FlowTriever Pulmonary Embolectomy Clinical Study-FlowTriever2 (FLARE-FT2)

Device
FlowTriever2 Catheter

Protocol Number
21-001

Version
4.0
11-Aug-2023

Sponsor
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PROTOCOL SYNOPSIS

Protocol Number	21-001
Study Title	**FlowTriever Pulmonary Embolectomy Clinical Study-FlowTriever2 (FLARE-FT2)**
Study Device	FlowTriever2 Catheter
Regulatory Status	Under US Regulations 510(k) number K201541, the FlowTriever2 Catheter is indicated for: • The non-surgical removal of emboli and thrombi from peripheral blood vessels. • Injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel. The FlowTriever2 Catheter is intended for use in the peripheral vasculature.
Sponsor	Inari Medical 6001 Oak Canyon Road, Suite 100 Irvine, CA 92618 USA
Study Objective	The primary study objective is to evaluate the safety and effectiveness of the FlowTriever2 Catheter for the treatment of pulmonary embolism (PE).
Study Population	This study will enroll 50 subjects
Number of Sites	Five to twelve (5-12) sites will participate in the study
Study Design	The FLARE-FT2 confirmatory study is a prospective, single-arm, multicenter study of the FlowTriever2 Catheter

Safety Endpoints	The study's primary safety endpoint is incidence of adjudicated Serious Adverse Events (SAE), which is a composite of:
	• Mortality through 48 hours after the index procedure related to FlowTriever2 Catheter
	• Major bleeding through 48 hours after the index procedure related to FlowTriever2 Catheter
	• Intra-procedural device or procedure-related adverse events, including:
	  ○ Clinical deterioration defined by hemodynamic or respiratory worsening
	  ○ Pulmonary vascular injury related to FlowTriever2 Catheter
	  ○ Cardiac injury related to FlowTriever2 Catheter
	
	The study's secondary safety endpoints will include incidence of adjudicated Adverse events, including:
	• All-cause mortality through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
	• Device-related SAE through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
	• Symptomatic recurrence of pulmonary embolism through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)

Effectiveness Endpoints	The study's primary effectiveness endpoint is the change in mean pulmonary arterial pressure from baseline pre-procedure and post-procedure The study's secondary effectiveness endpoints are: • The change in systolic pulmonary arterial pressure from baseline pre-procedure to post-procedure • Incidence of adjunctive thrombolytic use
Inclusion Criteria	Patients must meet each of the following criteria to be included in the study: 1. Age ≥ 18 and ≤ 75 years 2. Clinical signs and symptoms 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) 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/or clinical judgment. 9. FlowTriever2 Catheter enters the vasculature
Exclusion Criteria	Patients will be excluded from the study for any of the following 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
Follow-up Schedule	Subjects will have follow-up evaluations after the index procedure at: • 48 hours (+ 36 hours or at time of discharge, whichever comes first) • 30 days (-5 to +15 days)
Safety Monitoring	Safety events will be adjudicated by an external Clinical Events Committee (CEC).

ABBREVIATIONS

Abbreviation	Term
AC	Anticoagulation
ADE	Adverse Device Effect
AE	Adverse event
AHA	American Heart Association
BARC	Bleeding Academic Research Consortium
BNP	B-type natriuretic peptide
CDT	Catheter-directed thrombolysis
CRO	Contract research organization
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
DD	Device Deficiency
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
ECMO	Extracorporeal membrane oxygenation
eCRFs	Electronic case report forms
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FLARE	FlowTriever Clinical Embolectomy Clinical Study
FLASH	FlowTriever All-Comer Registry for Patient Safety and Hemodynamics
FT	FlowTriever
H-FABP	Heart type fatty acid binding protein
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-induced thrombocytopenia
ICF	Informed consent form
IFU	Instructions for use
INR	International normalized ratio
IRB	Institutional review board
LV	Left ventricle
MAE	Major adverse event
mMRC	Modified Medical Research Council Dyspnea Scale
NT-proBNP	N-terminal pro B-type natriuretic peptide
PAPi	Pulmonary Artery Pulsatility Index
PE	Pulmonary embolism
PERT	Pulmonary Embolism Response Team
PESI	Pulmonary Embolism Severity Index
PHI	Protected Health Information
PMT	Percutaneous mechanical thrombectomy

Abbreviation	Term
Post-PES	Post-pulmonary embolism syndrome
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
RVSWI	Right ventricular stroke work index
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SIV	Site initiation visit
sPESI	Simplified Pulmonary Embolism Severity Index
TLF	Tables, lists, and figures
TNK	Tenecteplase
TPVR	Total pulmonary vascular resistance
TTE	Transthoracic echocardiogram
SVI	Stroke volume index
UAT	Ultrasound-accelerated thrombolysis
USADE	Unanticipated Serious Adverse Device Effect
VTE	Venous thromboembolism

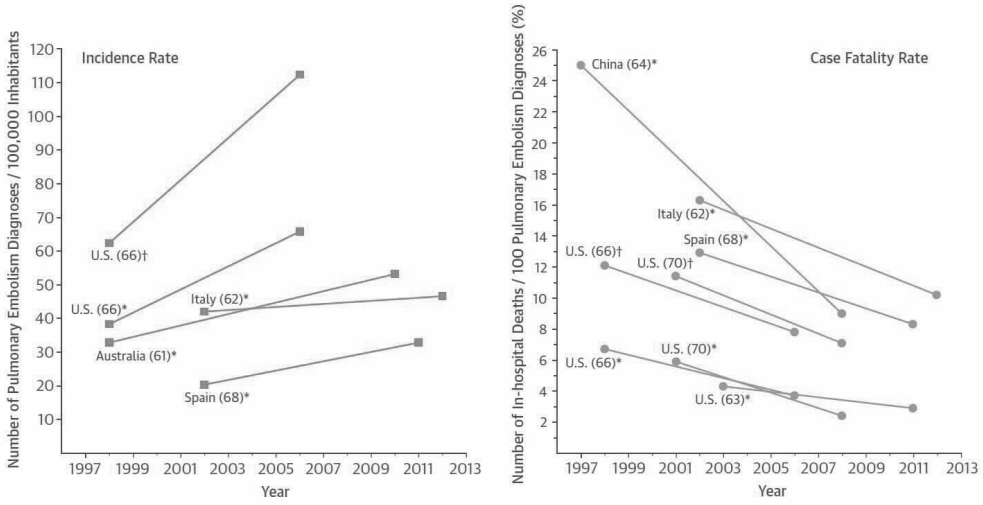
1 INTRODUCTION AND BACKGROUND

Pulmonary embolism (PE) comprises one element of venous thromboembolism (VTE), an entity that includes DVT and PE. PE occurs when venous thrombi travel from the peripheral veins, through the heart, and lodge in the pulmonary arterial circulation. The emboli arise from peripheral locations, usually the large deep veins of the leg and pelvis, but sometimes from the large veins of the upper extremities. While small PE may remain asymptomatic and go unnoticed, larger emboli may result in significant pulmonary artery obstruction, right heart decompensation, and mortality. Some PE are immediately fatal, particularly large PE that lodge at the bifurcation of the main pulmonary artery into its right and left branches; the so-called “saddle embolus.” On the other hand, PE may occur in a repeated fashion, often over months or even years, insidiously obliterating the pulmonary arterial outflow to culminate in debilitating pulmonary hypertension and the syndrome known as chronic thromboembolic pulmonary hypertension, or “CTEPH.”

1.1 INCIDENCE AND FATALITY RATE FOR PULMONARY EMBOLISM

Estimates of VTE incidence range from 75 and 269 cases per 100,000 population.[1] While the actual incidence of reported VTE differs by global geography, the VTE increases with age, rising to 700 cases per 100,000 population in patients aged 70 and older. PE itself occurs at differing rates in different countries; at least as reported. For instance, the rate of PE as a primary diagnosis of hospitalization in the United States is among the highest of the countries (**Figure 1**).[2] The rate of PE in the US rose from approximately 40 to approximately 60 per 100,000 population between 1998 and 2006. These findings are likely attributable to an increase in the use of computed tomographic pulmonary angiography (CTPA) over the years of study. At the same time, the case fatality rate dropped from approximately 7% to 4% over the same years in the US. By contrast, the fatality rate in China decreased from 25% in 1997 to less than 10% in 2008; a change likely accounted for by an increase in the rate of diagnosis of smaller PE and, possibly, improved treatment after recognition.[2]

Figure 1. Incidence and Case-Fatality Rate for Pulmonary Embolism by Country
Incidence is displayed on the left and fatality rate on the right. From Konstantinides et al.[2]



*PE as the primary diagnosis
†PE as any diagnosis, primary or secondary, during hospitalization

1.2 DIAGNOSIS OF PULMONARY EMBOLISM

Traditionally, clinical prediction rules have been utilized to guide appropriate patients toward imaging analyses. Patients can be subcategorized using, for instance, the Geneva or Wells prediction models. When using a 3-level classification, the probability of confirmed PE is 10%, 30%, and 65% in the low, intermediate, and high-probability categories.[3] Patients in the latter two categories should undergo imaging such as CTPA, while patients in the low-probability category should undergo D-dimer testing.[4] The sensitivity of the D-dimer test is high, but the specificity is low.[5] For this reason, a negative test safely excludes PE, but further imaging is necessary when the D-dimer test is positive.

CTPA imaging is performed in most centers today.[6] Except for the evaluation of CTEPH, CTPA has replaced V/Q scan as the imaging test of choice. The accuracy of CTPA, however, is not uniform. Respiratory motion, reconstruction artifacts (e.g., "stair-step" artifact), or beam-hardening artifacts from high-density structures such as a contrast-filled superior vena cava may be responsible for errors.[7] As well, CTPA can over-diagnose small, subsegmental emboli of little clinical consequence.[8] Irrespective of the clinical implications of small, subsegmental emboli on CTPA, these can be false-positive findings, and duplex ultrasonography of the lower extremity veins can be helpful in these cases.[7, 9]

1.3 PULMONARY EMBOLISM TREATMENT & RISK STRATIFICATION

The treatment of PE depends on its severity. The severity is defined by the risk of mortality; a risk tightly correlated with the hemodynamic consequences of the embolism, namely, acute right ventricular dysfunction. Right ventricular (RV) dysfunction is the principal determinant of a patient's clinical course.[4, 10] The risk of hemodynamic compromise is related to the interplay between the size of the embolus and the baseline cardiorespiratory state of the patient. For instance, a PE of moderate size in a healthy patient may be unassociated with hemodynamic compromise while the same embolus in an elderly patient with preexisting cardiac disease may result in fulminant right heart decompensation and mortality. In this regard, the severity of pulmonary embolism is only partially represented by the presenting hemodynamic condition of the patient, and baseline comorbidities should be considered.

A variety of indices have been used in the prediction of outcome after PE. One, the Pulmonary Embolism Severity Index (PESI), has been well-validated.[11] PESI risk strata I and II patients have a low risk of 30-day mortality. A simplified PESI score, sPESI, was also developed and validated.[12-14] Patients with a sPESI score of 0 have a very low risk of adverse early outcome. Adding the combination of a negative cardiac troponin further increases the negative predictive value of the scores.[13] It should be noted, however, that the PESI and sPESI risk stratifications were developed as epidemiologic tools and were not designed to guide the management of PE.

1.4 CLASSIFICATION SCHEMA FOR PULMONARY EMBOLISM

American Heart Association. The 2019 American Heart Association (AHA) Scientific Statement on Pulmonary Embolism reiterates the established classification of PE into three traditional categories utilized in the literature: massive, submassive, and low-risk.[15] The AHA document included definitions for each category. Massive PE is defined as hypotension with systolic blood pressure <90 mm Hg lasting more than 15 minutes or requiring ionotropic support, or persistent bradycardia to <40 bpm with shock. Submassive PE is defined as PE without hypotension, and either RV dysfunction or myocardial necrosis. RV dysfunction is identified when at least one of the following is present: RV/LV ratio >0.9, RV systolic dysfunction on echocardiography, elevation of BNP >90 pg/mL, elevation on N-terminal pro-BNP >500 pg/mL, electrocardiographic changes of new right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion. Myocardial necrosis is defined by elevation of troponin I >0.4 mg/mL or troponin T >0.1 ng/mL. Low-risk PE is a PE that falls short of the criteria for submassive PE; in other words, a PE without RV dysfunction or elevation of biomarkers.

While these categories correlate roughly with the risk of mortality, the AHA document stresses that concurrent comorbidities must be accounted for in the prediction of mortality. For instance, a non-massive PE in a patient with preexisting chronic obstructive lung disease or congestive heart failure. That said, the short-term mortality approximates 25-50% for massive PE, 1% for low-risk PE, and somewhere in between for submassive PE.

European Society of Cardiology. The 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) specified combinations of clinical presentation, imaging, biomarkers to better risk-classify patients (**Figure 2**).[4] The ESC risk stratification scheme utilizes four criteria to classify PE patients into four grades of mortality risk; high, intermediate-high, intermediate-low, and low.

Figure 2: European Society of Cardiology Risk Stratification
From Konstantinides et al[4]

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

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BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.
[a]One of the following clinical presentations (*Table 4*): cardiac arrest, obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).
[b]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are graphically presented in *Figure 3*, and their prognostic value is summarized in Supplementary Data *Table 3*.
[c]Elevation of further laboratory biomarkers, such as NT-proBNP ≥600 ng/L, H-FABP ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomized controlled trials.
[d]Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.
[e]Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I–II or an sPESI of 0.[234] Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

High-risk patients include those with all four criteria positive. These patients present in shock, PESI scores III or greater or sPESI scores greater than 0, RV dysfunction on imaging, and positive cardiac biomarkers indicative of myocardial necrosis. An intermediate-risk category is defined by the ESC guidelines, analogous to the submassive category in the literature. The intermediate-risk subgroup is divided into intermediate high-risk and intermediate low-risk subcategories, depending on whether both RV dysfunction and positive cardiac biomarkers are present (intermediate high-risk) or only one of the two are present (intermediate low-risk). The last category is the low-risk group and is similar to the AHA low-risk category. These patients present without hemodynamic compromise, have low PESI/sPESI scores, and normal imaging or laboratory assessments when they are performed.

While validation of the ESC risk scale has been studied in only one large randomized clinical trial, the scale is one method on which to guide treatment options.[16]

1.5 RISK-BASED TREATMENT OF PULMONARY EMBOLISM

High-risk (massive) PE is defined as when a patient presents with shock from acute right ventricular decompensation. Early, definitive treatment is necessary to prevent the rapid, downhill spiral that culminates in a patient's demise. Anticoagulation with the removal of the occluding pulmonary artery thrombus is indicated, either by pharmacologic, pharmacomechanical, or mechanical means. In certain cases, open surgical pulmonary embolectomy and even extracorporeal membrane oxygenation (ECMO) may be necessary. Fortunately, high-risk pulmonary embolism occurs in less than 10% of cases.[17]

The treatment of high-risk patients is clear; definitive intervention is indicated, up to and including open surgical thrombectomy with or without ECMO.[18] Treatment of low-risk patients is equally clear; anticoagulation alone is all that is necessary; sometimes even on an outpatient basis.[19] More controversial and less well-defined, however, is the treatment of intermediate -risk patients – analogous to the "submassive" category of PE. Currently, there is scant data on which to base therapeutic decisions for the intermediate-risk group. There has been recent enthusiasm for endovascular interventional treatment modalities, however, utilizing catheter-directed thrombolysis, ultrasound-accelerated thrombolysis, or mechanical thrombectomy.[20-25]

1.6 TREATMENT OPTIONS FOR PULMONARY EMBOLISM

1.6.1 ANTICOAGULATION

Anticoagulation is the mainstay of therapy for VTE, directed at decreasing the risk of recurrent embolic events and propagation of existing thrombi. Traditionally, unfractionated heparin followed by 3 months of oral vitamin K antagonists such as warfarin.[26] Longer treatment with oral agents has been controversial, but individualized therapy must balance the risk of hemorrhage and VTE recurrence.[26-28]

Some Investigators have studied low molecular weight heparin in place of unfractionated heparin and warfarin, with satisfactory results.[29] More recently, direct oral anticoagulants (DOACs) have been employed as alternatives to warfarin in the setting of PE.[30-32]

1.6.2 OPEN SURGICAL THROMBOEMBOLECTOMY

Open surgical thromboembolectomy is perhaps the first definitive interventional treatment for PE. Surgical thromboembolectomy was first conceived by Trendelenburg in 1908; while Kirschner was the first to publish the technique in a 1924 report.[33] Open surgical thromboembolectomy can result in rapid, life-saving hemodynamic improvement in patients with significant PE.[18, 34] However, open surgical thromboembolectomy is a major invasive procedure, fraught with complications in unstable patients. The in-hospital mortality rate is more than 25%, although this figure must be considered in the context of alternative therapies in this high-risk group. No randomized trials have been performed to compare the outcome with alternate therapies in similar patient populations. For these reasons, AHA and ESC guidelines suggest that open surgical intervention be reserved for hemodynamically-unstable patients with contraindications to thrombolysis.[4, 15] However, selected indications remain appropriate for open thromboembolectomy; for example, emboli in transit such as within the right heart or a patent foramen ovale. In this regard, the American College of Chest Physicians advocates open surgical intervention for patients who are severely compromised such that mortality is likely to occur before thrombolytic therapies can improve the patient's hemodynamic state.[35]

1.6.3 SYSTEMIC THROMBOLYSIS

While anticoagulation is effective in preventing recurrent PE, it does little to treat existing emboli. Treatment of obstructing pulmonary artery thromboembolism attains relevance in patients with intermediate-risk (submassive) and high-risk (massive) PE, where normalization of right heart function and reduction in mortality is important. Initially, intravenous, systemic thrombolysis was used for PE. After initial anecdotal success with intravenous urokinase for PE reported in 1968 by Sasahara,[36] the landmark randomized clinical trials upon which the initial US Food and Drug Administration (FDA) approval for urokinase was based demonstrated improved outcome with thrombolysis versus anticoagulation for submassive and massive PE.[37-42] The benefits were limited to short-term improvement in cardiac function, but the studies were not powered to detect mortality differences. For the first time, however, removal of pulmonary artery thrombus was demonstrated to be safe, effective, and appeared advantageous compared to anticoagulation alone.

Over the next five decades, intravenous, systemic thrombolysis was demonstrated to be effective in reducing the thrombus load after PE. However, this outcome was achieved at the cost of a five-fold increase in major bleeding, which in some

cases included intracranial hemorrhage.[16, 43, 44] These findings remained unchanged despite newer agents and better periprocedural patient management over the years.

1.6.4 CATHETER DIRECTED THROMBOLYSIS

Noting the hemorrhagic complications associated with systemic thrombolysis for PE, lower-dose, catheter-directed thrombolytic approaches were studied. Catheter-directed thrombolysis for PE was the subject of a meta-analysis published in 2009.[45] In sum, catheter-directed thrombolysis appeared effective and probably safer than the systemic approach. The authors recommended that catheter-directed thrombolysis be considered as a first-line therapy for acute, high-risk PE. However, recent work suggests that even a catheter-directed approach may be associated with significant bleeding complications,[46] although possibly at a lower rate than with systemic treatment.[47]

After demonstrating the possibilities of more effective thrombolysis using ultrasound to accelerate the process, catheter-directed, ultrasound-accelerated thrombolysis (UAT) was studied for submassive and massive PE. Two multicenter, prospective studies were completed, ULTIMA and SEATTLE-II. ULTIMA was a randomized analysis of UAT vs. anticoagulation alone in 59 subjects with submassive PE.[48] UAT was more effective than anticoagulation in normalizing RV function. No intracranial bleeding was observed. The SEATTLE-II trial evaluated differing doses of rt-PA PAT infused over varying timeframes in 150 subjects with submassive and massive PE.[49] These studies concluded that catheter-directed pulmonary artery thrombolysis with rt-PA was safe and effective in the treatment of submassive (intermediate-risk) PE, at least with respect to reductions in RV/LV ratio without intracranial hemorrhage. This conclusion, however, has not been without controversy. A 2017 review of 23 studies and 700 subjects found no difference in the rate of bleeding complications between UAT and standard, catheter-directed thrombolysis, 12% with UAT vs. 10% with standard catheter-directed thrombolysis.[21] The review, however, documented a trend toward improved survival with UAT; 4% vs. 9% in the UAT and standard thrombolytic subjects, respectively.

1.6.5 PERCUTANEOUS PULMONARY ARTERY THROMBOEMBOLECTOMY

Interest in percutaneous pulmonary artery thromboembolectomy flourished on a clinical landscape of effective but relatively slow thrombolytic treatment of PE and risk of thrombolytic-related bleeding complications even when drugs were administered with a lower-dose, catheter-directed approach. Direct pulmonary arterial thromboembolectomy offered the opportunity for rapid removal of thrombus while limiting hemorrhagic, thrombolytic-related complications in those cases where thrombectomy could be utilized as a sole therapy, without pharmacologic thrombolysis.

Historically, percutaneous thromboembolectomy for PE predated catheter-directed thrombolysis. The therapy began with the Greenfield suction catheter, first reported in 1969.[50] After that, other technologies were attempted, including fragmentation of proximal emboli,[51, 52] rheolytic thrombectomy,[53-57] and the use of various pulmonary artery thromboembolectomy devices.[58-60] To the extent that the percutaneous thromboembolectomy devices removed obstructing thromboembolism without the need for thrombolytic therapy, such devices presented the potential for normalization of pulmonary arterial flow without the hemorrhagic complications associated with thrombolytic agents. This is the rationale for FlowTriever as it has the advantages of a percutaneous procedure, with expectation that the bleeding complications of thrombolysis will be minimized.

1.6.6 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.[4, 15, 61]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 manypatients 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.

The FlowTriever System including use of the FlowTriever Catheter 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 anyresidual 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 INVESTIGATIONAL DEVICE

2.1 DEVICE DESCRIPTION

The FlowTriever Retrieval/Aspiration System ("FlowTriever System") is comprised of the FlowTriever2 Catheter and Triever Catheter.

2.2 OPERATING PRINCIPLE

The FlowTriever2 Catheter provides a mechanical means for the retrieval of blood clots, which can then be aspirated using the Triever Catheter, from the vasculature. These features facilitate the reperfusion of vasculature obstructed by acute clot.

The system is designed for use with a 0.035" guidewire. The outside diameter of the Triever Catheter is available in 16 Fr, 20 Fr, and 24 Fr sizes. The outside diameter of the FlowTriever2 Catheter is 17 mm.

An introducer sheath is used to access the appropriate vessel and place the 0.035" guidewire through and past the clot under fluoroscopic guidance. The Triever Catheter with dilator is then introduced over the guidewire and situated on the proximal side of the clot. The tip of the dilator and Triever Catheter contain radiopaque markers for fluoroscopic positioning. The dilator is removed from the Triever Catheter, and the FlowTriever2 Catheter is placed over the guidewire, through the Triever Catheter, and is passed through the clot. The delivery catheter component of the FlowTriever2 Catheter is retracted, causing the self-expanding wireform component of the FlowTriever2 Catheter to expand within the blood vessel distal to, and within, some portion of the clot. Expansion of the device may allow some blood flow to be restored. The proximal end of the self-expanding wireform contains a radiopaque marker to aid in maintaining proper position. The FlowTriever2 Catheter can be manually retracted into the Triever Catheter, and simultaneous aspiration of fluid and clot can be performed through the Triever Catheter using a provided large-bore syringe. The device with captured clot is removed from the body.

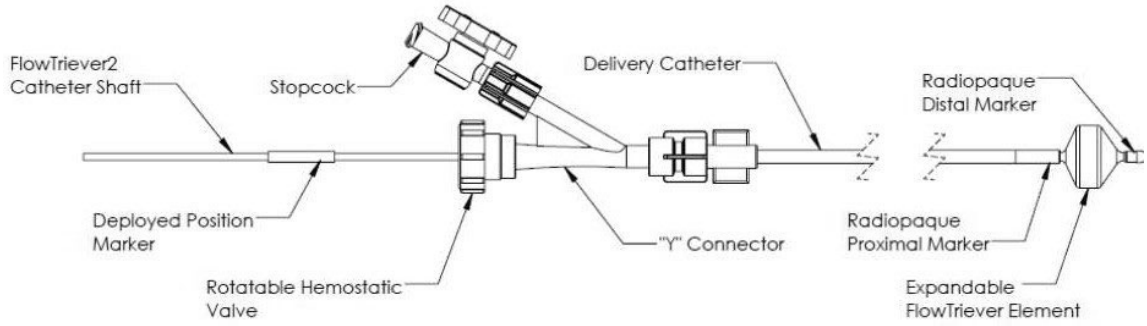
Pulmonary embolisms are caused by clots that typically originate in the leg in the form of a cast of the vessel from which they broke loose. The clots tend not to be the same diameter of the pulmonary artery. They travel en masse and often fold upon themselves, and/or collect together in the pulmonary artery, giving the appearance of a large clot. Retrieving the clot is similar to grabbing the head of the snake and pulling in the rest of the clot (body) as with retraction and aspiration. The elasticity of the clot, depending on its age, and various other factors, make it soft enough to deform during the retrieval process and fit into the Triever Catheter.

2.3 DEVICE CONSTRUCTION/OPERATION

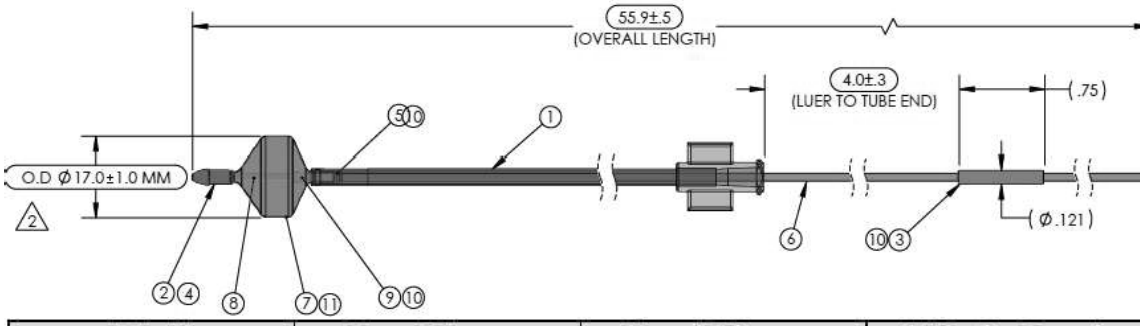
FlowTriever2 Catheter

The FlowTriever2 Catheter is comprised of a FlowTriever2 Catheter, delivery catheter, a hemostasis valve Y connector and one-way stopcock. The FlowTriever2 Catheter is preloaded into the delivery catheter and provided to the user in an assembled state (Figure 3.1).

Figure 3.1: FlowTriever2 Catheter



The outer diameter of the FlowTriever2 Catheter is 17 mm. The FlowTriever2 Catheter shaft is fabricated from stainless steel, Pebax, and PTFE/FEP/polyimide blend. Radiopaque platinum marker bands are positioned at the proximal end of the FT2 element to aid with fluoroscopic visualization (Figure 3.2).

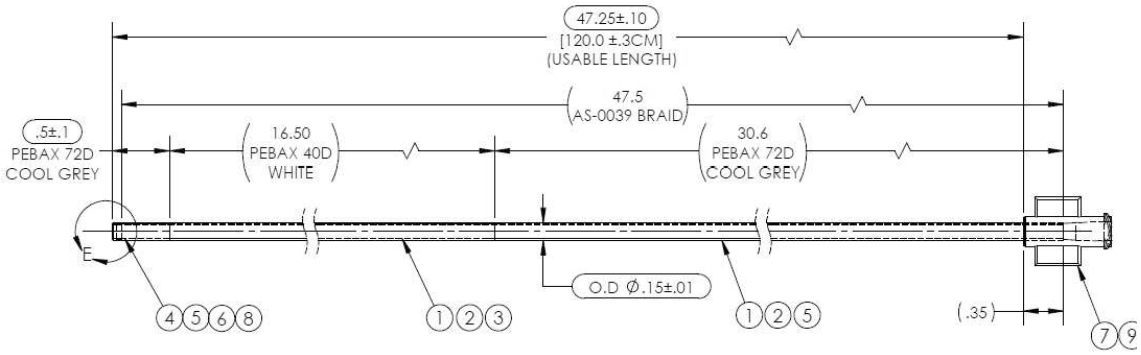


Model	Outer Diameter	Vessel Diameter	Effective Length
11-102	17 mm	6-16 mm	120 cm

Figure 3.2 FlowTriever2 Catheter Model, Sizes and Dimensions

The delivery catheter is a single lumen catheter comprised of a stainless-steel braid reinforced Pebax shaft with a polyethylene terephthalate (PTFE) liner with a proximal Luer fitting to connect to a "Y" connector with a rotatable hemostatic valve and stopcock. A radiopaque platinum marker is positioned near the distal tip to aid with fluoroscopic visualization (Figure 3.3).

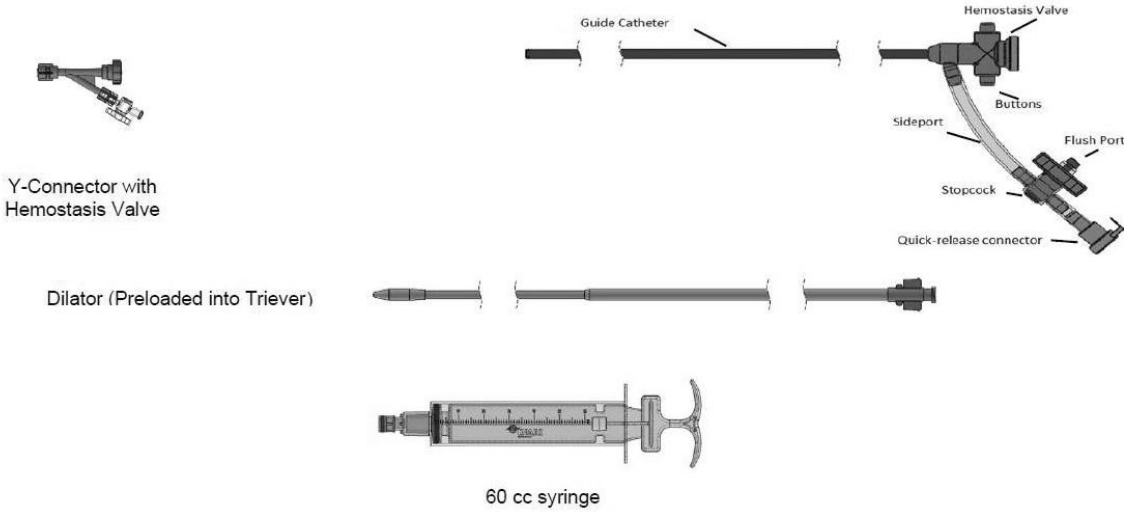
Figure 3.3: Delivery Catheter



Triever Catheter

The single-lumen Triever Catheter is available in three sizes: 16F, 20F, and 24F. The Triever Catheter and dilator are introduced together over a previously placed 0.035" exchange length guidewire (not provided). The Triever Catheter shaft is constructed from Pebax embedded with a stainless-steel coil and braid to prevent lumen collapse and provide flexibility, pushability, and strength. The shaft lumen is lined with PTFE. There is a Pebax/silicone hemostasis valve with a side-port terminating in a stopcock bonded to the proximal end of the Triever Catheter shaft. The dilator is constructed of low-density polyethylene (LDPE) with a Luer fitting at the proximal end to accommodate a "Y" connector with a rotatable hemostatic valve and stopcock. The dilator is compatible with the 0.035" guidewire and is provided to facilitate Triever Catheter advancement. The tip of the dilator is radiopaque, and a radiopaque platinum marker is positioned near the distal tip of the Triever Catheter to aid with fluoroscopic visualization. A large-bore, 60 cc VacLok Vacuum Syringe is used to aspirate clot from the Triever Catheter. The syringe is fitted with a quick-release connector compatible with the Triever Catheter's side port connector to establish an airtight seal. (Figure 3.4).

Figure 3.4: Triever Catheter Accessories and Model Dimensions



Model Number	Catheter Outer Diameter	Catheter Inner Diameter	Usable Length
25-101	16 Fr (5.3 mm)	13 Fr (4.5 mm)	113 cm
20-101	20 Fr (6.5 mm)	17 Fr (5.6 mm)	90 cm
22-101	24 Fr (7.6 mm)	21 Fr (6.9 mm)	90 cm

2.4 MANUFACTURER

Inari Medical
6001 Oak Canyon Road, Suite 100
Irvine, CA 92618 USA

2.5 INDICATIONS FOR USE

Under US Regulations 510(k) number K201541, the FlowTriever2 Catheter is indicated for:

- The non-surgical removal of emboli and thrombi from peripheral blood vessels.
- Injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel.

The FlowTriever2 Catheter is intended for use in the peripheral vasculature.

The FLARE-FT2 study is an IDE confirmatory study evaluating the FlowTriever2 Catheter for the treatment of pulmonary embolism.

At present, the FlowTriever2 Catheter is not cleared for the specific indication for which it is being tested (e.g., treatment of pulmonary embolism) and, thus, is not commercially available for this indication. The FlowTriever2 Catheter used to treat PE will be under clinical investigation at sites where the responsible Institutional Review Board (IRB) has approved the FlowTriever Pulmonary Embolectomy Clinical Study-FlowTriever2 (FLARE-FT2) 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.

3 PRIOR INVESTIGATIONS

The FlowTriever System was first evaluated in a US pivotal Investigational Device Exemption trial, the FlowTriever Clinical Embolectomy Clinical Study (FLARE) study, in subjects with submassive (i.e., intermediate-risk) PE. The study was a prospective, multicenter study to evaluate the safety and effectiveness of the FlowTriever System in subjects eligible for endovascular treatment of acute PE. The FLARE study was completed in 2017 and resulted in the FlowTriever System cleared indication for use in the peripheral vascular and for the treatment of PE.

Following this FDA clearance, a subsequent post-market registry (FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH)) was initiated to continue to evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli from the pulmonary arteries in a real-world patient population. The all-comer nature of the registry allows for the evaluation of FlowTriever outcomes in a real-world population including both intermediate-risk and high-risk PE patients, and enrollment in the study is ongoing.

3.1 FLARE STUDY

The FLARE study, IDE # G160002, was a prospective, single-arm, multicenter study conducted at 18 sites across the United States from April 2016 to November 2017. The study evaluated the treatment of 106 patients with intermediate risk PE using the FlowTriever System. The study met both of its primary endpoints, which demonstrated safety and effectiveness and represented a successful treatment of PE. Data from the study supported FDA 510(k) clearance (K180466) for the FlowTriever System.

All patients enrolled in the study were symptomatic for 14 days or less, with clinical signs and presentation consistent with PE, including documented proximal PE by computed tomography, or CT, angiography, and a site-reported right ventricle/left ventricle, or RV/LV, ratio of 0.9 or greater by CT.

The primary effectiveness endpoint was a reduction in core laboratory-assessed RV/LV ratio. The average RV/LV ratio decreased from 1.53 (n = 104) at baseline assessment to 1.15 (n = 101) in the 48 hours after treatment using the FlowTriever, representing a statistically significant reduction in RV/LV ratio of 0.38 on average (25.1%; $p < 0.0001$).

The primary safety endpoint was measured by device-related death, major bleeding, treatment-related clinical deterioration, pulmonary vascular injury or cardiac injury in the 48 hours after treatment using the FlowTriever. Four patients (3.8%) experienced six major adverse events in the 48 hours after treatment. All major adverse events were determined to be procedure related, with no device-related major adverse events. All four (3.8%) patients exhibited clinical deterioration. There was one major bleeding event (0.9%) and one pulmonary vascular injury. The major bleeding event experienced by one patient was also classified as a pulmonary vascular injury and as clinical deterioration.

Two patients (1.9%) experienced respiratory deterioration during or immediately after the procedure that required emergent intubation. One patient (0.9%) became agitated during the procedure, requiring increased sedation, and had a ventricular fibrillation event that required cardioversion and emergent intubation. An additional 10 patients experienced serious adverse events within 30 days after treatment, none of which were determined to be procedure- or device-related. In total, 14 patients (13.2%) experienced 26 serious adverse events within 30 days, with five patients (4.7%) experiencing multiple serious adverse events. One patient (0.9%) died within 30 days of treatment because of respiratory failure from undiagnosed metastatic breast cancer.

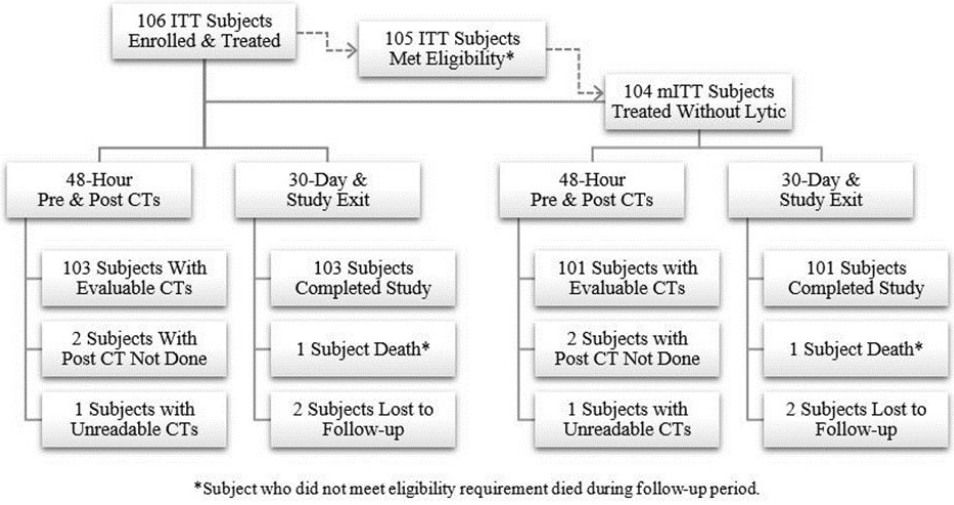
FLARE Study results were published in Tu T, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv 2019.[62]

3.2 FLARE STUDY RESULTS

A total of 106 subjects that met the eligibility criteria were consecutively enrolled and treated with the FlowTriever System comprising the full Intent-To-Treat ("ITT") population. Of these 106 subjects, two (2) subjects received thrombolytics during their index procedure and were therefore not included in the modified Intent-To-Treat (mITT) population. The mITT population was defined as all subjects in the "ITT Population" with no thrombolytics administered during the operative procedure. The primary effectiveness and safety analyses were done using the mITT population.

The disposition of subjects in the FLARE trial is depicted in **Figure 4**. In all, 106 subjects were enrolled and treated with the study device; 104 without thrombolytics. Among these, 101 had evaluable CTPA studies suitable for the primary effectiveness endpoint. There were also 101 subjects that had 48-hour data suitable for the primary safety endpoint. The mean baseline RV/LV ratio was 1.5 ± 0.4, and the mean 48-hour RV/LV ratio was 1.2 ± 0.3. Three subjects had missing values for the primary effectiveness endpoint at the 48-hour visit resulting in 101 subjects with both a pre-and post- RV/LV ratio for comparison. For these paired subjects, the mean change (reduction) in RV/LV ratio from pre- to post- was 0.38 ± 0.3, with a range from an increase of 0.4 to a decrease of 1.4. This mean change in RV/LV ratio was 0.38 and the p-value < 0.0001, indicating that the null hypothesis was rejected and the FlowTriever device met the performance goal.[a]

Figure 4. Disposition of Subjects in the FLARE Trial



*Subject who did not meet eligibility requirement died during follow-up period.

For the primary safety endpoint, 4 subjects (3.8%) in the mITT population experienced one or more MAEs. The composite endpoint of 3.8% was statistically lower than the performance goal of 25% (p-value <0.0001), with an upper one-sided 95% confidence limit of 8.6%. The upper one-sided 95% confidence limit for the ITT population was 8.4%, which was significantly less than the performance goal of 25%.

In summary, the FLARE trial met its primary safety and effectiveness endpoints. This trial was the basis for the US FDA 510(k) clearance of the device in May 2018.

[a] The p-value is from a one-sided t-test (Wald statistic) from the multiple imputation analysis, testing the null hypothesis that the mean change is not greater than the performance goal of 0.12.

3.3 DESIGN OF THE FLASH STUDY

The primary study objective of FLASH is to evaluate the safety and effectiveness of the next-generation FlowTriever System for use in the removal of emboli from the pulmonary arteries in the treatment of acute pulmonary embolism (PE). The use of the device is being assessed in a real-world population, with eligibility criteria that closely approximate its use in clinical practice.

The FLASH Study is a prospective, single-arm, multicenter all-comer registry of the FlowTriever System for intermediate-risk (submassive) and high-risk (massive) PE. While originally designed to enroll up to 500 subjects at up to 50 registry sites in the United States, the study has been expanded to enroll up to 1,000 subjects treated with FlowTriever, including up to 800 subjects in up to 70 US sites and up to 200 in up to 30 Europe sites. The study will also include an additional 300 subjects with anticoagulation treatment as the initial planned primary treatment strategy for intermediate-risk PE. Enrollment in the FLASH registry is ongoing.

The primary endpoint is the rate of Major Adverse Events (MAE). MAEs are defined as a composite, when one or more of the following events occur:

- Device-related mortality through 48 hours after the index procedure, or
- Major bleeding through 48 hours after the index procedure, or
- Intra-procedural device or procedure-related adverse events, including:
    - Clinic deterioration defined by hemodynamic or respiratory worsening, or
    - Device-related pulmonary vascular injury, or
    - Device-related cardiac injury

Secondary safety endpoints include individual components of the MAE composite endpoint, major access-site complications requiring open surgical or endovascular intervention or blood transfusion, all-cause mortality through 30 days, and device-related serious adverse events within 30 days. Secondary effectiveness endpoints include reduction in pulmonary artery pressure (PAP) and other hemodynamic improvements during the procedure, and reduction in RV/LV ratio from baseline to 30 days and 6 months.

3.4 FLASH INTERIM STUDY RESULTS

An interim analysis of outcomes out to 30 days on the first 250 subjects was recently published.[63] These subjects (60.9 ± 13.9 years, 52.4% male) were enrolled across 19 sites, with 93.2% having intermediate-risk PE and 6.8% high-risk PE. The average baseline RV/LV ratio was 1.5 ± 0.5 and sPESI was 1.6 ± 1.1. Elevated biomarkers were present in 96.2% of subjects, and 68.4% of subjects had concomitant DVT. The primary endpoint of composite MAEs occurred in three (1.2%) subjects, all of which were non-ICH major bleeds, and no deaths (0.0%) occurred within 48 hours.

In-hospital outcomes demonstrated significant improvements across several acute parameters. Subjects experienced significant on-table hemodynamic improvements, including a 22.2% decrease in mean pulmonary artery pressure (31.9 mmHg to 24.8 mmHg, $P < 0.001$) and a 13.3% increase in cardiac index in subjects with a low baseline cardiac index (1.7 to 1.9 l/min/m^2, $P = 0.005$). There was only one (0.4%) access site complication. The median post-procedure hospital length of stay was 3.0 [2.0 – 5.0] days and ICU length of stay was 0.0 [0.0 – 1.0] days.

Thirty day follow up data was available for 242 subjects in this analysis. In this population, there was one death (0.4% all-cause mortality), which was unrelated to the device, and there were 13 hospital readmissions, only one of which was related to the patient's acute PE. The average RV/LV ratio improved by 28.3% at follow up ($P < 0.001$) and subjects with confirmed baseline dyspnea had a significant improvement from baseline to 30 days (Modified Medical Research Council Dyspnea Scale, 2.9 ± 1.1 to 0.8 ± 1.1, $P < 0.001$).

These interim results of the FLASH all-comer registry demonstrate both safety and efficacy of the FlowTriever System, with a low all-cause mortality rate (0.0% at 48 hours, 0.4% at 30 days; no device-related deaths), along with significant and immediate hemodynamic improvements and continued improvements in RV/LV ratio and dyspnea out to 30 days.

4 FLARE-FT2 STUDY OBJECTIVES

The FlowTriever2 Catheter is a catheter-based mechanical thrombectomy device for percutaneous endovascular retrieval of emboli from vasculature and is intended for use in the peripheral vasculature. The FlowTriever2 Catheter is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing PE.

4.1 PRIMARY ENDPOINT - EFFECTIVENESS

The study's primary effectiveness endpoint is the change in mean pulmonary arterial pressure from baseline pre-procedure to post-procedure.

4.2 PRIMARY ENDPOINT - SAFETY

The study's primary safety endpoint is incidence of adjudicated Serious Adverse Events (SAE), which is a composite of:

- Mortality through 48 hours after the index procedure related to FlowTriever2 Catheter
- Major bleeding through 48 hours after the index procedure related to FlowTriever2 Catheter
- Intra-procedural device or procedure-related adverse events, including:
    - Clinical deterioration defined by hemodynamic or respiratory worsening
    - Pulmonary vascular injury related to FlowTriever2 Catheter
    - Cardiac injury related to FlowTriever2 Catheter

4.3 SECONDARY ENDPOINTS - EFFECTIVENESS

The study's secondary effectiveness endpoints are:

- The change in systolic pulmonary arterial pressure from baseline pre-procedure to post-procedure
- Incidence of adjunctive thrombolytic use

4.4 SECONDARY ENDPOINTS - SAFETY

The study's secondary safety endpoints will include incidence of adjudicated Adverse events, including:

- All-cause mortality through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Device-related SAE through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Symptomatic recurrence of pulmonary embolism through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)

5 STUDY DESIGN

The study is a prospective, single-arm, multicenter study to evaluate the safety and effectiveness of the FlowTriever2 Catheter in patients eligible for endovascular treatment of acute PE.

5.1 NUMBER OF SITES AND SUBJECTS

Five to twelve (5-12) sites will participate in the Study. The total population for the Study is 50 subjects with no more than 20% enrollment at any one site. Sites are selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficiency and adequately trained personnel, and availability of potential subjects. The criteria used for determination will be documented.

5.2 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 (-5 / +15 days) following treatment. Study participation includes screening, baseline, treatment, 48-hour visit, and 30-day follow-up.

5.3 STUDY POPULATION

The study population consists of subjects that have a PE. Subject eligibility is to be determined based on data available to the Investigator at the time of enrollment. Subjects must meet all inclusion and no exclusion criteria to be eligible for the study. Waivers will not be granted by the Sponsor regarding enrollment criteria. All subjects that complete the procedure and the follow-ups will be included in the analysis.

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.

Enrolled Subject: All patients who met the inclusion/exclusion criteria and in whom the FlowTriever2 Catheter is inserted into the vasculature. These subjects will comprise the "Enrollment Population."

Intent-To-Treat (ITT): All "Enrolled Subjects" in whom the procedure was attempted and the FlowTriever2 Catheter was deployed, whether successful or not.

Modified Intent-To-Treat (mITT): All subjects in the "ITT Population" who have no thrombolytics administered during the 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 (+36 hours or discharge, 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.

5.4 STUDY 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 FlowTriever2 Catheter will occur prior to the procedure and written informed consent will be obtained prior to all study-specific procedures.

If the FlowTriever2 Catheter is not inserted into the vasculature, the subject is considered a screen failure (not meeting inclusion criteria for use of FT2) and is not enrolled nor entered into the EDC.

5.5 INCLUSION CRITERIA

Subjects must meet all the inclusion criteria to be considered eligible for enrollment including:

1. Age ≥ 18 and ≤ 75 years
2. Clinical signs and symptoms 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)
6. Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90mmHg 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/or clinical judgment.
9. FlowTriever2 Catheter enters the vasculature

5.6 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

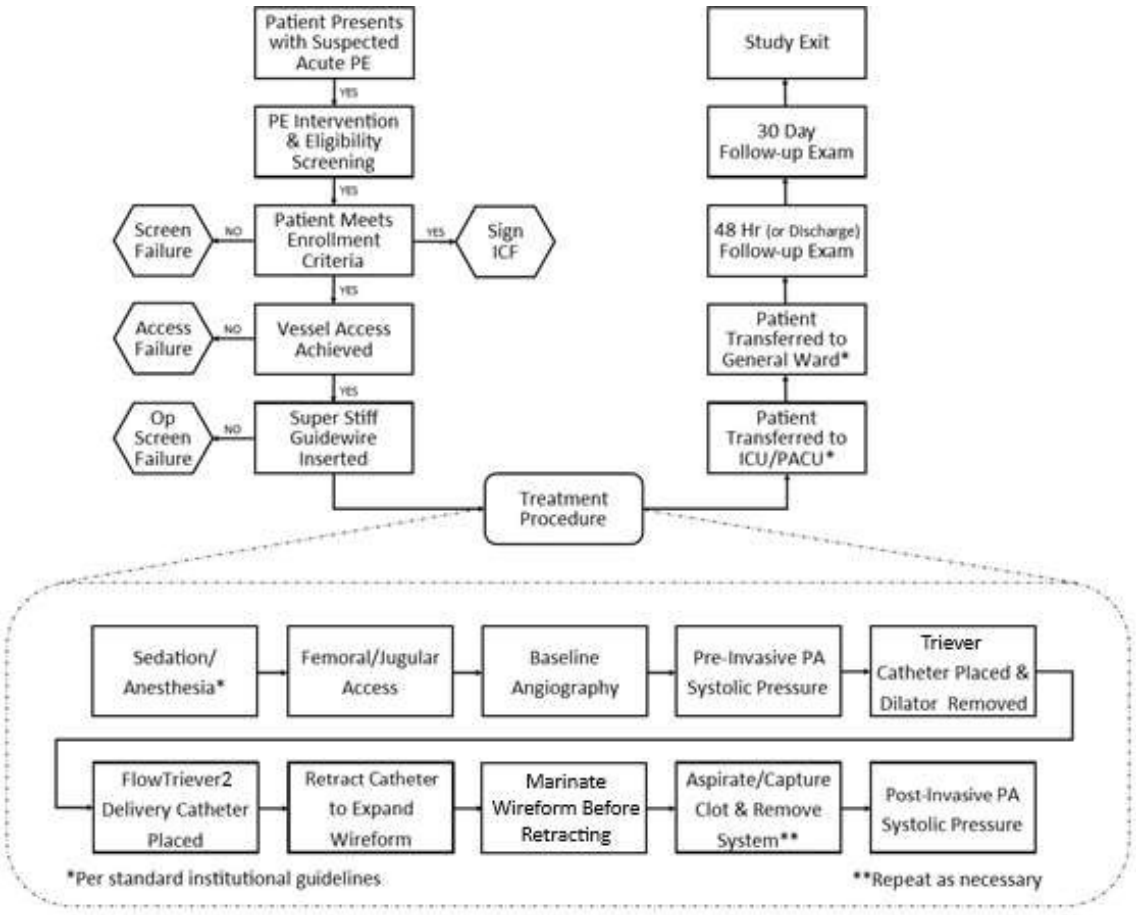
22. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated
23. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is notappropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location, predominately 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

6 FLARE-FT2 STUDY PROCEDURES

6.1 OVERVIEW OF STUDY FLOW

Subjects presenting with 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-FT2 Clinical Study. A representative overview of the study flow is shown in Figure 5.

FIGURE 5. Representative Study Flow from Screening to Discharge



6.1.1 SUBJECT SCREENING

Patients will be screened to determine their initial eligibility and interest in the study. Informed consent will be obtained once a patient has satisfied screening criteria and prior to any study-specific procedures not part of standard of care. All patients screened will be documented on the Screening/Enrollment Log.

6.1.2 INFORMED CONSENT

Written, study-specific informed consent will be obtained from each patient via the current IRB-approved Informed Consent Form (ICF) prior to the patient's de-identified medical record or personal health information (PHI) being shared with any study representative. The Investigator will keep the original ICF and a copy will be given to the patient. The patients will be informed that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The patients will also be informed about study purpose, alternative treatments, potential risks/benefits, and study assessment schedule.

6.1.3 NUMBERING OF STUDY SUBJECTS

Each site will be assigned a site number at the beginning of the Study and each enrolled Subject will be assigned a sequential subject number. All Subjects who provide informed consent and have the study procedure will be given a unique subject number and the subject number will be recorded on the Screening/Enrollment Log. The subject number will consist of the site number followed by a sequential number that begins with "001."

6.1.4 IMAGING AND INVASIVE PRESSURE

Computed Tomography Angiography (CTA)

The Study requires a CTA be obtained for subject screening to confirm pulmonary embolism and verify RV/LV ratio for inclusion.

Invasive Pulmonary Artery (PA) Systolic Pressure

Once access is achieved, a pre-procedure invasive PA systolic pressure will be obtained prior to beginning the FlowTriever part of the procedure. After the FlowTriever System has been removed, a post-procedure invasive PA systolic pressure will be obtained to assess change between end mean and pulmonary arterial pressures and baseline.

6.2 EXAMINATIONS

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.

All scheduled exams listed in Table 1 must be performed at the designated time point and the results documented.

Table 1: Schedule of Assessments

Assessment/Method	Baseline	Procedure (Day 0**)	48-Hr Visit (+36 hours, or time of discharge, whichever comes first****)	30-Day Visit (-5 to +15 days)
Verification of inclusion/exclusion criteria	√			
Medical/Surgical History	√			
Physical Examination/Vitals	√		√	√
Blood Labs	√			
CT Angiography	√			
Invasive PA Pressure (x2)*		√		
Concomitant Medications***	√	√	√	√
Adverse Events		√	√	√

*Invasive PA pressures required pre- and post-procedure
**Day 0 is the date of the FlowTriever procedure, Time 0 is when the FlowTriever2 Catheter enters the vasculature
*** Anticoagulation and Thrombolytics
****If discharged prior to 48 hours from Index Procedure, phone call to subject will be conducted to confirm if any SAEs occurred between time of discharge and 48 hours.

6.2.1 BASELINE

Baseline assessments will include the following:

- Verification of inclusion/exclusion criteria
- Medical history
- Physical examination/vitals
- Blood labs
- CT angiography to confirm PE and RV/LV ratio for inclusion
- Concomitant medications

Medical/Surgical History: Relevant medical and surgical history will be collected from all consented subjects at the time of enrollment.

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

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 routine care to treat 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).

6.2.2 ENDOVASCULAR TREATMENT/PROCEDURE

Once all inclusion/exclusion criteria have been satisfied, including imaging assessments, the subject will proceed with the mechanical thrombectomy procedure using the FlowTriever2 Catheter.

Sites will complete the procedure per standard institutional guidelines and physician discretion. The procedure requirements from the IDE-specific IFU for the use of the FlowTriever 2 Catheter are listed below. Refer to the IDE-specific IFU for more information on the appropriate use of the device for this study.

- 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.
  For use in Pulmonary Arteries:
  - Place an exchange length 0.035" guidewire into the target vessel through the right atrium and into the target pulmonary artery.
  - Using angiographic radiography, determine the location and size of the area to be treated.
  - Verify that the guidewire extends beyond the treatment area.
    WARNING: Do not treat vessels smaller than 6 mm diameter.
- Refer to the respective Instructions for Use (IFU) for Triever Preparation. Prepare and insert the Triever20 or Triever24.Attach the "Y" connector to the proximal Luer connector by sliding over the FlowTriever2 Catheter shaft.
- Flush the Delivery Catheter through the stopcock with sterile saline to remove all air. Tighten the rotatable hemostatic valve. Close stopcock.
- Place the FlowTriever2 Delivery Catheter containing the collapsed FlowTriever2 element over the guidewire, through the Triever Catheter, and advance through the target clot.
  WARNING: Avoid using excessive force to advance or retract against resistance. If excessive resistance occurs, retract, and collapse the distal element into the catheter and remove the device. Excessive force against resistance may result in damage to the device or vessel perforation.
- Pin the guidewire. While maintaining the Triever Catheter and FlowTriever2 Catheter position, manually retract the FlowTriever2 Delivery Catheter enough to allow the self-expanding element to expand within or beyond some portion of the clot.
  - The proximal and distal ends of the element contain a radiopaque marker to aid in maintaining proper position as the FlowTriever2 Delivery Catheter is retracted.
- Lock the FlowTriever2 Catheter and the Delivery Catheter together by tightening the Tuohy-Borst connector.
- Manually retract the FlowTriever2 Catheter inside the Triever Catheter to capture the targeted thrombus.
- Remove the FlowTriever2 Catheter from the Triever Catheter while maintaining the position of the Triever Catheter and guidewire. Depress the buttons on the Triever Catheter hemostasis valve as the FlowTriever2 element passes through the valve septum.
- Perform aspiration via the Triever Catheter side port using the 60-cc syringe provided in the package to capture additional thrombus. This step can be performed before and/or after the manual FlowTriever2 Catheter retraction.
- If thrombus remains, repeat steps 4-9.
  Caution: If the same FlowTriever2 Catheter device is used for another pass, the FlowTriever2 Catheter device and element should be thoroughly examined for damage and rinsed to prevent the introduction of thrombus to the patient.

- After the procedure is complete, remove the Triever Catheter and FlowTriever2 Catheter from the patient.
- Complete the procedure per standard institutional guidelines for thrombectomy procedures.

The FlowTriever System, including the FlowTriever2 Catheter, 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.

Procedure assessments will include the following:

- Invasive PA pressure (pre- and post-procedure)
- Record concomitant medications
- Record adverse events, as applicable

6.2.3 48-HOUR FOLLOW UP (+36 HOURS, OR AT TIME OF DISCHARGE, WHICHEVER COMES FIRST)

The sites will complete the following assessments on the subjects at the 48-hour visit or at time of discharge, whichever comes first:

- Physical examination and vitals
- Record adverse events, as applicable
- Record concomitant medications

Note: If discharged prior to 48 hours from Index Procedure, phone call to subject will be conducted to confirm if any SAEs occurred between time of discharge and 48 hours.

6.2.4 30-DAY VISIT (-5 TO + 15 DAYS)

The sites will complete the following assessments either remotely or in-person on the subjects at the 30-Day Visit (visit window = 30 days from procedure -5 days / +15 days):

- Physical examination and vitals
- Record adverse events, as applicable
- Record concomitant medications
- Complete Study Exit form

If the 30-Day Visit is completely remotely, the physical examination and vitals are not required.

Subjects who expire during their participation will be documented on an Adverse Event form and Study Exit form. Sites will fill out the Study Exit form for all enrolled subjects, regardless of reason, at the 30-Day Visit.

6.2.5 UNSCHEDULED VISITS

The unscheduled assessments should be done as clinically indicated and corresponding data must be documented on the case report forms and submitted to the Sponsor. The study will only record patient visits during the follow-up period that are related to the patient's PE condition and treatment including:

- Physical examination/vitals
- Concomitant medications
- Adverse events

6.3 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 two attempts to make contact and must be documented in the subject's medical records and appropriate study records.

6.4 STUDY DISCONTINUATION

The Sponsor and applicable regulatory authorities have the right to terminate the entire study or study activities at an individual site at any time. The circumstances which may warrant study termination include, but are not limited to:

- Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard, or
- Insufficient subject enrollment rates, or
- Recurrent protocol deviations or other non-compliances, or
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis, or
- Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

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

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.

6.5 WITHDRAWAL/PREMATURE DISCONTINUATION OF STUDY SUBJECTS

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.

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.

Withdrawal by Subject

If a Subject chooses to withdraw from the Study and also withdraws consent for disclosure of future information, no further 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.

The reason for, and date of, withdrawal must be recorded on the patient's Study Exit CRF. If the reason for the withdrawal is a device-related or procedure-related AE, the event must be reported to the Sponsor and recorded in the CRF.

7 RISK AND BENEFIT ANALYSIS

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

The FlowTriever2 Catheter 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 to endovascular clot retrieval in the treatment of pulmonary embolism include anticoagulation, thrombolytic therapy (systemic or catheter-directed), pharmacomechanical catheter-directed 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 the risk of hemorrhagic stroke, that may negate the potential benefit derived from this therapy and 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 FlowTriever2 Catheter is the safe and expeditious removal of the obstructing thrombi from the pulmonary arteries to facilitate right ventricular recovery.

7.1 ANTICIPATED RISKS

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.

7.1.1 RISKS DURING THE INTERVENTIONAL PROCEDURE

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
- Cardiac Perforation
- 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
- Perforation of pulmonary arteries
- 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

7.1.2 DEVICE WARNINGS

The following warnings are labeled for the FlowTriever2 Catheter:

- 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.
- Avoid using excessive force to advance or retract against resistance. If excessive resistance occurs, retract and collapse the distal element into the catheter and remove the device. Excessive force against resistance may result in damage to the device or vessel perforation.
- In the event of patient deterioration, remove FlowTriever2 Catheter/Triever device and assess situation.
- Ensure that FlowTriever2 element is withdrawn into Triever Catheter prior to removal from patient to avoid vascular damage.
- Do not use in blood vessels that have a history of therapeutic irradiation. Vessel perforation may occur.

7.1.3 RISKS OF CT

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

7.1.4 POTENTIAL RISKS OF THE PROPOSED INVESTIGATION

The risks associated with the FlowTriever2 Catheter 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 FlowTriever2 Catheter 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 FlowTriever2 Catheter will only be used in the main and lobar pulmonary artery branches and will not be attempted in smaller vessels (< 6 mm diameter).

Mechanical thrombus retrieval from the pulmonary arteries can, in theory, result in dispersion of some residual thromboembolic material distal to the central obstruction to the periphery of the lungs. With fragmentation devices, the fundamental objective is to eliminate central thrombi and fragment them so that they migrate to more distal branches, thus alleviating main pulmonary obstruction, which allows both an improved perfusion and a reduction of elevated pulmonary arterial pressures right ventricular pressure overload. Worsening of hemodynamic parameters due to distal embolization can occur, however, available clinical data does not associate serious adverse sequelae due to distal embolization in PE patients treated with fragmentation devices. Since the primary mode of action of the FlowTriever2 Catheter is clot retrieval, the potential for distal showering of thromboemboli does exist, but with the synchronized thrombus removal mechanism of the FlowTriever2 Catheter and aspiration capability of the Triever Catheter, it is anticipated to occur less frequently and to a lesser degree than devices that rely solely upon fragmentation. The minimal risk of distal embolization is outweighed by the anticipated benefits of the FlowTriever2 Catheter in the acute relief of the pulmonary arterial emboli.

Finally, while the intent of FlowTriever2 intervention is not to remove the entire embolic load, the risk of clot remaining after the embolectomy procedure is mitigated by the physician's ability to deliver thrombolytic to enhance both the impact of clot extraction and the body's natural lytic system. Future thrombolytic therapy is not precluded following FlowTriever2 treatment.

7.2 RISK MITIGATION

Awareness of the potential for serious complications is essential to the safe use of the FlowTriever2 Catheter. Additional risk mitigations include:

- Careful patient selection based on study inclusion/exclusion criteria,
- 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,
- Timely reporting of adverse events,
- Independent Clinical Events Committee, and
- Informed consent process.

7.3 POTENTIAL 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. Disruption of the emboli by the FlowTriever2 Catheter may enhance the effectiveness of thrombolytic agents by providing greater surface area contact of the therapeutic agent with the embolic mass. The aspiration of the emboli from the vasculature minimizes the potential for re-thrombosis and/or new emboli formation.

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

7.3.1 POTENTIAL BENEFITS OF THE PROPOSED INVESTIGATION

Endovascular interventions (e.g. catheterization) are well-established in medical practice and are substantiated to minimize the risks to patients, including: anesthesia complications, wound healing, bleeding, and infection. 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-FT2 trial does not exclude patients with recent surgeries nor those at a high risk of catastrophic bleeding.

7.3.2 ASSESSMENT OF UNCERTAINTY

There is a low degree of uncertainty regarding anticipated benefits of the clinical study since any amount of thrombus removal should be beneficial to the patient.

7.4 ALTERNATIVE TREATMENTS

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, fragment 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.

8 ADVERSE EVENT AND PRODUCT COMPLAINT RECORDING/REPORTING

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 PE condition or complications thereof will be recorded.

8.1 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

8.2 ADVERSE EVENTS (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 and whether anticipated or unanticipated. (ISO 14155:2020 3.2)

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

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

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

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 and subject is enrolled. 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.

8.2.1 ADVERSE DEVICE EFFECT (ADE)

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. (ISO 14155:2020 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 14155:2020 3.1)

NOTE 3: This includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)

8.2.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is an AE that:

- Led to death
- Led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
    - fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

(ISO 14155:2020 3.45)

Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

8.2.2.1 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 14155:2020 3.44)

8.2.3 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 assessment. (ISO 14155:2020 3.51)

8.2.4 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 14155:2020, 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 risk assessment. (ISO 14155:2020 3.51)

8.3 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.

8.4 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:** FlowTriever2 Catheter

  - **Ancillary Device:** Any device other than the FlowTriever2 Catheter, such as the Triever Catheter, 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 above-mentioned categories.
- **Unknown:** Event relationship is not known or unsure.

8.5 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 UADEs/USADEs to the Sponsor within 24 hours after first learning of the event, and all SAEs within 5 business days after 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.

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.

8.6 DEVICE DEFICIENCY (DD)

A Device Deficiency (DD) is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling.

NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)

8.7 CLINICAL EVENTS COMMITTEE

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 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 and adjudicate all adverse events according to the CEC Charter; 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 STATISTICS & DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATIONS

The sample size of 50 subjects reflects sample size to confirm the FlowTriever2 Catheter performance. The sample size of 50 subjects was estimated in order to provide at least 80% power with one-sided alpha = 0.05 for assuming FT2 safety event proportions of 11% vs. the performance goal of 25% from FLARE. Sensitivity analysis for this confirmatory study will be performed on a sub-population of the 50 subjects that did not receive adjunctive thrombolytics. Descriptive statistics on safety and effectiveness will be provided for all patients.

9.2 PRIMARY ENDPOINT - EFFECTIVENESS

The primary effectiveness endpoint will include an evaluation of the mean pulmonary arterial pressure changes between pre- and post-procedure.

9.3 PRIMARY ENDPOINT - SAFETY

The primary safety endpoint will include incidence of adjudicated Adverse Events including:

- Mortality through 48 hours after the index procedure related to FlowTriever2 Catheter
- Major bleeding through 48 hours after the index procedure related to FlowTriever2 Catheter
- Intra-procedural device or procedure-related adverse events, including:
    - Clinical deterioration defined by hemodynamic or respiratory worsening
    - Pulmonary vascular injury related to FlowTriever2 Catheter
    - Cardiac injury related to FlowTriever2 Catheter

9.4 SECONDARY ENDPOINTS - EFFECTIVENESS

The study's secondary effectiveness endpoints will include:

- The change in systolic pulmonary arterial pressure from baseline pre-procedure to post-procedure
- Incidence of adjunctive thrombolytic use

9.5 SECONDARY ENDPOINTS - SAFETY

Secondary safety endpoint will include incidence of adjudicated Adverse Events including:

- All-Cause mortality through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Device-related SAE through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Symptomatic recurrence of pulmonary embolism through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)

10 STUDY MANAGEMENT CONSIDERATIONS

10.1 QUALITY CONTROL AND QUALITY ASSURANCE

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel before the Study commences, and periodic on-site monitoring visits by the Sponsor as deemed appropriate by the Sponsor.

10.1.1 SPONSOR COMPLIANCE

The Sponsor is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the data generated are recorded and reported in accordance with established procedures. The Study will be organized, performed, and reported in compliance with this Clinical Protocol, Standard Operating Procedures, working practice documents, and applicable regulations and guidelines. The Sponsor also will confirm that the Study is performed in accordance with all applicable regulatory requirements.

The Sponsor will secure an agreement with all parties to allow direct access to all study- related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and/or its designee(s) and inspection by regulatory agencies.

The Sponsor will apply quality control measures to all stages of data collection and handling to ensure reliability and accuracy. In addition, the Sponsor will confirm that the data are processed correctly.

Data from CRFs and other external data (i.e., core laboratory data) will be entered into a clinical database as specified in the Data Management Plan (DMP). Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification in accordance with the DMP. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail. An internal quality control audit by Data Management will be performed and documented prior to database lock.

During the course of the Study, an amendment to the protocol may be necessary. Only the Sponsor is allowed to amend this protocol. Any amendments or modifications must be approved by the research site's IRB prior to research-study staff implementation, unless the modifications increase subject safety. The research sites will receive the following for their regulatory file, and if applicable, IRB submission:

- A memorandum outlining the changes and justification for modifications
- An updated protocol
- Updated appendices (if necessary)
- Changes to ICF template (if necessary)

10.1.2 INVESTIGATOR COMPLIANCE

The Principal Investigator assumes full responsibility for performance of the Study in accordance with the Clinical Research Agreement, this Clinical Protocol, ICH E6 GCP, 21 CFR Part 812, 21 CFR Part 50, 54 and 56, ISO 14155:2020 and all regulatory requirements applicable to the jurisdictions in which the Study is being conducted.

10.1.3 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.

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.

10.1.4 PROTOCOL DEVIATIONS

A protocol deviation is a divergence or non-adherence from the protocol-specific study procedures. Protocol deviations should be recorded for all assessments not collected, and issues related to eligibility criteria. Any protocol deviation must be documented in CRFs and reported to the Sponsor in a timely manner. Protocol deviations will be evaluated to see if they impact the descriptive analysis for this confirmatory study.

Reporting deviations to the IRB will be determined by individual IRB reporting requirements.

10.2 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.

Each Investigator who will participate in the investigation of the FlowTriever2 Catheter will sign a copy of the "Investigator's Agreement" and approval of the institutional review board ("IRB") will be obtained prior to beginning the study.

No Investigator is permitted to begin clinical studies until Inari Medical has received a copy of the signed "Investigator's Agreement."

No Investigator will be added to the investigation until he/she has signed the "Investigator's Agreement".

10.3 STUDY 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
- Protocol review
- Delegation of authority for study-related tasks
- Informed consent process, including any relevant IRB/Confidentiality/HIPAA requirements
- Case Report Forms and completion instructions
- Documentation of protocol deviations
- Adverse/serious adverse event reporting
- Product malfunction reporting
- IDE Instructions for Use and device accountability
- Responsibilities and obligations of the Investigator/staff
- 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.

10.4 PHYSICIAN DEVICE TRAINING

Each physician selected to participate in this trial will be required to have experience treating pulmonary embolism using the FlowTriever System. In addition, each physician will be trained on the use of the FlowTriever2 Catheter.

10.5 DEVICE ACCOUNTABILITY

The investigational site shall supply the device from the Institution's stock. Study-specific devices will not be provided to the site for the study. The Investigational Device Instructions for Use will be provided to the Principal Investigator and the Principal Investigator and Sub-Investigator(s) (if applicable) will be trained to the Investigational Device Instructions for Use prior to enrollment.

Sites will document device accountability for any Inari Medical devices utilized during the index procedure.

10.6 SITE INITIATION AND ADDITION OF SITE PERSONNEL

A Site Initiation Visit (SIV) will be conducted by the Sponsor or designee, either in-person or via teleconference to ensure proper training of the Investigator and study staff members prior to participation in the study. The SIV will cover training to the study protocol and data collection, as well as to any applicable regulatory requirements, and will be documented in the study record.

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 documentation to verify the appropriate study staff has been trained on the protocol, device, CRFs and study conduct.

Additional site personnel added to the study after the SIV will be required to undergo protocol training, to be performed by the Sponsor, or designee, and documented in the study record.

10.7 SITE CLOSE-OUT

Close-out visits will be conducted by the Sponsor or designee in-person or remotely to ensure compliance with the protocol, and other written instructions and regulatory guidelines.

Final close-out visits at the sites will be conducted at the end of the Study.

The purpose of the final visit is:

- Collect any outstanding study data document
- Ensure the Investigator's files are accurate and complete
- Review record retention requirements with the Investigator
- Make a final accounting of all study supplies shipped to the Investigator/Site
- Provide for appropriate disposition of any remaining supplies
- Ensure that all applicable requirements are met for the Study

10.8 DATA COLLECTION AND ELECTRONIC CASE REPORT FORMS (ECRF)

Clinical study data will be collected using source document worksheets and eCRFs. A web-based electronic data capture system (EDC) will be used to record and manage study data. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

Electronic Case Report Forms (eCRFs) have been developed to collect all study-related information and data points. Inari Medical will provide eCRFs for each Subject enrolled in the Study to each investigational site. The appropriate eCRF will be completed after each Study visit. eCRF Completion Guidelines will be provided to the sites.

The Investigator may keep a separate subject identification list showing enrollment numbers, names, and dates of birth to provide a local key for unambiguous identification of each subject included in the study. This list will not be collected by the Sponsor.

The Investigator will sign the appropriate eCRF pages and source documentation. Pertinent eCRF corrections will be made electronically and signed electronically by the Investigator. An embedded audit trail will capture the date, time and user making entries and changes to the electronic data.

Because it is important to have proper data collection in a timely manner, it is recommended that the Investigator or designee complete eCRFs within 5 business days of data availability. When the monitor or designee requests additional data or clarification of data for the eCRF (queries), the request must be answered satisfactorily as soon as possible.

10.9 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 photocopied if required. The Monitor will also check the Investigator Site File (ISF) to ensure that all study related documents are current.

10.9.1 MONITORING REPORTS

After each monitoring visit, the Monitor will send to the Investigator an e-mail or letter summarizing the monitoring visit. A monitoring report will be sent to the Sponsor. The report will include:

- Date of the monitoring visit
- Monitor name
- Site name
- Investigator name
- Individual names present for visit
- Items reviewed during the visit, findings, and any required follow-up

The Investigator will be responsible for ensuring that follow-up action items requiring resolution at the site are completed in an accurate and timely manner.

10.10 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, and billing information) 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.

10.11 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.

10.12 RECORD STORAGE AND RETENTION

10.12.1 INVESTIGATOR RECORD 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 the GCP.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

10.12.2 SPONSOR RECORD RETENTION

The Sponsor will maintain all study documentation in its possession and/or contact and institute measures to prevent accidental or premature destruction of any data and/or documents related to the research Study.

The Sponsor shall retain the study documentation for at least ten (10) years after formal discontinuation of Study or 10 years after the last FlowTriever2 Catheter has been placed on the market (whichever is longer).

11 ETHICS AND CONFIDENTIALITY

11.1 ETHICAL CONDUCT OF THE 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
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 812, 50, 54, and 56)
- The Declaration of Helsinki concerning medical research in humans (64th WMA General Assembly, Fortaleza, October 2013)
- ISO 14155

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.

11.2 INSTITUTIONAL REVIEW BOARDS (IRB)

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

This study must be approved by an appropriate IRB/EC at each registry site. Securing the approval is the responsibility of the Investigator, as defined by ICH E6, ISO 14155 and FDA regulations (21 CFR Part 56), prior to starting the study.

The IRB and/or Investigator is required to forward to the Sponsor a copy of the IRB approval to begin the Study. 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.

11.3 STUDY PATIENT CONFIDENTIALITY

The Investigator must ensure that the privacy of all patients, including their personal identity and all personal health information. In CRFs and other documents, patients will not be identified by their names, but by an individual identification code (i.e., patient identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. A monitor or Sponsor designee may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential and handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

11.4 INVESTIGATOR RESPONSIBILITIES

Investigator responsibilities include, but are not limited to, the following:

- Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study patients
- Ensuring that informed consent is obtained for each study patient in accordance with applicable regulations (e.g., ICH E6, ISO 14155, 21 CFR Part 50)
- Ensuring that IRB/EC approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
- Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to a conflict of interest (financial disclosure is required)

11.5 PUBLICATION POLICY

Publications from the FT2 Study will be handled according to Standard Operating Procedures and as indicated in the CTA.

Clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all Investigators, IRBs and the FDA
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding Investigator after the completion of the study, if requested

12 TERMS AND DEFINITIONS

Term	Definition
Primary Safety Definitions	
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.
Device Related Death	Device-related death is defined as any death directly related to thedevice not performing as expected. Device-related death would include death from: • Vascular or cardiovascular injury • Device malfunction • Device-induced cardiac arrhythmia
Life Threatening or Disabling Bleeding (VARC-2)	• Fatal bleeding, OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome, OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, OR • Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 units*
Major Bleeding (VARC- 2)	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
Minor Bleeding (VARC- 2)	Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening or disabling bleeding or major bleeding.
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.
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.
Additional Definitions	
Adverse Event (AE)	An Adverse Event (AE) is an 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 and whether anticipated or unanticipated (ISO 14155:2020, 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.
Serious Adverse Event (SAE)	An AE that led to any of the following: • death, • serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

Term	Definition
	○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function, including chronic disease, or ○ in-patient or prolonged hospitalization, or ○ medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Minor Complications (SIR Classification)	Minor complications: • No therapy, no consequence • Nominal therapy, no consequence (includes overnight admission for observation only)
Major Complications (SIR Classification)	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
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device **NOTE 1**: This definition includes AEs 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 includes any event resulting from an error use or from intentional misuse of the investigational medical device. **NOTE 3**: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Unanticipated Serious Adverse Device Effect (USADE) (pre-market term only)	USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. (ISO 14155:2020, 3.51)
Anticipated Serious Adverse Device Effect (ASADE) (pre-market term only)	ASADE is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. (ISO 14155:2020, 3.51)
Unanticipated Adverse Device Effect (UADE) (pre-market term only)	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 a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

Term	Definition
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device Deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
High-Risk PE	Per ESC guidelines 2019: High-Risk PE determined by hemodynamic instability, PESI III-V or sPESI ≥ 1, RV Dysfunction, and Elevated cardiac troponins. Note Definition of hemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation). 1. Cardiac Arrest: Need for cardiopulmonary resuscitation, 2. Obstructive Shock: Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite adequate filling status AND End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate), OR 3. Persistent Hypotension: Systolic BP < 90 mmHg or systolic BP drop ≥ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis.
Intermediate High-Risk PE	Per ESC guidelines 2019: Intermediate High-Risk PE determined by no hemodynamic instability, PESI III- V or sPESI ≥ 1, RV Dysfunction, and Elevated cardiac troponins.
Intermediate Low-Risk PE	Per ESC guidelines 2019: Intermediate Low-Risk PE determined by no hemodynamic instability, PESI III- V or sPESI ≥ 1, and 1 or none of the following: RV Dysfunction; Elevated cardiac troponins.
Patient/ Subject	Participants in the study.
Recurrent PE	Symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure with documentation of a change on CTPA or other suitable imaging modality, as determined by the CEC.

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