FlowTriever Pulmonary Embolectomy Clinical Study (**FLARE**)

CLINICAL PROTOCOL

Protocol: **15-001**
Version: **2.0**
Version Date: **30 June 2016**

National Principal Investigator:
Kenneth Rosenfield, MD, MHCDS
Massachusetts General Hospital

National Principal Investigator:
Victor F. Tapson, MD, FCCP, FRCP
Cedars-Sinai Medical Center

Sponsor Contact:
Natasha Behrmann
Director, Clinical Research
Inari Medical, Inc.
9272 Jeronimo Road, Suite 124
Irvine, CA 92618
Direct: 949.600.8433 x118

Core Lab:
Syntactx
7 World Trade Center
250 Greenwich Street
46th Floor
New York, NY 10007
Phone: 212.266.0135

Sponsor Signature:

_____

Natasha Behrmann
Director, Clinical Research

Date: 30 June 2016

CLINICAL PROTOCOL INVESTIGATOR AGREEMENT

I have read the Clinical Protocol and agree to adhere to the requirements.

I agree to conduct the FLARE study ("Study") in accordance with the current protocol and will only make changes in the protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of Subjects.

I agree to personally conduct or supervise the herein described Study and ensure all appropriate participating Investigators and research staff are appropriately informed and/or trained regarding the conduct of the Study prior to participating in any Study-related activities.

I will ensure that the requirements relating to obtaining Informed Consent in 21 CFR Part 50, ICH E6 and Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the Study are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.145 and ICH E6.

I will ensure that the IRB complies with the requirements of ICH E6 and 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the Study. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human Subjects or others. Additionally, I will not make any changes in research without IRB approval, except where necessary to eliminate apparent immediate hazards to human Subjects.

I agree to comply with all other requirements regarding the obligations of Clinical Investigators and all other pertinent requirements in ICH E6 and 21 CFR Part 812, and/or the laws and regulatory requirements of the state in which the site resides.

_____ Date: _____

Principal Investigator Signature

_____

Principal Investigator Printed Name

PROTOCOL SYNOPSIS

SPONSOR:

Inari Medical, Inc.
9272 Jeronimo Road, Suite 124
Irvine, CA 92618
949.600.8433

PROTOCOL TITLE:
FlowTriever Pulmonary Embolectomy Clinical Study

PROTOCOL NUMBER / NAME: 15-001 / FLARE Study

PROTOCOL VERSION / DATE: 2.0 / 30 June 2016

OBJECTIVE:

Evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli from the pulmonary arteries in the treatment of acute pulmonary embolism (PE).

STUDY DESIGN: A prospective, single-arm, controlled, multicenter study of the FlowTriever System.

DEVICE DESCRIPTION AND STUDY PROCEDURE:

The FlowTriever Retrieval/Aspiration System ("FlowTriever System") is a catheter-based mechanical thrombectomy device for percutaneous endovascular retrieval of emboli and is intended for use in the proximal pulmonary arterial system. The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

The FlowTriever System is comprised of the FlowTriever Catheter with an integral self-expanding wireform, an Aspiration Guide Catheter (which also allows for the infusion of clinician-specified fluids, such as contrast) and a Retraction Aspirator. The FlowTriever must be the first and primary device used for thrombectomy. Additional adjunctive devices or drugs may be used at the discretion of the Investigator.

NUMBER OF SITES: Up to 20 Sites

NUMBER OF SUBJECTS: Up to 150 Subjects

TREATMENT/FOLLOW-UP:

- Screening and Enrollment
- Study Procedure
- 48 hour Follow-up (±8 hours)
- 30 day Follow-up (±3 days)

DURATION OF STUDY PARTICIPATION:

- Enrollment: 18 months
- Follow-up Period: 30 days
- Analysis: 3 months
- Total Study Duration: 22 months

EFFECTIVENESS ENDPOINT: Reduction in RV/LV ratio from baseline to 48 hours

SAFETY ENDPOINTS:

Primary – Major Adverse Events, a composite of:

- Device-related death within 48 hours
- Major bleeding within 48 hours
- Treatment-related AEs within 48 hours, incl.:
  - Clinical deterioration
  - Pulmonary vascular injury
  - Cardiac injury

Secondary:

- Device-related death within 48 hours
- Major bleeding within 48 hours
- Clinical deterioration within 48 hours
- Pulmonary vascular injury within 48 hours
- Cardiac injury within 48 hours
- Any-cause mortality within 30 days
- Device-related SAEs within 30 days
- Symptomatic recurrence within 30 days

SCHEDULE OF ASSESSMENTS:

Assessment/Method	Screening	Pre-Procedure	Post-Procedure	48 ± 8 Hours* Follow-up	30 ± 3 Days Follow-up
Medical/Surgical History	✓				
Physical Examination/Vitals	✓			✓	✓
Blood Labs	✓				
CT Angiography	✓			✓	
Pulmonary Angiography		✓	✓		
Invasive PA Pressure		✓	✓		
Concomitant Medications	✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓

*or discharge; whichever occurs 1st

ENTRY CRITERIA: *Asterisks indicate entry criteria that can be evaluated during prescreening without obtaining informed consent as they are part of standard of care in PE management. Asterisks in parentheses indicate entry criteria that can be evaluated during prescreening without obtaining informed consent at Sites that routinely perform CTA as part of standard of care in PE management.*

INCLUSION CRITERIA:

1. *Age ≥ 18 and ≤ 75 years
2. *Clinical signs, symptoms and presentation consistent with acute PE
3. *PE symptom duration ≤ 14 days
4. (*)CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery)
5. (*)RV/LV ratio of ≥ 0.9 (NOTE: Enrollment qualification assessment based on Investigator's interpretation of RV/LV ratio at baseline; CoreLab results are not available until after the 48 hour CTA)
6. *Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with fluids)
7. *Stable heart rate < 130 BPM prior to procedure
8. *Patient is deemed medically eligible for interventional procedure(s), per institutional guidelines and clinical judgment

EXCLUSION CRITERIA:

1. *Thrombolytic use within 30 days of baseline CTA
2. *Pulmonary hypertension with peak pulmonary artery pressure > 70 mmHg by right heart catheterization
3. *Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg
4. *FiO2 requirement > 40% or > 6 LPM to keep oxygen saturation > 90%
5. *Hematocrit < 28% (NOTE: hematocrit required within 6 hours of index procedure)
6. *Platelets < 100,000/µL
7. *Serum creatinine > 1.8 mg/dL
8. *International normalized ratio (INR) > 3
9. *Major trauma injury severity score (ISS) > 15
10. *Presence of intracardiac lead in the right ventricle or right atrium placed within 6 months
11. *Cardiovascular or pulmonary surgery within last 7 days
12. *Actively progressing cancer
13. *Known bleeding diathesis or coagulation disorder
14. *Left bundle branch block
15. *History of severe or chronic pulmonary arterial hypertension
16. *History of chronic left heart disease with left ventricular ejection fraction ≤ 30%
17. *History of uncompensated heart failure
18. *History of underlying lung disease that is oxygen dependent
19. *History of chest irradiation
20. *History of heparin-induced thrombocytopenia (HIT)
21. *Any contraindication to systemic or therapeutic doses of heparin or anticoagulants
22. *Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated
23. (*)Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location, predominately chronic clot or non-clot embolus)
24. *Life expectancy of < 90 days, as determined by Investigator
25. *Female who is pregnant or nursing
26. *Current participation in another investigational drug or device treatment study

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ABBREVIATIONS

Abbrv	Abbreviated Term	Definition
AGC	Aspiration Guide Catheter	Guide catheter component of the FlowTriever System.
CC	Completed Cases	All subjects in the mITT population that have successfully received the procedure and have completed all follow-up visits.
CDA	Confidentiality Disclosure Agreement	A contract through which the parties agree not to disclose information covered by the agreement.
CDT	Catheter-Directed Thrombolysis	Percutaneous procedure used to dissolve blood clots (thrombus) by administering a lytic directly into the clot through a catheter.
CEC	Clinical Events Committee	An independent group of individuals chosen to adjudicate the relationship and severity of adverse events.
CSA	Clinical Study Agreement	A contract through which the parties agree-upon terms and conditionsof a basic relationship between investigational site and a sponsor.
CTA	Computed Tomography Angiography	A specialized x-ray that examines blood flow in blood vessels when they are filled with a contrast material.
DSMB	Data Safety and Monitoring Board	An independent group of individuals chosen to assess at specified intervals: the progress of a clinical study, the safety data and the critical endpoints, and to recommend to the sponsor whether to continue, modify or stop a study.
FDF	Financial Disclosure Form	Term referring to the requirement of an applicant (i.e., Sponsor) for a marketing application (IDE) to certify to the absence of certain financial interest of Clinical Investigators or to disclose those financial interests.
FAS	Full Analysis Set	All subjects in the mITT population that have successfully received the procedure and have completed the 48 hour post-procedure follow-up (or are discharged, whichever comes first) per study protocol.
FDC	FlowTriever Delivery Catheter	The delivery catheter component of the FlowTriever System containing the integral self-expanding wireform.
FTC	FlowTriever Catheter	The self-expanding wireform component of the FlowTriever System contained with the delivery catheter.
ITT	Intent-to-Treat	All patients who met the inclusion/exclusion criteria and in whom the Amplatz SS (or equivalent guidewire) is attempted; enrollment occurs when the Amplatz SS (or equivalent guidewire) enters the venous system.
mITT	Modified Intent-to-Treat	All subjects in the ITT population who have no thrombolytics administered during the operative procedure.
NPI	National Principal Investigator	Study advisors who provide study leadership and guidance; they oversee all clinical study activities including protocol development and any changes that may be desired or required during the conduct of the study.
RA	Retraction Aspirator	The device component of the FlowTriever System that enables aspiration and retraction of captured clot.

TERMS AND DEFINITIONS

Category	Term or Phrase	Definition
Device	Ancillary Device	Any device other than FlowTriever System, such as an infusion catheter or guidewire.
Pulmonary Embolism	Asymptomatic PE	PE detected on an imaging study in a patient without clinical symptoms.
Injury	Cardiac Injury	Cardiac injury is defined as any damage to the heart requiring intervention to avoid permanent injury.
Alternative Therapy	Catheter-Directed Therapy	Pharmacomechanical delivery of intrapulmonary thrombolytics, with or without ultrasound assistance.
Study Population	Completed Cases (CC)	All subjects in the mITT population that have successfully received the procedure and have completed all follow-up visits.
Event Relationship	Concomitant Disease Related	Event is attributable to disease other than the study disease with no temporal relationship to the device, treatment or medication.
Event Relationship	Device Related	Event has a strong temporal relationship to the device and alternative etiology is less likely.
Event Relationship	Device Related Death	Any death directly related to the device not performing as expected.
Event Relationship	Device Unknown	Device related but unable to attribute a specific device relationship.
Study Population	Full Analysis Set (FAS)	All subjects in the mITT population that have successfully received the procedure and have completed the 48 hour post-procedure follow-up (or are discharged, whichever comes first) per study protocol.
Study Population	Intent to Treat (ITT)	All patients who met the inclusion/exclusion criteria and in whom the Amplatz SS (or equivalent guidewire) is attempted; enrollment occurs when the Amplatz SS (or equivalent guidewire) enters the venous system.
Bleeding	Life-threatening or Disabling Bleeding	(1) Fatal bleeding, OR (2) bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome, OR (3) bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, OR (4) overt source of bleeding with drop in hemoglobin ≥ 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion of ≥ 4 units.
Bleeding	Major Bleeding	Overt bleeding that (1) is associated with a drop in the hemoglobin level of at least 3 g/dL, OR (2) requires transfusion of 3 units of whole blood/RBC, OR (3) causes hospitalization, permanent injury, or requiring surgery, AND does not meet criteria of “life-threatening or disabling bleeding.”
Complications	Major Complication	Require therapy, minor hospitalization (≤ 48 hours); require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours); permanent adverse sequelae; or death.
Alternative Therapy	Mechanical Thrombectomy Device	An alternate FDA cleared catheter-based device designed to remove or dissolve blood clot.
Alternative Therapy	Medical Therapy	Includes the use of anticoagulation therapy alone and/or systemic thrombolytics.
Event Severity	Mild	No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.

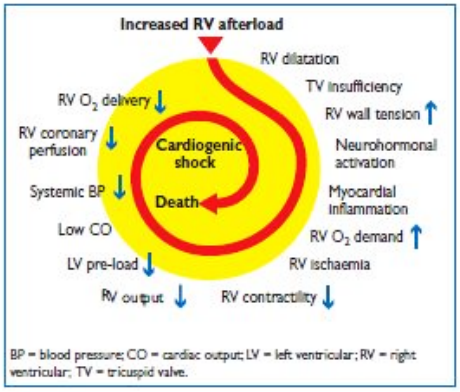
Category	Term or Phrase	Definition
Bleeding	Minor Bleeding	Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as “life-threatening or disabling bleeding” or “major bleeding”.
Complications	Minor Complication	No therapy, no consequence; or nominal therapy, no consequence (includes overnight admission for observation only)
Event Severity	Moderate	Some limitation of usual activities or specific therapy is required.
Study Population	Modified Intent to Treat (mITT)	All subjects in the ITT population who have no thrombolytics administered during the operative procedure.
Study Population	Operative Screen Failure	Any eligible patient in whom the Amplatz SS or equivalent guidewire is not attempted for any reason. Up until this point, the procedure may be converted to another therapeutic treatment or discontinued without the patient receiving any investigational treatment. The subjects are not part of the “ITT Population.” No further information will be collected on this patient; no CRFs are required for these patients, however, if a case report book has been initiated, a study exit form (CRF) is required to close the loop.
Event Relationship	Procedure-Related	Event has a strong temporal relationship to the procedure or treatment of the device implantation or any user handling.
Pulmonary Embolism	Proven PE	PE proven by a positive pulmonary angiogram, an unequivocally positive helical CT scan, a high-probability ventilation-perfusion scan, or autopsy.
Injury	Pulmonary Vascular Injury	Pulmonary vascular injury is defined as perforation or injury of a major pulmonary arterial branch requiring intervention to avoid permanent injury.
Pulmonary Embolism	Recurrent PE	Symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure. “Successful” means a clear clinical improvement of subject symptoms and signs.
Study Population	Screen Failure	Any screened patient who does not meet the inclusion and exclusion criteria. No CRFs are required for these patients.
Event Severity	Severe	Inability to carry out usual activities, hospitalization, emergency room treatment, life-threatening events, or death.
Event Relationship	Study Disease-Related	Event is clearly attributable to underlying disease state with no temporal relationship to the device, treatment or medication.
Device	Study/ Investigational	FlowTriever Catheter, Aspiration Guide Catheter or Retraction Aspirator.
Alternative Therapy	Surgical Embolectomy	Surgical removal of the pulmonary embolism.
Pulmonary Embolism	Suspected PE	PE suspected based on clinical symptoms and/or signs but for which definitive diagnosis has not been made by imaging or autopsy.
Pulmonary Embolism	Symptomatic PE	Clinical PE symptoms and/or signs such as chest pain, dyspnea, hemoptysis, palpitations, or tachycardia.
Event Relationship	tPA-Related	Event is clearly attributable to tPA medication with no temporal relationship to the device or treatment.
Event Relationship	Unknown	Event relationship is not known or unsure.
Event Relationship	Unrelated	Event has no relationship to any of the defined categories.

1. CLINICAL BACKGROUND

Venous thromboembolism (VTE) is the third most common cardiovascular disease worldwide, after ischemic heart disease and stroke,[1] and is the most common avoidable cause of hospital death.[2] The worldwide incidence of VTE is 1 per 1,000.[3,4] VTE, defined as deep vein thrombosis (DVT), pulmonary embolism (PE) or both, affects an estimated 300,000-600,000 individuals in the U.S. each year[5] and with estimates ranging from 1 to 2 per 1,000 to as high as 1 in 100 for people over 80.[1] It is a disorder that can occur in all races and ethnicities, all age groups and both genders.

PE is a blood clot blocking one or more vessels in the lungs. Once in the lung, the blood clot may block the circulation, causing sudden death or long-term damage to the lungs and other vital organs, particularly the heart. The consequences depend on the size and number of emboli, the underlying condition of the lungs, how well the right ventricle (RV) is functioning, and the ability of the body's intrinsic thrombolytic system to dissolve clots; death occurs due to RV failure.[6] Approximately 30–40% of patients with VTE will present with symptomatic PE[7] and nearly a third (34%) of VTE deaths are from sudden fatal PE.[8] Symptoms of PE include acute shortness of breath, chest pain, and rapid heart rate; some people also cough blood. It is estimated that 1 in 10 deaths that occur in the hospital is caused by pulmonary emboli.[9] In the U.S., sudden death is the first symptom in one-quarter (25%) of people who have PE.[3] RV failure due to pressure overload is considered the primary cause of death in severe PE; **Figure 1** illustrates the key factors contributing to hemodynamic collapse in acute PE.[10]

FIGURE 1
Key Factors Contributing to Hemodynamic Collapse



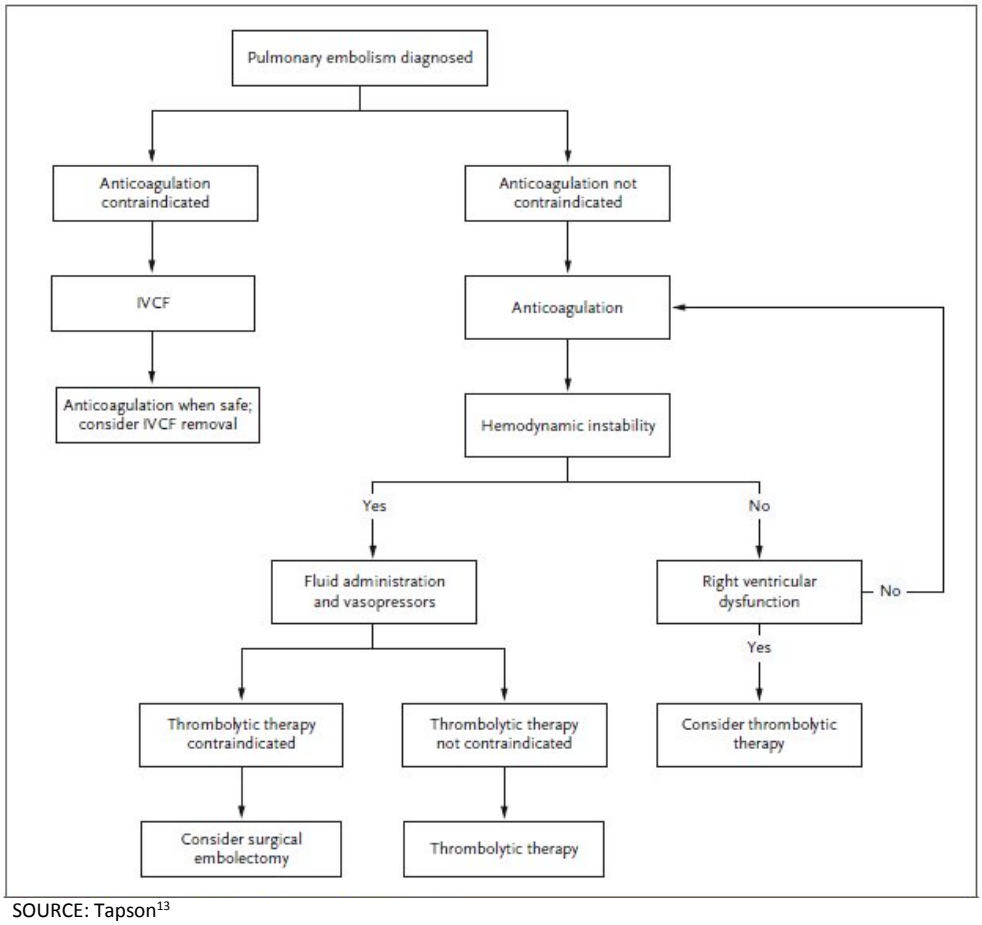
SOURCE: ESC Guidelines[10]

1.1 Current Approved Treatment

The clinical classification of the severity of an episode of acute PE is based on the estimated PE-related early mortality risk and is divided into three (3) categories based on outcome: low-risk, submassive/intermediate risk and massive/high risk. Recommendations concerning the treatment of massive and submassive PE are published by the American College of Chest Physicians (ACCP),[11] the American Heart Association (AHA),[12] and the European Society of Cardiologists (ESC).[10]

Currently, the following clinical options are used in the treatment of PE: anticoagulation therapy, thrombolytic therapy, and surgical or percutaneous catheter-directed treatment, or a combination thereof (see **Figure 2**).

FIGURE 2
Treatment of Acute Pulmonary Embolism



SOURCE: Tapson[13]

1.1.1 Anticoagulation Therapy

PE will be fatal in up to 25% of patients in whom the diagnosis has been made if left untreated,[14] with anticoagulation substantially reducing the risk of fatal PE during the initial treatment period to less than 2%.[15] Small, peripheral PE commonly do not result in systematic manifestations and these are typically either left untreated or treated with anticoagulants only. The current standard of care for treatment of PE includes a complex dual drug approach of heparin [unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux] followed by new oral anticoagulant (NOAC) or vitamin K antagonist (VKA), such as Warfarin.

Initial anticoagulation with heparins requires administration by injection or IV infusion, which can cause inconvenience and discomfort. In addition, some patients taking heparin experience a severe reaction known as HIT (heparin-induced thrombocytopenia), which can lead to new or worsening thrombosis. Managing patients on VKAs can also be challenging. VKAs have a narrow therapeutic window and can therefore require frequent dose adjustments, as well as a need for routine coagulation safety screening. Furthermore, VKAs have a slow onset of action, as well as many food and drug interactions.[16,17]

1.1.2 Thrombolytic Therapy

According to the ESC Guidelines, "thrombolytic treatment of acute PE restores pulmonary reperfusion more rapidly than anticoagulation with UFH alone. The early resolution of pulmonary obstruction leads to a prompt reduction in pulmonary artery pressure and resistance, with concomitant improvements in RV function."[10]

The ACCP, AHA and ESC Guideline (the "Guidelines") recommendations for the use of thrombolytic agents to treat massive and submassive PE are described in **Table 1**.

TABLE 1
Guideline Recommendations for the Use of Thrombolytic Agents

Guideline	Massive PE	Submassive PE
American College of Chest Physicians[11]	For patients with evidence of hemodynamic compromise, use of thrombolytic therapy is recommended unless patient has major contraindications because of risk for bleeding.	In selected high-risk patients without hypotension who are judged to have a low risk for bleeding, administration of thrombolytic therapy is suggested.
American Heart Association[12]	The use of thrombolytic agents is reasonable for patients with massive acute PE and an acceptable risk for bleeding complications.	The use of thrombolytics may be considered for patients with submassive PE judged to have clinical evidence of adverse prognosis and low risk for bleeding complications.
European Society of Cardiology[10]	Thrombolytic therapy is the first-line treatment in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension, with very few absolute contraindications.	Routine use of thrombolysis in patients not at high risk for bleeding is not recommended, but may be considered in selected patients with intermediate-risk PE and after thorough consideration of conditions increasing the risk for bleeding.

At present, there are three agents (streptokinase, urokinase, alteplase) approved by FDA for thrombolysis of PE. All are administered intravenously for direct clot lysis in patients without contraindications. Alteplase (tPA) is the most common thrombolytic used for the treatment of PE.[18] Systemic thrombolysis with a 2 hour continuous intravenous infusion of 100 mg of tissue plasminogen activator (tPA) is approved by FDA for patients with massive PE. However, a meta-analysis including 13 randomized clinical trials of systemic thrombolysis versus heparin treatment alone showed no significant reduction in recurrent PE or death.[12] Systemic thrombolysis has absolute and relative contraindications, most of which are characteristics that would predispose a patient to a bleeding event. Absolute contraindications include any prior intracranial hemorrhage, known structural intracranial cerebrovascular disease (e.g., arteriovenous malformation), known malignant intracranial neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active bleeding or bleeding diathesis, recent surgery encroaching on the spinal canal or brain, or significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury. Even in selected patients without absolute contraindications to systemic thrombolysis, major hemorrhages (up to 20%) and intracranial bleeding complications (3-5%) have been reported.[19,20]

Catheter placement in the pulmonary artery allows for the delivery of thrombolytic agents proximal to or intra-emboli. Catheter-directed thrombolysis (CDT) in the treatment of PE has the potential to offer similar clinical benefits as systemic thrombolytics while resulting in less bleeding by using a lower total drug dose. Studies have suggested that doses of tPA that are less than the FDA-approved dose are safe and effective in both massive and submassive PE patients.[21,22,23] This is further supported by a recent meta-analysis that demonstrated that the use of low-dose tPA was beneficial in preventing major bleeding events and had similar efficacy when compared with standard dose regimens.[24] With localized delivery of a therapeutic agent, bleeding complications seem to occur less frequently than with full-dose systemic thrombolysis and this approach is often performed in patients with submassive and massive PE in the presence of relative contraindications to systemic thrombolysis or those who are hemodynamically unstable.[25]

Three prospective studies (ULTIMA, SEATTLE II, and PERFECT) have recently analyzed the short-term safety and efficacy of CDT in the setting of submassive PE and confirmed that CDT effectively lyses thrombi and rapidly restores RV function; there was no major bleeding reported in either the ULTIMA or PERFECT studies, however, in the SEATTLE II study, major bleeding was reported in 11% of the patients, all requiring blood

transfusion. CDT may be theoretically safer, but the studies thus far have not been sufficiently powered to definitively make this conclusion.[26] The optimal dose and mode of administration for local thrombolytic treatment is still to be determined. The use of tPA for treatment of submassive PE has not been approved by the FDA and remains a widely debated topic; nevertheless, tPA is often used off-label to treat submassive PE.[27,28]

1.1.3 Surgical and Percutaneous Catheter-Directed Treatments

Traditionally, surgical embolectomy has been reserved for patients with massive PE who are either in cardiogenic shock or those cases where less invasive measures (including thrombolysis) have failed or are contraindicated. Similarly, inferior vena cava (IVC) filters are traditionally placed in the presence of contraindications to anticoagulation, major bleeding complications during anticoagulation or recurrent embolism while the patient is receiving adequate therapy.[13]

Percutaneous catheter-based interventions are increasingly being used in experienced centers when systemic thrombolysis is contraindicated or urgent recanalization of PE is warranted. Contemporary catheter intervention techniques can be separated into five (5) categories: (1) thrombus fragmentation, (2) rheolytic thrombectomy, (3) suction thrombectomy, (4) rotational thrombectomy and (5) ultrasound-assisted thrombolysis. The goal of the catheter intervention is the removal/dissolution of the obstructing thrombi from the pulmonary arteries, to facilitate right ventricle recovery, and to improve symptoms and survival.

1.2 Limitations of Currently Approved Therapy

Generally the Guidelines agree that the mainstay of treatment for massive and submassive PE is anticoagulation and that thrombolysis should be offered to unstable patients.[10,11,12] They further suggest that thrombolytics not be routinely used to treat submassive PE but should instead be considered on a per patient basis. The benefit of thrombolysis for patients with submassive PE is not clear and treatment may cause more harm than benefit for many patients; lytic therapy must be weighed against the risk of major bleeding, including the risk of intracranial hemorrhage.

The goal of a successful interventional procedure is to restore RV outflow through the pulmonary artery, thereby disrupting the potentially lethal cascade towards hemodynamic collapse. There is a strong clinical need to develop a reliable, rapid, percutaneous method of clot removal for the treatment of clinically significant acute PE. The need is especially strong for a mechanical method that does not rely on the use of thrombolytics, as physicians are reluctant to administer lytics given the high bleeding risk and because many patients cannot tolerate lytics. The FlowTriever System was developed to meet this need to rapidly restore blood flow through the pulmonary vasculature in patients experiencing acute submassive pulmonary embolism. Once the immediate clot burden is removed, the blood flow is restored and the acute physiological effects from pressure overload should begin to dissipate and be evident in the reduction of RV/LV ratio (an increased RV/LV diameter ratio is a well-established independent predictor of short-term mortality, hemodynamic collapse and other adverse clinical events in patients with acute PE).[10,11,12]

The FlowTriever System was designed to remove emboli and restore blood flow through the pulmonary arteries. The goal in using this device is not 100% removal of clot, but rather to remove enough clot to make a clinically significant difference in the patient by reducing the patient's risk level for further complications and enable the endogenous thrombolysis mechanism to further reduce any residual clot. Should there be any residual or distal clot that is not part of the immediate emergent issue it should be treated according to the medical judgment of the Investigator on a case-by-case basis.

2. TREATMENT DECRIPTION

2.1 Investigational Device

The FlowTriever Retrieval/Aspiration System ("FlowTriever System") will be used in this study. The FlowTriever System is a catheter-based mechanical thrombectomy device for percutaneous endovascular retrieval of emboli and is intended for use in the proximal pulmonary arterial system. The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

The FlowTriever must be the first and primary device used for thrombectomy. Additional adjunctive devices or drugs may be used at the discretion of the Investigator.

2.2 Regulatory Status

The FlowTriever System is a commercially marketed embolectomy catheter device (marketed under K143563). At present, the device is not cleared for the specific indication for which it is being tested (e.g., acute PE) and, thus, is not commercially available for this indication. The FlowTriever System to treat acute PE will be under clinical investigation at sites where the responsible Institutional Review Board (IRB) has approved the FlowTriever Pulmonary Embolectomy Clinical Study (FLARE) protocol.

Neither Inari Medical nor the Investigator may represent the investigational device as safe or effective for the purpose for which it is under clinical study or otherwise promote the product for this indication.

2.3 Device Description

The FlowTriever System is comprised of the FlowTriever Catheter with an integral self-expanding wireform (**Figure 3**), an Aspiration Guide Catheter (which also allows for the infusion of clinician-specified fluids, such as contrast) (**Figure 4**) and a Retraction Aspirator (**Figure 5**).

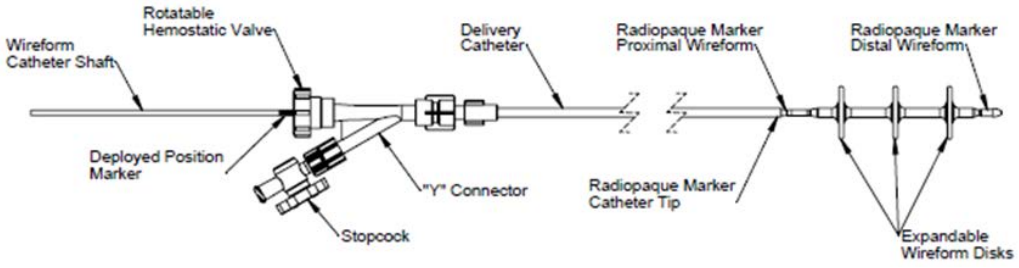


FIGURE 3: FLOWTRIEVER CATHETER WITH INTEGRAL SELF-EXPANDING WIREFORM COMPONENT ILLUSTRATION

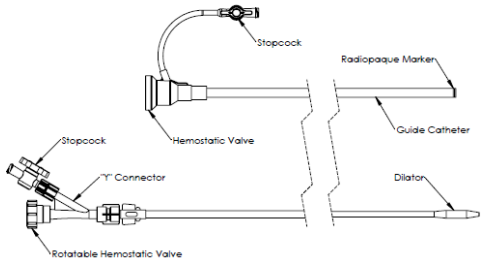


FIGURE 4: ASPIRATION GUIDE CATHETER COMPONENT ILLUSTRATION

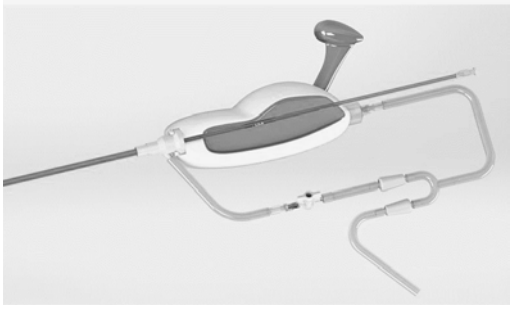


FIGURE 5: RETRACTION ASPIRATOR

The system is designed for use with a 0.035" guidewire. The outside diameter of the Aspiration Guide Catheter is 20F. The outside diameter of the FlowTriever Delivery Catheter is 12Fr. The FlowTriever Catheter with self-expanding wireform will be available in 10 mm, 14 mm and 18 mm sizes to accommodate a variety of vessel diameters. The FlowTriever System is compatible with the Gore DrySeal 22F Sheath and the Cook 22F Introducer.

2.4 Intended Use of Device

The FlowTriever Retrieval/Aspiration System ("FlowTriever System") is a catheter-based device for percutaneous endovascular retrieval of emboli and is intended for use in the proximal pulmonary arterial system. The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

The FlowTriever System will be deployed and in use for typically less than two hours with no element of the device left behind.

2.5 Device Label

Even though this device is commercially available, the device to be used as part of this study is considered investigational. It is required to be used per protocol and as specified in the IDE Instructions for Use document. The investigational devices will be identified with additional labeling indicating the following:

> CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

2.6 Release to Investigators

No investigational device will be released until the Investigator has received IRB approval to conduct the study. Once released to the Investigator, all investigational device inventories will be monitored and accounted for throughout the course of the study.

All investigational devices will be stored in a secure location, segregated from any commercial inventory to minimize the possibility of a study device being used in a non-study patient. Access is to be limited to key study personnel. NOTE: There is no difference between a commercial device and an investigational device other than the device label and IFU. There is no safety risk to a patient should a device labeled as investigational be inadvertently used in a non-study patient.

All unused investigational devices will be returned to Inari Medical.

3. STUDY OBJECTIVES

The FlowTriever Retrieval/Aspiration System ("FlowTriever System") is a catheter-based mechanical thrombectomy device for percutaneous endovascular retrieval of emboli from vasculature and is intended for use in the proximal pulmonary arterial system. The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

The primary study objective is to evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli in the treatment of acute PE.

3.1 Primary Endpoint - Safety

The study's primary safety endpoint is Major Adverse Events, which is a composite of:

- Device-related death within 48 hours (± 8 hours) of the procedure
- Major bleeding within 48 hours (± 8 hours) of the procedure
- Treatment-related adverse events within 48 hours (± 8 hours), including:
    - Clinical deterioration
    - Pulmonary vascular injury
    - Cardiac injury

3.2 Secondary Endpoint - Safety

The study's secondary safety endpoints are:

- Device-related death within 48 hours (± 8 hours) of the procedure
- Major bleeding within 48 hours (± 8 hours) of the procedure
- Clinical deterioration within 48 hours (± 8 hours) of the procedure
- Pulmonary vascular injury within 48 hours (± 8 hours) of the procedure
- Cardiac injury within 48 hours (± 8 hours) of the procedure
- Mortality due to any cause within 30 days (± 3 days) of the procedure
- Device-related serious adverse events within 30 days (± 3 days) of the procedure
- Symptomatic recurrence of embolism within 30 days (± 3 days) of the procedure

3.3 Primary Endpoint - Effectiveness

The study's primary effectiveness endpoint is the reduction in RV/LV ratio from baseline to 48 hours (± 8 hours, or discharge, whichever occurs first) as assessed by Computed Tomography Angiography (CTA).

3.4 Endpoint Definitions

3.4.1 Recurrent PE

The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE. The goal in using this device is not 100% removal of clot, but rather to remove enough clot to make a clinically significant difference in the patient. As this is a mechanical procedure where many, possibly all, patients will not receive any concomitant thrombolytic therapy, new recurrence is not unexpected.

Recurrence in this study is defined as a symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure. Based on the International Society on Thrombosis and Haemostasis (ISTH) guidance, "successful" means a clear clinical improvement of Subject symptoms and signs.[29] Symptomatic recurrent PE will be confirmed by CTA. "Symptomatic" means clinical symptoms and/or signs such as chest pains, dyspnea, hemoptysis, palpitations, or tachycardia.

3.4.2 Device Related Death

Device related death is defined as any death directly related to the device not performing as expected. Device related death would include death from:

- Vascular or cardiovascular injury
- Device malfunction
- Device-induced cardiac arrhythmia
- Worsening pulmonary or right heart function (exclusive of worsening from recurrent PE)

All device-related deaths will be CEC adjudicated.

3.4.3 Bleeding

The Valve Academic Research Consortium-2 (VARC-2) bleeding definitions will be used in this study.[30]

Life-threatening or disabling bleeding:

(1) Fatal bleeding, OR
(2) Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome, OR
(3) Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, OR
(4) Overt source of bleeding with drop in hemoglobin ≥ 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion of ≥ 4 units*

Major bleeding:

- Overt bleeding that is:
    - Associated with a drop in the hemoglobin level of at least 3 g/dL, OR
    - Requires transfusion of 3 units of whole blood/RBC, OR
    - Causes hospitalization, permanent injury, or requiring surgery, AND
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding:

- Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening or disabling bleeding or major bleeding.

According to the VARC-2 Consensus Document, "it is critical to acknowledge that a bleeding complication has to be the result of *overt bleeding* and cannot be adjudicated based on blood transfusion alone." As a result of hemodilution and clot extraction, controlled bleeding is a deliberate outcome in a thrombectomy procedure. To meet the primary safety endpoint definition for major bleeding, the complication must be the result of overt bleeding; blood loss that occurs as part of the procedure without an overt source and without clinical consequence will be reported in the procedural data. The safety endpoint reporting major bleeding with 48 hours of the procedure will include events that meet either the "life-threatening or disabling bleeding" or the "major bleeding" definition.

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* Given that 1 unit of packed RBC typically will raise the hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.

3.4.4 Clinical Deterioration

Clinical deterioration will include treatment-related events, such as unplanned endotracheal intubation, unexpected requirement for mechanical ventilation, arterial hypotension (>1 hour or requiring vasopressors) or shock, cardiopulmonary resuscitation, persistent worsening in oxygenation, and emergency surgical embolectomy.

3.4.5 Pulmonary Vascular Injury

Pulmonary vascular injury is defined as perforation or injury of a major pulmonary arterial branch during the index procedure requiring intervention, including but not limited to blood transfusion, open or endovascular intervention, to avoid permanent injury.

3.4.6 Cardiac Injury

Cardiac injury is defined as any damage to the heart during the index procedure requiring intervention, including but not limited to blood transfusion, open or endovascular intervention, to avoid permanent injury.

4. STUDY DESIGN

The study is a prospective, single-arm, controlled, multicenter study to evaluate the safety and effectiveness of the FlowTriever System in patients eligible for endovascular treatment of acute PE.

4.1 Number of Sites and Subjects

A maximum of 20 sites will participate in the Study. The total population for the Study is expected to be a maximum of 150 Subjects. No single site may enroll more than 25% of the total Subjects enrolled.

4.2 Study Duration

The Subjects who meet the inclusion/exclusion criteria will be enrolled in the study. The enrollment period is expected to last over a period of approximately 12 months. Each study Subject will actively participate for up to 30 days (±3 days) following treatment. Study participation includes screening, treatment, 48 hour follow-up or discharge, and 30-day follow-up. The screening through discharge visits will take place at the treating hospital. Subjects will be requested to return for 30-day follow-up at a location designated by research staff.

4.3 Study Population

The study population consists of Subjects that have an acute PE. Subject eligibility is to be determined based on data available to the Investigator at the time of enrollment. Subjects must comply with all inclusion and exclusion criteria to be eligible for the study. Waivers will not be granted by the Sponsor regarding enrollment criteria.

In this Study, Subjects will be categorized as follows:

Screen Failure: Any screened patient who does not meet the inclusion and exclusion criteria. No case report forms (CRFs) are required for these patients. All patients screened will be documented on the Screening/ Enrollment Log.

Operative Screen Failure: Any eligible patient in whom the Amplatz SS or equivalent guidewire is not attempted for any reason. Up until this point, the procedure may be converted to another therapeutic treatment or discontinued without the patient receiving any investigational treatment. These Subjects are not part of the "ITT Population." No further information will be collected on this patient; no CRFs are required for these patients, however, if a case report book has been initiated, a study exit form (CRF) is required to close the loop.

Intent-To-Treat (ITT): All patients who met the inclusion/exclusion criteria and in whom the Amplatz SS (or equivalent guidewire) is attempted; enrollment occurs when the Amplatz SS (or equivalent guidewire) enters the venous system.

Modified Intent-To-Treat (mITT): All Subjects in the "ITT Population" who have no thrombolytics administered during the operative procedure.

Full Analysis Set (FAS): All Subjects in the "mITT Population" that have successfully received the procedure and have completed the 48 hour post-procedure follow-up (or are discharged, whichever comes first) per study protocol.

Completed Cases (CC): All Subjects in the "mITT Population" that have successfully received the procedure and have completed all follow-up visits.

4.4 Subject Enrollment Criteria

Only patients who meet all inclusion criteria and none of the exclusion criteria are considered eligible for enrollment. The decision to use the FlowTriever System will occur prior to the procedure and written informed consent will be obtained prior to all study-specific procedures.

The following criteria will be used to determine the patient's eligibility for enrollment in the study. Asterisks * indicate entry criteria that can be evaluated during prescreening without obtaining informed consent as they are part of standard of care in PE management. Asterisks in parentheses (*) indicate entry criteria that can be evaluated during prescreening without obtaining informed consent at sites that routinely perform CTA as part of standard of care in PE management.

4.4.1 Inclusion Criteria

Subjects must meet all of the following general inclusion criteria:

1. *Age ≥ 18 and ≤ 75 years
2. *Clinical signs, symptoms and presentation consistent with acute PE
3. *PE symptom duration ≤ 14 days
4. (*)CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery)
5. (*)RV/LV ratio of ≥ 0.9 (NOTE: Enrollment qualification assessment based on Investigator's interpretation of RV/LV ratio; CoreLab results are not available until after the 48 hour CTA)
6. *Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with fluids)
7. *Stable heart rate < 130 BPM prior to procedure
8. *Patient is deemed medically eligible for interventional procedure(s), per institutional guidelines and clinical judgment

4.4.2 Exclusion Criteria

Subjects must not meet any of the following general exclusion criteria:

1. *Thrombolytic use within 30 days of baseline CTA
2. *Pulmonary hypertension with peak pulmonary artery pressure > 70 mmHg by right heart catheterization
3. *Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg
4. *FiO2 requirement > 40% or > 6 LPM to keep oxygen saturation > 90%
5. *Hematocrit < 28% (NOTE: hematocrit required within 6 hours of index procedure)
6. *Platelets < 100,000/µL
7. *Serum creatinine > 1.8 mg/dL
8. *INR > 3
9. *Major trauma Injury Severity Score (ISS) > 15
10. *Presence of intracardiac lead in the right ventricle or right atrium placed within 6 months
11. *Cardiovascular or pulmonary surgery within last 7 days
12. *Actively progressing cancer
13. *Known bleeding diathesis or coagulation disorder
14. *Left bundle branch block
15. *History of severe or chronic pulmonary arterial hypertension
16. *History of chronic left heart disease with left ventricular ejection fraction ≤ 30%
17. *History of uncompensated heart failure
18. *History of underlying lung disease that is oxygen dependent

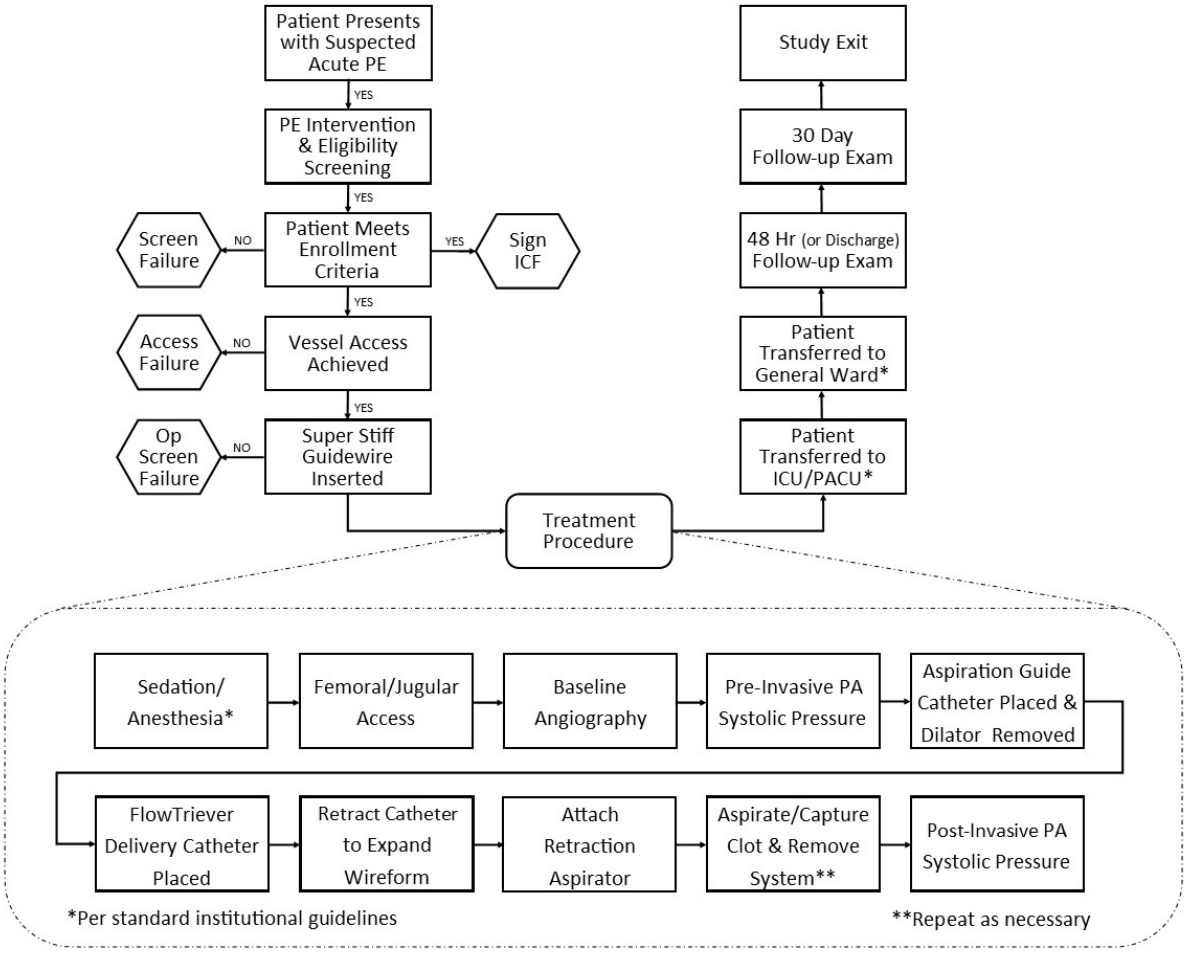
19. *History of chest irradiation
20. *History of heparin-induced thrombocytopenia (HIT)
21. *Any contraindication to systemic or therapeutic doses heparin or anticoagulants
22. *Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated.
23. (*)Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location, predominately chronic clot, or non-clot embolus)
24. *Life expectancy of < 90 days, as determined by Investigator
25. *Female who is pregnant or nursing
26. *Current participation in another investigational drug or device treatment study

5. STUDY PROCEDURES

5.1 Overview of Study Flow

Subjects presenting with acute PE will be evaluated by the Investigator, in accordance with their institutional practices, to establish an appropriate treatment plan based on the patient's medical condition and available diagnostic screening procedures prior to recruitment in the FLARE Clinical Study. Informed Consent will be obtained prior to proceeding to the treatment suite. A representative overview of the study flow is shown in **Figure 6**.

FIGURE 6 Representative Study Flow from Screening to Discharge



5.2 Subject Screening

Patients will be screened to determine their initial eligibility and interest in the study. Screening criteria indicated with an asterisk * in the Inclusion/Exclusion criteria are considered standard of care in PE management. Therefore, most, if not all, patient eligibility criteria can be evaluated without obtaining informed consent. Informed consent will be obtained once a patient has satisfied screening criteria and prior to any study-specific procedures that are not part of standard of care. All patients screened will be documented on the Screening/Enrollment Log.

5.3 Informed Consent

The nature of the planned treatment and objectives of the FLARE Clinical Study will be thoroughly explained to the patient, or the patient's legally authorized representative. Details of the Study should include, but are not limited to, the following items:

- Purpose of the study
- Alternative treatments
- Potential risks/benefits for participation
- Participation is voluntary and there is no penalty for withdrawal
- Need to return to clinic for follow-up visit
- Contact information to ask questions or voice concerns

5.4 Numbering of Study Subjects

Each site will be assigned a unique site number at the beginning of the Study and each enrolled Subject will be assigned a unique sequential Subject number. All Subjects who provide informed consent and have the study procedure will be given a Subject number and the Subject number will be recorded on the Screening/ Enrollment Log.

5.5 Imaging and Invasive Pressure

Given the importance of imaging to Subject assessment, before and during the study, the Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer associated with the Study.

5.5.1 Computed Tomography Angiography (CTA)

The Study requires a CTA be obtained for Subject screening to confirm pulmonary embolism, assess RV/LV dysfunction and determine the Modified Miller Score (MMS). A 48 hour (or discharge, whichever occurs first) follow-up imaging study will also be obtain to assess for residual emboli, RV/LV status and determine the MMS.

5.5.2 Invasive Pulmonary Artery (PA) Systolic Pressure

Once access is achieved, a pre-procedure invasive PA systolic pressure will be obtained prior to starting the FlowTriever System procedure. After the FlowTriever System has been removed, a post-procedure invasive PA systolic pressure will be obtained.

5.5.3 Procedural Angiography

Angiography images obtained during the procedure will consist of the following:

- Baseline angiogram: prior to the device deployment while assessing the clot location
- Post device use angiogram: immediately after each pass of study device use
- Final post procedural angiogram: after all treatments have been completed

5.6 Medical/Surgical History

Relevant medical and surgical history will be collected from all consented Subjects at the time of enrollment.

5.7 Laboratory

Blood tests are required for Subject inclusion/exclusion criteria evaluation. Study informed consent is not required in order to obtain blood tests as the required tests are a standard of care in assessing PE treatment.

The following blood values must be available to assess Subject eligibility for the study: hematocrit, platelet count, serum creatinine, and International Normalized Ratio (INR).

5.8 Concomitant Medications

It is required that the Subject's relevant concomitant medication use during the study be documented at pre-procedure, procedure and follow-up visits.

As part of the standard of care to treat acute PE, anticoagulation medication is administered to impede blood clotting and thrombolytic medication may be administered to dissolve blood clots. The specific dose and course of administration is at the discretion of the Investigator and will be recorded on the case report form (CRF).

5.9 Endovascular Treatment/Procedure

Once all inclusion/exclusion criteria have been satisfied, including imaging assessments, the Subject will proceed with the thrombectomy procedure using the FlowTriever System.

The procedural requirements for the use of the FlowTriever System are listed below. Refer to the IDE-specific IFU for more information on the appropriate use of the device for this Study.

- NOTE: Hematocrit requirement (< 28%) must be confirmed within 6 hours of index procedure. Please obtain prior to procedure if necessary.
- Administer IV sedation or general anesthesia, as appropriate, to assure Subject comfort and safety.
- Administer/continue to administer anticoagulation medications per standard institutional guidelines.
- Access the target area via femoral or jugular vein per standard institutional guidelines for thrombectomy procedures.
- Determine the location and size of the area to be treated (baseline angiography). Do not treat vessels smaller than 6 mm diameter.
- Obtain invasive pulmonary artery systolic pressure (pre-procedure).
- Select the appropriate FlowTriever Catheter size (available in 10 mm, 14 mm and 18 mm sizes to accommodate a variety of vessel diameters).
- After an Amplatz SS or equivalent guidewire is positioned at the treatment site/through the clot, perform catheterization procedure with the FlowTriever System.
    - Introduce the Aspiration Guide Catheter ("AGC") with dilator over the guidewire and advance the AGC to the proximal end of the clot. The tip of the AGC contains a radiopaque marker for fluoroscopic positioning.
    - Remove the dilator from the AGC.
    - Place the FlowTriever Delivery Catheter ("FDC") containing the FlowTriever Catheter ("FTC") into the AGC over the guidewire; advanced it past the distal end of the AGC and through the clot in the main or lobar artery. Again, do not treat vessels smaller than 6 mm diameter.
    - Pin the guidewire. While maintaining the AGC and FTC position, manually retract the FDC enough to allow the self-expanding wireform to expand within some portion of the clot.
        - Dependent upon the length of the treatment area, deployment of all three wireform disks is not required.
        - The proximal and distal ends of the wireform contain a radiopaque marker to aid in maintaining proper position as the FDC is retracted.
    - After proper placement of the wireform, lock the position of the FTC and the FDC together by tightening the Tuohy-Borst connector.
    - Connect the waste bag fittings to the Retraction Aspirator ("RA") and AGC. Open the stopcock.
    - Attach the RA to the AGC and FDC.
    - Continue to pin the guidewire. With the RA, provide simultaneous aspiration and retraction of the FTC into the AGC to capture the clot. Close the stopcock.
    - Continue to pin the guidewire. Remove the entire FlowTriever System with captured clot from the body.

        - Obtain angiographic results after each pass with the device.
        - Continue to perform additional clot retrieval with the FlowTriever System, if needed.
- Obtain invasive pulmonary artery systolic pressure (post-procedure).
- After the final pass and removal of the FlowTriever System and guidewire, continue to manage the Subject as medically appropriate.
- Complete the procedure per standard institutional guidelines for thrombectomy procedures and transfer the Subject to ICU (if appropriate) or post-surgical ward to monitor Subject safety according to institutional guidelines.
    - Continue to monitor for vital signs, oxygenation and new symptoms.
    - For symptomatic residual clot, distal embolization or new PE, continue to treat with anticoagulation and consider thrombolytics.
- Record adverse events and technical complications, as applicable.

The FlowTriever must be the only device used for thrombectomy. Additional adjunctive drugs may be used at the discretion of the Investigator. Post-procedure, the Investigator will review all images, clinically assessing the PE status and looking for evidence of vessel injury (perforation/dissection). An Inari Medical representative may be present during the thrombectomy procedure.

5.9.1 Access Failures

There may be cases where the FlowTriever System is not deployed due to access failure. Access failure is defined as: 1) the guidewire cannot be introduced, or 2) vessel spasm precludes continuing the procedure. If an adverse event occurs prior to discharge, they will be followed for safety until resolution or for 30 days, whichever occurs first. A study exit form (CRF) is required for these Subjects.

5.9.2 Operative Screen Failures

There may be cases where the Amplatz SS or equivalent guidewire is not attempted for any reason. Up until this point, the procedure may be converted to another therapeutic treatment or discontinued without the patient receiving any investigational treatment. No further information will be collected on this patient; no CRFs are required for these patients, however, if a case report book has been initiated, a study exit form (CRF) is required to close the loop.

5.10 Examinations

All scheduled exams listed in **Table 2** must be performed at the designated time point and the results documented. The following table details the clinical and laboratory procedures required from Screening through the 30 day follow-up visit. The majority of these tests and procedures are considered standard of care for all patients under treatment of clinically significant PE.

TABLE 2: Schedule of Assessments

Assessment/Method	Screening	Pre-Procedure	Post-Procedure	48 ± 8 Hr* Follow-up	30 ± 3 Days Follow-up
Medical/Surgical History	✓				
Physical Examination/Vitals	✓			✓	✓
Blood Labs	✓				
CT Angiography	✓			✓	
Pulmonary Angiography		✓	✓		
Invasive PA Pressure		✓	✓		
Concomitant Medications	✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓

*or discharge; whichever occurs first

5.10.1 48 Hour Follow-up Evaluation (± 8 Hours or discharge)

- Physical examination and vitals
- Repeat CTA consistent with baseline imaging study
- Record adverse events, as applicable
- Record concomitant medications

5.10.2 30 Day Follow-up Evaluation (± 3 Days)

- Physical examination and vitals
- Record adverse events, as applicable
- Record concomitant medications
- Complete study Exit form (CRF)

5.10.3 Unscheduled Visit

Unscheduled assessments should be done as clinically indicated and corresponding data must be documented on the case report forms and submitted to the Sponsor.

5.11 Handling of Lost to Follow-up Subjects

Every attempt must be made to have all Subjects complete the follow-up visit schedule. A Subject will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact and must be documented in the Subject's medical records and appropriate study records.

5.12 Study Discontinuation

5.12.1 Study Discontinuation by IRB

The IRB may choose to discontinue the Study at any center(s) for which they granted approval if the:

- Research study is not conducted in accordance with the IRB's requirements
- Research study indicates unexpected serious harm to Subjects

5.12.2 Study Discontinuation by Sponsor

The Sponsor may choose to discontinue the Study should the Sponsor discover additional information during the Study that may cause harm to Subject safety. If the Study is terminated or suspended, the Sponsor will promptly inform all Investigators of the termination or suspension and the reason(s) for this. The IRB will also

be informed, either by the Sponsor or Investigator if a local IRB is utilized, promptly and provided with the reason(s) for the termination or suspension. If applicable, regulatory authorities will be informed.

5.13 Withdrawal/Premature Discontinuation of Study Subject

Subjects may withdraw from the Study at any time upon written request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety or administration reasons.

5.13.1 Subject Discontinuation by Investigator

An Investigator may discontinue a Subject from the Study, with or without the Subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the Subject.

5.13.2 Withdrawal by Subject

If a Subject chooses to withdraw from the Study, and also withdraws consent for disclosure of future information, no further Study-related evaluation(s) will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected prior to the withdrawal of consent, unless specified by the Subject or legally authorized representative.

6. RISK & BENEFIT ANALYSIS

A risk analysis according to ISO 14971 (Application of Risk Management to Medical Devices) has been conducted. Risks have been minimized or eliminated through appropriate design control, and confirmed by pre-clinical bench, laboratory and animal testing.

The FlowTriever System provides a means for the removal of pulmonary emboli to facilitate the restoration of circulation to the pulmonary vasculature by minimally invasive means. Alternative therapies in the treatment of pulmonary embolism for endovascular clot retrieval include anticoagulation, systemic thrombolysis, pharmacomechanical thrombolysis, catheter intervention, and surgical thrombectomy.

Anticoagulation therapy has bleeding risks and a slow onset of action. Thrombolytic therapy has a risk of major hemorrhage, including a risk for hemorrhagic stroke; these risks may negate the potential benefit derived from this therapy. Furthermore, thrombolysis is not available to patients with absolute and relative contraindications to its use. As with anticoagulation therapy, thrombolytics' onset of action is prolonged. Pharmacomechanical catheter-directed devices may allow lower dosages of thrombolytics but are nevertheless not appropriate or effective in certain patient populations. Catheter interventions have not been studied in a trial with anticoagulation alone and are often used in combination with thrombolytics. Open surgical embolectomy is a highly invasive surgical technique with a significant mortality rate.

The goal of the FlowTriever System is the safe and expeditious removal of the obstructing thrombi from the pulmonary arteries to facilitate right ventricular recovery.

6.1 Potential Risks during the Interventional Procedure

The risks associated with the FlowTriever System are on the order of coronary endovascular interventions and catheter-directed embolectomies. Potential risks and complications include those resulting from anticoagulation and contrast dye, including bleeding, contrast-induced nephropathy, and anaphylactic reactions to iodine contrast. Potential vascular access complications include bleeding, hematoma, arteriovenous fistula, and pseudoaneurysm. The most serious complication resulting from catheter-directed procedures is perforation or dissection of a pulmonary artery, causing massive pulmonary hemorrhage and immediate death. The risk of perforation increases with smaller vessels. Other serious complications include pericardial tamponade, pneumothorax, cardiac rupture and cardiac arrest. Transient, periprocedural complications include arrhythmias when the catheter advances through the right heart, right heart block or bradycardia, worsening hypoxemia, and hemodynamic deterioration. The above risks are no greater with the use of the FlowTriever System than that of any coronary endovascular intervention or catheter-directed embolectomy procedure.

Malfunction of the device could result in cardiac damage and artery dissection/perforation of the artery; these are thought to be the most severe complications associated with the FlowTriever procedure. Manufacturing controls are in place to ensure consistent product quality and to minimize defective devices entering distribution.

Under fluoroscopic guidance, the device is tracked over the guidewire into the pulmonary artery to the site of the pulmonary emboli. Use of fluoroscopic guidance for vascular access minimizes the risk of access failure and vascular complications, such as vessel perforation and vessel trauma. To further minimize the risk of perforation or dissection, the FlowTriever system will only be used in the main and lobar pulmonary artery branches and will not be attempted in smaller vessels (< 6 mm diameter).

Possible complications may occur during an interventional procedure. These complications include but are not limited to the following:

- Access site hematoma
- Adverse reaction to device materials
- Aneurysm
- Angina
- Air embolism
- Arrhythmias
- Arteriovenous fistula
- Bradycardia
- Cardiac tamponade
- Cardiogenic shock
- Death
- Distal embolism
- Drug reaction to contrast, thrombolytic or anticoagulation
- Embolism
- Fever
- Foreign body embolism
- Fistulation
- General discomfort, tenderness or pain
- Hemoglobinuria
- Hemolysis
- Hemoptysis
- Hypo/Hypertension
- Hypoxemia
- Infection
- Inflammatory response
- Myocardial infarction
- Nausea/vomiting
- Neurological deficit
- Organ impairment
- Pericardial effusion
- Peripheral nerve damage
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary infarction
- Renal failure
- Respiratory failure
- Retroperitoneal hemorrhage
- Right bundle branch block
- Stroke/transient ischemic attack
- Tachycardia
- Valvular disruption/injury
- Vascular spasm
- Vasovagal reaction
- Ventricular rupture
- Vessel dissection/perforation
- Vessel stenosis

6.2 Potential Risks from CT

- High radiation exposure in cases of repeated examinations; possible increase in risk of cancer
- Rise in serum creatinine levels
- Nephropathy

6.3 Risk Mitigation

Awareness of the potential for serious complications is essential to the safe use of the FlowTriever System. Additional risk mitigations include:

- Use of study sites that have sufficient expertise and resources to manage adverse events and provide appropriate additional therapies if needed
- Specialized/Experienced Investigators with appropriate training
- Careful patient selection based on study inclusion/exclusion criteria
- Informed consent process
- Timely reporting of adverse events
- Independent Clinical Events Committee
- Independent Data and Safety Monitoring Board

6.4 Benefits

There are no guaranteed benefits from participation in this study. In general, endovascular interventions (e.g., catheterization) are well-established in medical practice and are substantiated to minimize the risks to patients of: anesthesia complications, wound healing, bleeding and infection. The tissue and other bodily

trauma associated with open surgical procedures are much greater compared to minimally invasive techniques. As more tissue is exposed to air in an open surgical procedure, the risk of infection is greatly increased. As such, the medical option of an open surgical procedure is far inferior to the safer, less traumatic, endovascular procedure. The reduced tissue trauma may benefit the Subject by reducing pain as well as faster recovery time. By minimizing tissue manipulation, the FlowTriever System may also benefit medical practice by reducing the operative time offering potential cost savings.

Systemic administration of thrombolytic agents carries significant risk of bleeding, especially when predisposing conditions or comorbidities exist. FlowTriever intervention has an immediate impact on the vascular obstruction. The FlowTriever intervention is not reliant on the use of thrombolytics and therefore the FLARE trial does *not* exclude patients with recent surgeries nor those at a high risk of catastrophic bleeding.

Information gained from the conduct of this Study may be of benefit to other persons with the same medical condition.

6.5 Warnings

The following warnings are labeled for the FlowTriever System:

- Intended for single use only. Do not re-sterilize or reuse this device
- Should be used in conjunction with fluoroscopic guidance and proper anticoagulation agents.
- Examine the catheter before use to verify it is not damaged.
- Use before the “Use By” date specified on the product packaging.
- Do not exceed the maximum infusion pressure. Excess pressure may result in catheter damage or patient injury.
- Avoid using excessive force to advance or retract against resistance. If excessive resistance occurs, retract and collapse the distal disks into the catheter and remove the device. Excessive force against resistance may result in damage to the device or vessel perforation.
- Exercise caution when placing guidewire distal to the treatment site due to the risk of vessel perforation.
- Do not treat vessels smaller than 6 mm diameter.
- In the event of patient deterioration, remove FlowTriever Catheter/Aspiration Guide Catheter and assess situation.
- Ensure that FlowTriever wireform disks are withdrawn into Aspiration Guide Catheter prior to removal from patient to avoid vascular damage.

6.6 Alternative Treatment

There is no obligation for a Subject to take part in this Study. Alternative treatments may include:

- **Medical Therapy**: Includes the use of anticoagulation therapy alone and/or systemic thrombolytics.
- **Catheter-Directed Therapy**: Pharmacomechanical delivery of intrapulmonary thrombolytics, with or without ultrasound assistance.
- **Mechanical Thrombectomy Device**: An alternate FDA cleared catheter-based device designed to remove or dissolve blood clot.
- **Surgical Embolectomy**: Surgical removal of the pulmonary embolism.

The Investigator will inform the Subject as to what alternative methods are suitable and available.

7. ADVERSE EVENTS

7.1 Safety Monitoring

Subject safety is of the utmost importance. Each Investigator has the responsibility for the safety of the Subjects under his/her care. For purposes of understanding data and relevant confounders, assessment of clinical outcomes and/or SAEs possibly related or probably related to the condition or complications thereof will be recorded.

7.2 Complications

Complications should be reported on a per-Subject basis and categorized according to the SIR Classification of Complications by Outcome as follows:

- Minor Complications
  - No therapy, no consequence
  - Nominal therapy, no consequence (includes overnight admission for observation only)
- Major Complications
  - Require therapy, minor hospitalization (≤ 48 hours)
  - Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours)
  - Permanent adverse sequelae
  - Death

7.3 Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users or other persons, whether or not related to the investigational medical device. (ISO 14155:2011 3.2)

NOTE 1: This definition includes events related to the investigational medical device.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Disease signs and symptoms that existed prior to study participation are not considered AEs unless the condition recurs after the Subject has recovered from pre-existing condition, or the condition worsens in intensity or frequency during the study.

Collection of adverse events will start after the time that informed consent form is signed. Adverse events will be monitored throughout the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor or its designated representative. All reported AEs will be documented on the appropriate CRF and will include the event description (sign, symptom, or diagnosis), onset, resolution, seriousness, severity, cause and action taken. The Investigator must assess causality and severity for all AEs.

All AEs will be followed by the Investigator until resolution or until the 30-day follow-up visit.

7.4 Adverse Device Event (ADE)

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. (ISO 14155:2011 3.1)

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition also includes any event from use error or from intentional misuse of the investigational medical device. (ISO 14155:2011 3.1)

7.5 Serious Adverse Event (SAE)

An SAE is an AE that:

- Led to death
- Led to serious deterioration in the health of the Subject, that resulted in
    - a life-threatening illness or injury, OR
    - a permanent impairment of a body structure or a body function, OR
    - in-patient or prolonged hospitalization, OR
    - medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Note: Examples of such medical events include but are not limited to: allergic bronchospasm requiring intensive treatment in an ED or at home, blood dyscrasia or convulsions that do not result in Subject hospitalization, or the development of drug dependency or drug abuse. (ISO 14155:2011 3.37)

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

7.6 Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 3.36)

7.7 Anticipated Serious Adverse Device Effect (ASADE)

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)

7.8 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) means 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 study protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects. (21 CFR 812.3 (s))

Similarly, according to ISO 14155:2011, an unanticipated serious adverse device effect (USADE) is a serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011 3.42)

7.9 Event Severity

The severity of an adverse event is a qualitative judgment of the degree of intensity, as determined by the Investigator or as reported by the Subject. The severity of the adverse event should be evaluated according to the following scale:

- **Mild:** No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- **Moderate:** Some limitation of usual activities or specific therapy is required.
- **Severe:** Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

The assessment of severity should be made independent of the relationship to the investigational device and therapy or the seriousness of the event.

7.10 Event Relationship

The Investigator will categorize the relationship of the adverse event as follows:

- **Study Disease-related:** Event is clearly attributable to underlying disease state with no temporal relationship to the device, treatment or medication.
- **Concomitant Disease-related:** Event is attributable to disease other than the study disease with no temporal relationship to the device, treatment or medication.
- **Procedure-related:** Event has a strong temporal relationship to the procedure or treatment with the device deployment or any user handling.
- **Device-related:** Event has a strong temporal relationship to the device and alternative etiology is less likely.
  - Primary Study Device: FlowTriever Catheter, Aspiration Guide Catheter or Retraction Aspirator
  - Ancillary Device: Any device other than FlowTriever System, such as a guidewire, pressure monitoring catheter, or infusion catheter
  - Device Unknown: Device related but unable to attribute a specific device relationship
- **tPA-related:** Event is clearly attributable to tPA medication with no temporal relationship to the device or treatment.
- **Unrelated to the above categories**: Event has no relationship to any of the ab ove mentioned categories.
- **Unknown:** Event relationship is not known or unsure.

7.11 Adverse Event Reporting

Subjects will be carefully monitored during the study for possible adverse events. Any adverse event that occurs after the time of informed consent and a study specific exam or procedure through end of study participation will be fully evaluated by the Investigator. Appropriate treatment will be initiated and the study follow-up will continue as completely as possible.

The Investigator will document all observations and clinical findings of adverse events, including the nature, severity and relationship, on the appropriate CRFs. The Investigator is required to report all SAEs and UADEs/USADEs to the Sponsor within 24 hours after first learning of the event. The Investigator must follow their local IRB policy for SAE/UADE/USADE reporting.

The Investigator will send the completed SAE Report form and all available supporting documentation to the Sponsor. The Sponsor contact information is as follows:

Natasha Behrmann
Director, Clinical Research
Inari Medical, Inc.
9272 Jeronimo Road, Suite 124
Irvine, CA 92618
Direct: 949.600.8433 x118
Email: natashab@inarimedical.com

As additional information becomes available, the Investigator will record all adverse events (serious and non-serious), adverse device effects (anticipated and unanticipated), device malfunction, product complaints or other reportable safety events on the appropriate CRFs. Copies of source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports and patient summaries etc. are required for evaluation of the event. Copies of such documentation shall be obtained from the Investigator (de-identified as to the Subjects' identity) and provided to the Sponsor.

Regarding Subject deaths, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor when available. Any other source documents related to the death should also be provided to the Sponsor. In the event that no source documents are available, the PI is required to describe the circumstances of the Subject's death in a letter, e-mail or other written communication.

UADEs/USADEs have special reporting requirements. The Sponsor will notify the sites, IRBs and regulatory bodies as per specific regulations.

In addition, the Sponsor will comply with Medical Device Reporting (MDR) requirements.

8. STUDY ADVISORS

The Study will utilize National Principal Investigators (NPIs) as advisors to provide study leadership and guidance. The NPIs will oversee all clinical study activities including protocol development or any changes that may be desired or required during the conduct of the Study. The NPIs will also assist in obtaining evaluation and feedback from peers throughout the course of the Study. The Study will have two NPIs who will oversee all clinical study activities.

9. MEASURES TO AVOID AND MINIMIZE BIAS

Several measures have been implemented to avoid and minimize bias, namely, establishment of a Clinical Events Committee, Data and Safety Monitoring Board, and Imaging Core Lab.

9.1 Clinical Events Committee (CEC)

A Clinical Events Committee (CEC), an independent group of individuals knowledgeable in the appropriate medical specialties pertinent to the disease state being evaluated in this Study, will be responsible for the review and validation of all endpoint-related adverse events that occur over the course of the Study and the subsequent classification of these events as related to the device or procedure. The CEC will review these adverse events and adjudicate them; they can request additional source documentation and any imaging obtained in support of the adverse event to assist with adjudication. The CEC adjudicated results will overrule Investigator assessments.

9.2 Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be an independent group that will serve as a data monitoring committee to the Sponsor of this Study. The DSMB will be comprised of representatives from multiple disciplines including but not limited to pulmonology, interventional radiology/cardiology, and biostatistics/epidemiology. In the safety monitoring role, the DSMB shall provide recommendations to the Sponsor regarding stopping/continuing enrollment in the Study. The DSMB will establish proposed safety monitoring criteria, a mission statement and operating procedures.

9.3 Imaging Core Laboratory

Syntactx is the Core Lab designated for the FLARE Clinical Study. The objectives of the Core Lab are to provide an unbiased assessment of the RV/LV ratio.

For each Subject treated with the FlowTriever System, the investigational site will be instructed to follow a standard procedure developed by the Core Lab for obtaining study specific angiographic images. CT imaging studies will be obtained at baseline and 48 hours (± 8 hours) follow-up.

Images will be sent directly from the site to the Core Lab. Core Lab definitions and procedures will be documented in the Core Lab Manual of Operations (MOP).

10. STATISTICAL DESIGN AND METHODS

10.1 Analysis Populations

The populations are defined as follows:

- The Intent-To-Treat (ITT) is defined as all patients who met the inclusion/exclusion criteria and in whom the Amplatz SS (or equivalent guidewire) is attempted; enrollment occurs when the Amplatz SS (or equivalent guidewire) enters the venous system.
- The modified Intent-To-Treat (mITT) population is defined as all Subjects in the ITT population who have no thrombolytics administered during the operative procedure. These subjects comprise the "Enrollment Population."
- The Full Analysis Set (FAS) population is defined as all mITT Subjects that have successfully received the procedure and have completed the 48 hour post-procedure follow-up (or are discharged, whichever comes first) per the study protocol.
- The Completed Cases (CC) population is defined as all mITT Subjects that have successfully received the procedure and have completed all follow-up visits.

10.2 Primary Endpoints - Safety

The primary safety endpoint is a composite of device-related death within 48 hours of procedure; major bleeding within 48 hours; and treatment-related adverse events, including: a) clinical deterioration, b) pulmonary vascular injury, and c) cardiac injury within 48 hours of the procedure. The null and alternative hypotheses are provided below.

$$H_0: PT \geq PG_2 \text{ versus } H_a: PT < PG_2$$

where PT is the percentage of patients that experience the composite endpoint and PG_2 is a performance goal derived in the section below. This hypothesis test will determine if the observed percentage of patients experiencing the composite AE is less than a performance goal derived from patients in studies who received a heparin control to an active pharmaceutical drug.

10.3 Secondary Endpoints - Safety

The study's secondary safety endpoints are:

- Device-related death within 48 hours (± 8 hours) of the procedure
- Major bleeding within 48 hours (± 8 hours) of the procedure
- Clinical deterioration within 48 hours (± 8 hours) of the procedure
- Pulmonary vascular injury within 48 hours (± 8 hours) of the procedure
- Cardiac injury within 48 hours (± 8 hours) of the procedure
- Mortality due to any cause within 30 days (± 3 days) of the procedure
- Device-related serious adverse events within 30 days (± 3 days) of the procedure
- Symptomatic recurrence of embolism within 30 days (± 3 days) of the procedure

10.4 Primary Endpoint - Effectiveness

The primary effectiveness endpoint of this study is the RV/LV ratio change from baseline to 48 hours (± 8 hours, or discharge; whichever occurs first) as assessed by Computed Tomography Angiography (CTA). The null and alternative hypotheses for this endpoint are presented below.

$$H_0: \mu_{Td} \leq PG_1 \text{ versus } H_a: \mu_{Td} > PG_1$$

where μTd is the mean difference in the RV/LV ratio treated from baseline to 48 hours (or discharge whichever comes sooner) and PG_1 is a performance goal derived for this endpoint in the section below. This hypothesis will determine if the mean change from baseline in RV/LV ratio (taken as a positive number) is greater than a performance goal derived from studies in the group in which heparin was a control to an active pharmaceutical drug.

11. ETHICAL CONDUCT OF STUDY

This Study is to be conducted in accordance with U.S. and international standards for GCP, as described in the following documents:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- Directive 91/507/EEC, the Rules Governing Medicinal Products in the European Community
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations)
- The Declaration of Helsinki concerning medical research in humans (59th WMA General Assembly, Seoul, October 2008)

The Investigator agrees by participating in the conduct of this protocol to adhere to the instructions and procedures described and to adhere to the principals of GCP.

12. SITE SELECTION & TRAINING

12.1 Site Selection

The Sponsor or designee will assess each potential site to ensure the Investigator and his/her staff has the facilities and expertise required for the Study. Sites will be selected based upon a site assessment, appropriate facilities, and the qualifications of the Investigator(s). Individual Investigators will be evaluated by the Sponsor based on experience with the intended procedures and ability to conduct the Study according to the Clinical Protocol. Investigators and sites will be selected based upon the following factors:

- Previous experience with clinical research and mechanical thrombectomy procedures
- Experience in conducting clinical studies
- Willingness to observe confidentiality at all times
- Currently treating Subjects who meet the inclusion/exclusion criteria
- Ability to enroll an adequate number of Subjects
- Ability to perform required clinical testing, including angiography and CT
- Ability and willingness to provide the Sponsor's representatives access to the hospital records, study files, and Subject files as they pertain to the study
- Willingness to participate, including compliance with all aspects of the study
- Adequate staffing to conduct the study. This includes:
    - Principal Investigator (PI): Responsible for overall clinical management of Subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each Subject participating in the study. Ensures compliance with the protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs CRFs indicating documents are accurate and complete.
    - Sub-Investigator (Sub-I)**:** Responsible for study activities in coordination with PI and in accordance to the Clinical Protocol. Assume the responsibility of the PI should the PI resign from the study. A site is not required to have a sub-Investigator.

- Study Coordinator (SC)**:** Assists PI with study activities as delegated by the PI, including tracking Subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing CRFs to the Sponsor in a timely manner.

12.2 Site Training

Each investigational site will be trained to the Clinical Protocol. Investigator/site personnel will undergo training prior to performing any Study-related procedures. All training must be documented. Training to the Clinical Protocol will include the following topics:

- Study objectives and protocol review
- Responsibilities and obligations of the Investigator and delegation of authority for Study-related tasks
- Informed Consent process, including any relevant IRB/Confidentiality/HIPAA requirements
- IDE Instructions for Use, device accountability and product malfunction reporting
- Case Report Forms and completion instructions and image submission procedure
- Documentation of protocol deviations
- Adverse/Serious Adverse Event reporting
- General guidelines for good clinical practices
- Study documentation requirements (essential documents)

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the Clinical Protocol, as appropriate.

12.3 Study Initiation

The Sponsor or designee will conduct a training session with the Investigator/site personnel as described above. Prior to enrolling Subjects at an investigational site, the following documentation must be provided to the Sponsor:

- IRB approval for the Clinical Protocol
- IRB and Sponsor approved study-specific Informed Consent Form for the study
- Investigator(s') curriculum vitae (CV)
- Financial Disclosure(s) for the PI and Sub-I(s)
- Signed Confidentiality Disclosure Agreement (CDA)
- Signed Clinical Study Agreement (CSA), and if applicable, Sub-I Agreement(s)
- Training Log documentation to verify the appropriate study staff has been trained on the protocol, device, CRFs and study conduct

13. INSTITUTIONAL REVIEW BOARDS

The Sponsor and/or Investigator must submit this protocol to the appropriate IRB. The informed consent form (ICF) to be used by the Investigator must be reviewed and approved by the Sponsor prior to submission to the IRB for approval. The Sponsor must also approve all IRB requested changes to the ICF prior to finalization.

The IRB and/or Investigator is required to provide a copy of the IRB approval to the Sponsor. The Study (study number, protocol title, and version) documents reviewed (e.g., protocol, ICF, etc.) and the date of the review should be clearly stated on the written IRB approval. The Study will not start and Subjects will not be enrolled until a copy of written and dated approval has been received by the Sponsor.

Any amendment or modification to the protocol should be sent to the IRB. The IRB should also be informed of any event likely to affect the safety of Subjects or the conduct of the Study.

14. INFORMED CONSENT FORM (ICF)

Written informed consent will be obtained from all potential study participants via the current approved Informed Consent Form (ICF). The Study will be explained to the prospective patient by the Investigator or designee. The nature of the device and treatment options will be explained together with the potential hazards of the procedure, including any possible adverse events. The patient and the Investigator will sign and date the ICF. One copy of the ICF will be retained with the patient's record and a copy will be provided to the Subject.

15. CASE REPORT FORMS (CRF)

An Electronic Data Capture (EDC) system will be used to document study data. Electronic Case Report Forms (CRFs) will be developed to collect all Study-related information and data points. Inari Medical will provide CRFs for each Subject enrolled in the Study to each investigational site. The appropriate CRF will be completed after each Study visit. EDC and CRF completion guidelines and training will be provided to the sites.

16. STUDY MONITORING

Inari Medical (the "Sponsor") is responsible for ensuring that adequate monitoring at each site is completed to ensure the rights and safety of Subjects is protected, and the quality and integrity of the data collected and submitted is in compliance with Title 21 CFR Part 812 Subpart C. Appropriately trained personnel (Monitors) appointed by the Sponsor will conduct monitoring visits according to the clinical Monitoring Plan. Monitors will consist of Sponsor clinical staff and/or qualified contract services (e.g., CRO) appointed by the Sponsor.

Study Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate Subject enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed Investigator Agreement, and compliance with IRB conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the Investigator/site staff is cause for the Sponsor to put the Investigator/site staff on probation or withdraw the Investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

All Subject treatment, follow-up visits and phone conversations/interviews will be fully documented either on the source document or in the Subject's medical records. Information entered into the CRFs will be verified against the source documents and Subject's medical records according to the monitoring plan. Additional Subject medical record review may be required for AE adjudication. Source documents may be de-identified and photocopied, if necessary. The Monitor will also check the Investigator Site File (ISF) to ensure that all Study-related documents are current.

16.1 Direct Access to Source Documents

By participating in this research study, the Investigator agrees to permit monitoring and auditing by the Sponsor and/or its designee(s) and inspection by applicable regulatory authorities. The Investigator also agrees to allow the Sponsor's Monitors/Auditors/FDA Investigators to have direct access to (and copying of, if appropriate) his/her research-related study records (e.g., medical records, source documentation, etc.) for review to ensure study integrity and data validation.

If an Investigator is notified of a pending investigation by a regulatory agency, standards organization, or other similar organization, he/she will inform the Sponsor promptly.

16.2 Confidentiality of Protected Health Information

Protected health information (PHI) of study Subjects will be kept as confidential as possible in accordance with the Health Insurance and Portability and Accountability Act of 1996 (HIPAA) and any other data privacy laws, as applicable. However, complete confidentiality cannot be assured.

16.3 Compliance to the Protocol

The Sponsor intends to monitor all research sites. Monitoring will be performed using qualified, trained representatives. Except for a change that is intended to eliminate an immediate hazard to a Subject, the Clinical Protocol will be followed as described. Any protocol deviation must be documented in CRFs and reported to the Sponsor in a timely manner. Reporting deviations to the IRB will be determined by individual IRB reporting requirements.

A copy of the written approval from the IRB must be provided to the Sponsor prior to initiation of the Study. Any amendment(s) that affect the informed consent require a revised Sponsor and IRB-approved informed consent before changes in study procedures are implemented. These requirements should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor to preserve the safety of any Subjects included in the Study, as necessary. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the Sponsor should be notified immediately.

The Investigator must provide reports on the progress, completion, termination or discontinuation of the Study to the IRB(s) at appropriate intervals as designated by the Sponsor and per IRB requirements.

16.4 On Site Audits

Representatives of the Sponsor may visit the study site(s) to conduct an audit of the Study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy will be respected.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of the Study in support of a regulatory submission. The Investigator agrees to immediately notify the Sponsor if he/she has been contacted by a regulatory agency concerning an upcoming inspection.

17. RECORD STORAGE AND RETENTION

The Investigator shall maintain all study documentation in his/her possession and/or control and institute measures to prevent accidental or premature destruction any data and/or documents related to the Study. After discontinuation of the Study, the Investigator shall retain study documentation for a minimum of three (3) years or in accordance with GCP.

18. DATA OWNERSHIP

Rights, duties, and obligations regarding ownership of any ideas, concepts, inventions, or results, whether patentable or not, shall be in accordance with the terms and conditions set forth in the Clinical Agreement by and between the Institution and Sponsor unless otherwise expressly set forth in the Clinical Agreement, the Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this Study. The Sponsor reserves the right to use the data from the database in the present Study.

19. CONFIDENTIALITY

The Investigator shall consider all information, results, discoveries; records accumulated, acquired, or deduced in the course of the Study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, records to any third party without the Sponsor's prior written consent. IRB members have the same obligation of confidentiality.

20. PUBLICATION POLICY

Typically, a Publication Committee will be responsible for the primary publication and/or presentation arising from the Study once all study sites are closed. No other publication or presentations of the results of the Study are allowed before the primary publication and/or presentation is released. All publications and/or presentations are Subject to additional requirements more specifically addressed within each institution's research-study agreement.

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