - Resulted in permanent impairment of a body structure or a body function
  - Required in-patient hospitalization or prolongation of existing hospitalization
  - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect
- **Death**
  Report if death was the outcome of an adverse event. The primary cause of death should be reported as the adverse event term.
- **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.
- **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).
- **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.

- **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.
- **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 bronchospasm (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.

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 investigational plan, investigator brochure, or 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.

16.2 Events of Interest

Definitions are adapted from the TOTAL study, the Fourth Universal Definition of Myocardial Infarction (2018), and the Academic Research Consortium's Clinical Endpoints Standardized Definitions.[14,30,31]

Cardiogenic shock: defined as Systolic Blood Pressure less than 90 mmHg or MAP <60 mmHg not responsive to fluid resuscitation and or heart rate correction for at least 1 hour or need for vasopressor/inotropic therapy to maintain SBP>90 mm Hg or MAP >60 mmHg for at least 1 hour and, believed to be secondary to cardiac dysfunction and associated with at least 1 of the following: 1) signs of pulmonary edema, 2) signs of hypoperfusion (cool clammy skin, oliguria, or altered sensorium), or 3) CI <2.2 L/min.

Death: will be classified as cardiovascular or non-cardiovascular. All deaths with a clear cardiovascular or unknown cause will be classified as cardiovascular. Only deaths due to a documented non-cardiovascular cause (e.g., cancer) will be classified as non-cardiovascular.

Major bleeding: fatal or leading to a drop in hemoglobin of ≥5 g/dl, or significant hypotension with the need for inotropes, or requiring surgery (other than vascular site repair), or symptomatic intracranial hemorrhage (ICH)), or requiring transfusion of two or three units of red blood cells or equivalent whole blood.

Myocardial Infarction:

a. **Non ST-Elevation Myocardial Infarction (NSTEMI):**
Symptoms of myocardial ischemia OR new ischemic ECG Changes OR development of pathological Q waves OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

AND

Rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit

AND

Without ECG changes indicating STEMI.

b. Recurrent MI:
Diagnosis of MI that occurs after the initial MI. For recurrent MI within 48 hours of PCI or CABG, specific diagnostic criteria are listed below.

c. ST-Elevation Myocardial Infarction (STEMI):
Symptoms of myocardial ischemia OR new ischemic ECG Changes OR development of pathological Q waves OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

AND

Rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit

AND

Definite ECG changes indicating STEMI, defined as ST elevation of greater than 0.1 mV in two contiguous limb leads or 0.2 mV in two contiguous precordial leads, or presumed new left bundle branch block.

d. MI Associated with Percutaneous Coronary Intervention (≤ 48 hours after index procedure)
Elevation of cardiac troponin values greater than five times the 99th percentile upper reference limit in patients with normal baseline values. In patients with elevated pre-procedural cardiac troponins in whom the cardiac troponin levels are stable (≤ 20% variation) or falling, the post procedure cardiac troponin must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile upper reference limit.

In addition, one of the following elements is required:
New ischemic ECG changes OR development of new pathological Q waves OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology OR angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization

e. MI Associated with Coronary Artery Bypass Grafting (≤ 48 hours after the index procedure)
Elevation of cardiac troponin values greater than ten times the 99th percentile upper reference limit in patients with normal baseline values. In patients with elevated pre-procedural cardiac troponins in whom the cardiac troponin levels are stable (≤ 20% variation) or falling, the post procedure cardiac troponin must rise by >20%. However, the absolute post-procedural value must still be at least ten times the 99th percentile upper reference limit.

In addition, one of the following elements is required:
Development of new pathological Q waves OR angiographic documented new graft occlusion or new native coronary artery occlusion OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

New or worsening NYHA Class IV heart failure: defined heart failure symptoms at rest and a physician decision to treat HF with IV diuretic, inotropic agent or vasodilator plus at least one of the following: 1) presence of pulmonary edema or pulmonary vascular congestion on chest radiograph thought to be due to HF; 2) rales reaching above the lower 1/3 of the lung fields thought to be due to HF; or 3) PCWP or LVEDP ≥ 18 mm Hg.

No reflow: defined as an acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm or high-grade residual stenosis at the original target lesion.

Recurrent Ischemia: Recurrent chest pain (with documented ST depression > 1mm in at least 2 contiguous leads on transient ST elevation) lasting more than 5 minutes and leading to additional intervention such as thrombolytic therapy for threatened MI, cardiac catheterization leading to repeat intervention, or insertion of intra-aortic balloon pump or urgent revascularization (UR) by midnight of next calendar day following the initial symptoms.

Stent thrombosis: (Categorized by Timing & Level of Certainty)

a. Timing
i. Acute Stent Thrombosis: 0 to 24 hours after stent implantation
ii. Subacute Stent Thrombosis: > 24 hours to 30 days after stent implantation
iii. Late Stent Thrombosis: >30 days to 1 year after stent implantation

iv. Very Late Stent Thrombosis: >1 year after stent implantation

b. Level of Certainty

i. Definite Stent Thrombosis:

Angiographic confirmation of stent thrombosis: (incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis).

The presence of an intracoronary thrombus that originates in the stent or in the segment 5mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

1. Acute onset of ischemic symptoms at rest
2. New ischemic ECG changes that suggest acute ischemia
3. Typical rise and fall in cardiac biomarkers
4. Nonocclusive thrombus:

   Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
5. Occlusive thrombus:

   TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

OR

Pathological confirmation of stent thrombosis: evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

ii. Probable Stent Thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

1. Any unexplained death within the first 30 days
2. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

iii. Possible Stent Thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Stroke: Any stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours

Target Vessel Revascularization (TVR): defined as any revascularization procedure (PCI or CABG) involving the vessel treated during the index PCI procedure for MI.

17. Appendix II - TIMI Thrombus Grade[32]

TIMI 0	No cineangiographic characteristics of thrombus present
TIMI 1	Possible thrombus is present, angiography demonstrates characteristics such as reduced contrast density, haziness, irregular lesion contour, or smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus
TIMI 2	Definite thrombus, with largest dimension $\leq$ ½ vessel diameter
TIMI 3	Definite thrombus, with largest dimension of thrombus > ½ but < 2 vessel diameters
TIMI 4	Definite thrombus, with largest dimension of thrombus $\geq$ 2 vessel diameters
TIMI 5	Total occlusion

18. Appendix III - TIMI Flow Grade[33]

Grade 0 (no perfusion)	There is no antegrade flow beyond the point of occlusion.
Grade 1 (penetration without perfusion)	The contrast material passes beyond the area of obstruction but "hang up" and fail to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.
Grade 2 (partial perfusion)	The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. The rate of entry of the contrast material into the vessel distal to the obstruction or the rate of clearance from the distal bed are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
Grade 3 (complete perfusion)	Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

19. Appendix IV – Myocardial Blush Grade[34]

0	No myocardial blush or contrast density
1	Minimal myocardial blush or contrast density
2	Moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery
3	Normal myocardial blush or contrast density comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery

20. Appendix V - NYHA Classification, Stages of Heart Failure[35]

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 heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

21. Appendix VI - Killip Classification[36]

Class I	No evidence of heart failure
Class II	Mild heart failure with rales involving one third or less of the posterior lung fields and systolic blood pressure of 90mm Hg or higher
Class III	Pulmonary edema with rales involving more than one third of the posterior lung fields and systolic blood pressure of 90 mm Hg or more
Class IV	Cardiogenic shock with any rales and systolic blood pressure of less than 90 mm Hg

22. Appendix VII – Canadian Cardiovascular Society Classification[37]

Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing 1 flight of stairs in normal conditions and at normal pace.
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

23. Acronyms

ACS	Acute coronary Syndrome
ADE	Adverse Device Effect
AE	Adverse Event
CABG	Coronary Artery Bypass Graft
CFR	Code of Federal Regulations
CHD	Coronary Heart Disease
CI	Cardiac Index
CK	Creatine Kinase
CK-MB	Creatine Kinase-MB iso-enzyme
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
ECG/EKG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ID	Inner Diameter
IFU	Instructions for Use
IMR	Independent Medical Reviewer
IRB	Institution Review Board
ISO	International Organization for Standardization
LAR	Legally Authorized Representative
LTFU	Lost to Follow Up
MACE	Major Adverse Cardiac Events
MBG	Myocardial Blush Grade
MI	Myocardial Infarction
NSTEMI	Non-ST Elevation Myocardial Infarction
NYHA	New York Heart Association
OD	Outer Diameter
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PTFE	Polytetrafluoroethylene
RHV	Rotating Hemostasis Valve
SAE	Serious Adverse Event
SC	Steering Committee
SOC	Standard of Care
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
TMF	Trial Master File
TVR	Target Vessel Revascularization
UA	Unstable Angina
ULN	Upper Limit of Normal
US	United States

STATISTICAL ANALYSIS PLAN

CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion

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Protocol CLP-15298

Contents

1 Overview

The objective of the CHEETAH study is to demonstrate the safety and performance of the Indigo® Aspiration System using the CAT RX Aspiration Catheter in a population presenting with acute high thrombus burden coronary vessel occlusion who are referred for Percutaneous Coronary Intervention (PCI). Patients will be enrolled who meet the inclusion and none of the exclusion criteria, who (or Legally Authorized Representative, LAR) consent to participate, and in whom the study device has been inserted.

The study allows for enrollment of up to 400 subjects at up to 25 sites in the United States. Each site will be limited to a maximum enrollment of approximately 80 patients (~20% of total enrollment).

The primary endpoint of the study is the composite of cardiovascular (CV) death, recurrent Myocardial Infarction (MI), cardiogenic shock, or new or worsening New York Heart Association (NYHA) Class IV heart failure, within 30 days. Secondary endpoints of the study are as following:

Performance:

1. Final TIMI Flow Grade
2. Final TIMI Thrombus Grade
3. Myocardial Blush Grade
4. Distal Embolization Rate
5. Stent thrombosis at 180 days

Safety:

1. Stroke within 30 days
2. Major bleeding within 30 days
3. All-cause mortality within 180 days
4. Cardiovascular (CV) death within 180 days
5. Recurrent MI within 180 days
6. Cardiogenic shock within 180 days
7. NYHA Class IV heart failure within 180 days
8. Incidence of device-related SAE(s)

This Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions. The SAP will be approved prior to database lock.

2 Sample Size for the Primary Outcome

The sample size calculation assumes that 6.1% (22/360) of the study subjects experience a primary safety event as compared to 6.1% (272/4454) of the TOTAL trial high thrombus burden subset. Based on a binomial analysis with a non-inferiority margin of 10%, a study of 360 Indigo System subjects will have 99% power with a one-sided alpha of 0.025. The sample size was adjusted to 400 subjects to account for up to 10% attrition rate.

3 Interim Analysis

No interim analyses are planned for the purpose of terminating the study for a positive result. No adjustments will be made to the confidence bounds for the final analysis. Interim analysis may be performed for purpose of regulatory submissions and/or publication of study results.

4 General Statistical Considerations

Baseline data including, but not limited to demographics, clinical characteristics, and angiographic characteristics will be summarized using descriptive statistics.

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, which includes the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables and counts and percentages for discrete variables. Analyses will be conducted using SAS (SAS Institute, Cary, NC).

Results collected at multiple visits will be summarized at each visit for which they are collected as described under Schedule of Assessments Table 2 in CHEETAH study protocol version at the time of database lock. Summaries for all measures will include all observed data for each visit. See Section 10 in SAP for lost to follow-up and missing data.

5 Definition of Populations

The number of subjects for each of the following categories will be summarized for final analysis:

- **Screened:**

  Screened patients are all patients considered for participation in the study, whether or not they sign informed consent.

- **Screen Failure:**

  Screen failure patients are all patients considered for participation in the study, who failed to meet inclusion criteria or met exclusion criteria. These patients may or may not have signed an informed consent form. Screen failure patients with their reasons for screen failure will be summarized.

- **Enrolled:**

  Enrolled subjects are all subjects in which the Indigo CAT RX Aspiration Catheter enters the body and informed consent is obtained (whichever is later).

- **Completed:**

  Completed subjects are all subjects who were enrolled and completed the study follow-up or were known to have died prior to the final follow-up time point. The completed subject metric will be provided for 180-day follow-up.

- **Early Termination:**

  Early termination subjects are all subjects who were enrolled but did not complete follow-up and were not known to have died. The early termination subject metric will be provided for 180-day follow-up.

6 Definition of Analysis Populations

- **Intent to Treat Sample**:

  As the primary analysis, all performance and safety outcome measures will be analyzed under the Intent-To-Treat (ITT) principle. Under this principle, the ITT sample includes all subjects who are enrolled. This population is the primary analysis population.

- **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 ITT population who do not have significant protocol deviations (e.g. eligibility violation) according to the CHEETAH study protocol version at the time of database lock.

7 Statistical Analysis

7.1 Primary Endpoint Analysis

The primary endpoint is the composite of cardiovascular (CV) death, recurrent Myocardial Infarction (MI), cardiogenic shock, or new or worsening New York Heart Association (NYHA) Class IV heart failure within 30 days. The primary safety analysis will be the difference between the composite endpoint rate and the historical control at 30 days rate of 6% observed in TOTAL trial high thrombus burden subset.

The null hypothesis is that the difference between the composite endpoint rate and the historical control at 30 days is greater than or equal to 10%. The alternative hypothesis is the difference at 30 days is less than 10%. Formally, the null and alternative hypotheses to be tested are as follows:

$$H_0: P_{study} - 0.06 \geq 0.10$$

$$H_A: P_{study} - 0.06 < 0.10$$

Where P_{study} is the proportion of subjects experiencing a composite endpoint event at the 30-day follow-up timepoint.

Statistical analysis of the primary endpoint will be conducted using a binomial comparison to test the one-sided null hypothesis that the difference in proportions is less than or equal to 0.10.

The primary safety endpoint is met if the upper limit of the 95% confidence interval of the composite primary endpoint rate is less than 16% at a one-sided alpha of 0.025. The primary analysis will be unadjusted.

7.2 Secondary Endpoint Analysis

The secondary performance and safety endpoints (listed in Section 1) will be assessed via proportions based on the endpoint criteria and 95% confidence intervals will be presented. The Imaging Core Lab data supersede the Investigator-reported data in all analyses of imaging-based endpoints (Final TIMI Grade Flow, Final TIMI Thrombus Grade, Myocardial Blush Grade, Distal Embolization Rate). The IMR data will supersede the Investigator-reported data in all analyses of adverse events. See section 7.3 for analysis of adverse events.

Survival estimate will also be utilized for the following secondary safety endpoints to evaluate the time-to-event using Kaplan-Meier methodology: All-cause mortality within 180 days,

Cardiovascular (CV) death within 180 days, Recurrent MI within 180 days, Cardiogenic shock within 180 days, NYHA Class IV heart failure within 180 days. With the date of procedure set at day 0, any event occurring on or before day 180 will be included.

7.3 Analysis of Adverse Events

All adverse events will be summarized by showing the number and percent of subjects which report the event. Events will also be reported by relationship to the procedure or device. Adverse events judged as probably or definitely related to the Indigo® Aspiration System will be analyzed as device-related; events judged as probably or definitely related to the Index Procedure will be analyzed as procedure-related. The IMR data will supersede the Investigator-reported data in all analyses of adverse events.

All serious and non-serious adverse events will be coded using the MedDRA dictionary. The number and percentage of subjects with AEs and SAEs, and all events leading to death (cause of death) will be summarized by body system and preferred term. Each subject will be counted only once within a category. Additionally, non-serious AE will be summarized for events that are reported by at least one (1) percent of the subjects.

8 Subgroup Analysis

To evaluate the impact of baseline condition on outcomes, subgroup analyses will be performed for the primary endpoints and secondary safety variables (listed in Section 1). The subgroups below will be used for these analyses:

- Age: < 65 years, ≥ 65 years
- Gender: Male, Female
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Unknown or Not Reported
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown or Not Reported
- Baseline NYHA: Class I and II, Class III and IV
- Index event diagnosis: STEMI, NSTEMI

Descriptive statistics will be presented for each subgroup. The subgroup analysis will be conducted using Fisher's exact test, Wilcoxon rank sum, Kruskal-Wallis test for univariate analyses and logistic or linear regression for multivariate analyses. These analyses will be

performed on both the Intent-to-Treat and the Per Protocol populations. Subgroup comparisons will be considered secondary analyses and will not be adjusted.

9 Pooling Across Centers

To assess the validity of data pooling, heterogeneity across sites will be examined using relevant methods, such as random effect models (continuous variables), contingency tables or binary logistic regression (categorical variables), or Cox proportional hazards (event time variables). Any sites containing fewer than 10 subjects will be aggregated in this analysis.

Monitoring efforts will be allocated to assess whether sites are adhering to the protocol in a standardized manner to minimize the presence of heterogeneity across study centers.

10 Lost to Follow-Up and Missing Data

Every effort will be made to keep all missing data, particularly the 30-day outcomes, to a minimum. Some data may be missing, mainly due to lost-to-follow-up (LTFU) subjects. Subject discontinuation rates will be tabulated by the reason for early termination.

The primary analysis will be data as observed. Sensitivity analyses of the primary safety endpoint will be performed for subjects with missing primary safety endpoint at 30-day follow-up as follows:

- The subjects will be excluded from analysis
- Their primary safety outcome will be imputed using the worst clinical scenario assuming the subject experienced a primary safety event
- Their primary safety outcome will be imputed using the best clinical scenario assuming the subject did not experience a primary safety event

11 Reviewers and Core Lab

11.1 Independent Medical Reviewer (IMR)

The Independent Medical Reviewer will review and adjudicate safety events based on criteria established in the IMR charter.

11.2 Imaging Core Lab

The independent imaging core lab will review and score images from the periprocedural angiograms to determine at minimum: final TIMI flow grade, final TIMI thrombus grade, myocardial blush grade, and occurrence of distal embolization. Additional details related to the core lab are specified in the Imaging Core Lab Charter.

12 Changes to Planned Analyses

All changes to the statistical analysis plan (SAP) will be documented in a revised SAP or in the clinical trial report.

13 References

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Penumbra Inc. *CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion,* Charter for Independent Medical Review (IMR)

Penumbra Inc. *CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion,* CLP-15298 Protocol

Penumbra Inc. *CHEETAH: A Prospective, Multicenter Study to Evaluate the Safety and Performance of the CAT RX Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion,* Imaging Core Lab Charter

14 Revision History

Version	Prepared By	Description of Changes
1.0	[redacted]	Initial Release
2.0	[redacted]	• Section 1 Overview: included "Recurrent MI within 180 days" • Section 7.2 Secondary Endpoint Analysis: specified the secondary safety endpoints through 180 days with KM estimates • Section 7.3 Analysis of Adverse Events: included definition of procedure and device related events.
3.0	[redacted]	• Section 7.3 Analysis of Adverse Events: included definition of procedure and device related events – inadvertently not reflected in version 2.0
4.0	[redacted]	• Section 2: reordered text to match the protocol verbatim • Section 7.3: added MedDRA analysis for all cause of death, additional summary of non-serious AE • Section 8: added diagnosis subgroup analysis