FLowTriever **A**ll-Comer Registry for Patient **S**afety and **H**emodynamics **(FLASH)**

Device: FlowTriever® Retrieval/Aspiration System
Protocol Number: 18-002
Version: 8.0
March 15, 2021

Sponsor
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PROTOCOL SIGNATURE PAGE

Investigator Name	Title
Site Name	Site Number

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by the Sponsor, to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

I agree to keep records on all patient information (e.g., source documents and informed consent forms) and all other information collected during the study, in accordance with local and national regulations.

Investigator's Signature	Date

SYNOPSIS

Protocol Number	18-002
Study Title	**FL**owTriever **A**ll-Comer Registry for Patient **S**afety and **H**emodynamics **(FLASH)**
Study Device	FlowTriever Retrieval/Aspiration System
Regulatory Status	The FlowTriever System is cleared for the treatment of Pulmonary Embolism under US Regulations 510(k) number K180466 and CE Mark 518259. The FlowTriever System is indicated for use in the peripheral vasculature and for the treatment of pulmonary embolism.
Sponsor	Inari Medical 9 Parker, Suite 100 Irvine, CA 92618 (USA)
Study Objective	The primary study objective is to evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli from the pulmonary arteries in the treatment of acute pulmonary embolism (PE). The use of the device will be assessed in a real-world population, with eligibility criteria that closely approximate its use in clinical practice.
Study Population	This study will enroll up to 1000 patients (up to 800 in the US and up to 200 in Europe) with PE treated with FlowTriever.
Number of Sites	This study will be conducted at up to 100 Registry sites (up to 70 in the US, up to 30 in Europe).
Study Design	The FLASH Registry is a prospective, single-arm, multicenter study of the FlowTriever System for intermediate-risk (submassive) and high-risk (massive) PE.
Conservative Therapy Sub-study (US Only)	Up to 300 additional patients with anticoagulation treatment as the initial planned primary treatment strategy for intermediate risk PE will be evaluated. Clinical assessments will be performed at Baseline, 48h, 30d, and 6m.

Primary Endpoint	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:
	  ○ Clinical deterioration defined by hemodynamic or respiratory worsening, or
	  ○ Device-related pulmonary vascular injury, or
	  ○ Device-related cardiac injury

Secondary Endpoints	<u>Secondary Safety Endpoints:</u> • 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 • Device-related serious adverse events within 30 days

Secondary Endpoints	Secondary Effectiveness Endpoints: • Reduction in pulmonary artery pressures during the procedure; • Hemodynamic improvements during the procedure, including cardiac index (CI) and stroke volume index (SVI), right ventricular stroke work index (RVSWI), pulmonary artery pulsatility index (PAPi) and total pulmonary vascular resistance (TPVR) • Reduction in right-ventricular/left-ventricular (RV/LV) ratio from baseline to 30 days and 6 months; as measured by echocardiography Utility Measures: • Fluoroscopy time • Contrast used • Thrombectomy time • Estimated blood loss during the index procedure • Length of intensive care unit stay, if any • Length of total hospital stay
Inclusion Criteria	Patients must meet each of the following criteria to be included in the study: 1. Age ≥ 18 years 2. Clinical signs and symptoms consistent with acute PE 3. Echo, CTPA or pulmonary angiographic evidence of proximal filling defect in at least one main or lobar pulmonary artery 4. Scheduled for PE treatment with the FlowTriever System per the Investigator's discretion* **US only: Patients enrolled in the Conservative Therapy Sub-study are not required to meet this inclusion criteria but must instead be scheduled for primary anticoagulation therapy as the primary treatment strategy.*
Exclusion Criteria	Patients will be excluded from the study for any of the following criteria: 1. Unable to anticoagulate with heparin or alternative 2. Diagnosis with a minor PE with a less than 0.9 RV/LV ratio 3. Known sensitivity to radiographic contrast agents that, in the Investigator's opinion, cannot be adequately pre-treated* 4. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the patient is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location or predominately chronic clot) * 5. Life expectancy <30 days, as determined by the Investigator 6. Current participation in another drug or device treatment study that, in the Investigator's opinion, would interfere with participation in this study **US Only Patients enrolled in the Conservative Therapy Sub-study are not required to meet these exclusion criteria*
Analytic Datasets	The analytic dataset will comprise all patients enrolled, where enrollment is defined when the FlowTriever System enters the patient's vasculature or the patient is diagnosed with PE and the primary treatment strategy of anticoagulation is administered (Conservative Therapy Sub-study) and the patient provides consent to share his/her personal health information.

Follow-up Schedule	Patients will have follow-up evaluations after the index procedure* at: • 48 hours (± 36 hours) • 30 days (± 15 days) • 6 months (± 90 days) **US Only: Conservative Therapy Sub-study patient follow up evaluations will occur after the primary treatment of anticoagulation is administered at Baseline.* (US Only Patients) In addition to the follow-up schedule, approximately 100 patients receiving treatment with the FlowTriever System and approximately 100 patients receiving anticoagulation treatment will be asked to participate in ongoing data collection for 6 months utilizing an Apple iWatch.
Medical Monitor	An independent Medical Monitor will review adverse events and other important safety occurrences as specified in the Safety Manual.
Global Principal Investigator	Catalin Toma, M.D. Director, Interventional Cardiology Heart and Vascular Institute University of Pittsburgh Medical Center, Pittsburgh, PA

Schedule of Assessments

Assessment	Baseline (≤ 48 hrs.)	Procedure* (Day 0)	48 Hours[Þ] (± 36 hrs.)	30 Days (± 15 days)	6 Months (± 90 days)
Inclusion/exclusion review	X				
Demographics	X				
Medical History and Risk Factors	X				
Clinical Diagnosis (CTEPH, CTED/Post PE Syndrome)	X			X	X
Current PE Condition	X				
Clinical Condition on Arrival to ED/Hospital	X				
Clinical Condition prior to treatment administration	X				
Anticoagulation regimen	X	X	X	X	X
Clinical Labs: HGB, CBC, Troponin, BNP, Lactate, INR, Creatinine, D-Dimer	X	X	X		
Echocardiogram (Required)	X			X	X
CTPA (Requested) [†]	X				
mMRC Dyspnea Score (Required)	X		X	X	X
Thrombectomy Time		X			
Vitals	X		X	X	X
Invasive hemodynamic measures with HGB, SvO2% (Required)		2X[Δ]			
Pulmonary angiograms		2X			
Bleeding measures		X	X		
FlowTriever Devices used		X			
Access Site information		X			
Procedure Summary (e.g. treatment location, EBL, Fluoro time, clot removal score, HR, pressures)		X			

Adjunctive therapy (thrombolysis and/or additional thrombectomy)	X**	X		X	
6-minute walk test (Required)				X	X
PEmb QOL (Required)				X	X
Adverse event assessment		X	X	X	X
Wearables assessment[G]			X	X	X

[*] Procedural assessments are not required nor will be captured for patients in the Conservative Therapy Sub-study.

[†] The time to assessment clock starts after TrieverCatheter is removed for the final time.

[†] CTPA imaging will be performed as per the local standard of care. If a CTPA is ordered, imaging data is requested.

[Δ] Invasive hemodynamic measures will include RA, RV, and PA pressures from the tip of the pulmonary catheter, record the mixed venous PA sat (SvO2), RA pressure, and the PA pressures. Then, flush the catheter and draw the HGB sample from the PA and simultaneously record the heart rate, peripheral artery O2 sat (SaO2) and the oxygen level the patient is receiving. These measurements are obtained pre-FlowTriever insertion and at least 5 minutes after removing the FlowTriever for the final time.

[G] Data collection occurring from the 48-hour visit through the 6-month visit

*** For Conservative Therapy Sub-study, collect if adjunctive therapy was used at Baseline*

NOTE: Consenting can be done 48hr pre-index procedure OR within 7 days post index procedure. Enrollment occurs when consent signed AND FlowTriever enters the body. For the US Only Patients, Conservative Therapy Sub-study, consenting can be done 48hr prior to the administration of anticoagulation therapy as the primary treatment strategy OR within 7 days after. Enrollment occurs when consent is signed AND the primary treatment strategy to administer anticoagulation has commenced.

NOTE: Please collect COVID status at all visits as applicable on the supplemental EDC form.

ABBREVIATIONS

Abbreviation	Term
AC	Anticoagulation
AE	Adverse event
AHA	American Heart Association
BSA	Body surface area
CDT	Catheter-directed thrombolysis
CO	Cardiac output
CRO	Contract research organization
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
ECMO	Extracorporeal membrane oxygenation
eCRFs	Electronic case report forms
ESC	European Society of Cardiology
EC	Ethics Committee
FDA	Food and Drug Administration
FLARE	FlowTriever Clinical Embolectomy Clinical Study
GDPR	General Data Protection Regulation 2016/679
H-FABP	Heart type fatty acid binding
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-induced thrombocytopenia
ICF	Informed consent form
IRB	Institutional review board
ITT	Intent to treat
LV	Left ventricle
MAE	Major adverse events
mMRC	Modified Medical Research Council Dyspnea Scale
PAPi	Pulmonary Artery Pulsatility Index
PE	Pulmonary embolism
PEmb-QOL	Pulmonary Embolism Quality of Life
PESI	Pulmonary Embolism Severity Index
PHI	Protected Health Information
PMT	Percutaneous mechanical thrombectomy
Post-PES	Post-pulmonary embolism syndrome
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
RVSWI	Right ventricular stroke work index
SAE	Serious adverse event
SAP	Statistical analysis plan
SIV	Site initiation visit
sPESI	Simplified Pulmonary Embolism Severity Index

Abbreviation	Term
SVI	Stroke volume index
TPVR	Total pulmonary vascular resistance
UAT	Ultrasound-accelerated thrombolysis
VTE	Venous thromboembolism

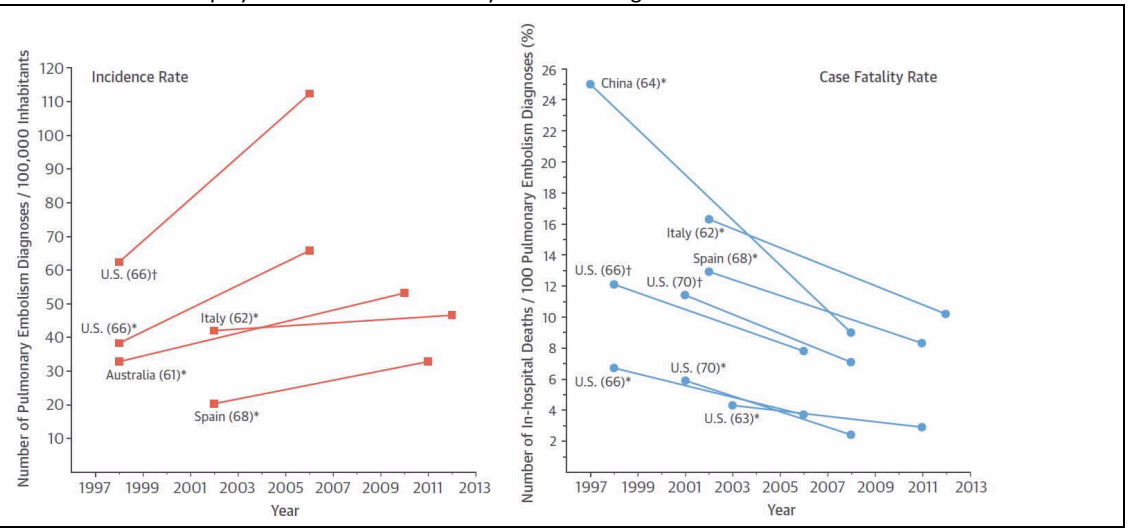
1 INTRODUCTION AND BACKGROUND

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**). 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 2011 American Heart Association (AHA) Scientific Statement on Pulmonary Embolism classified 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 2014 European Society of Cardiology (ESC) guidelines 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.[2]

Early Mortality Risk		Risk Parameters and Scores			
		Shock or Hypotension	PESI Class III-V or sPESI ≥1	Signs of RV Dysfunction on an Imaging Test	Cardiac Laboratory Biomarkers*
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	+	Both positive	
	Intermediate-low	–	+	Either 1 (or none) positive	
Low		–	–	Assessment optional: If assessed, both negative	

*Markers of myocardial injury, e.g., elevated cardiac troponin, or heart type fatty acid-binding (H-FABP] plasma concentrations), or of right ventricular dysfunction, e.g., elevated natriuretic peptide plasma concentrations.

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

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, massive 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.

1.6.3 Pharmacologic 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,[35] 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.[36-41] 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.[16,42,43] These findings remained unchanged despite newer agents and better periprocedural patient management over the years.

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.[44] 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, massive PE. However, recent work suggests that even a catheter-directed approach may be associated with significant bleeding complications,[45] although possibly at a lower rate than with systemic treatment.[46]

1.6.4 Ultrasound-Accelerated Thrombolysis

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.[47] 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.[48] 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-does, 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.[49] After that, other technologies were attempted, including fragmentation of proximal emboli,[50,51] rheolytic thrombectomy,[52-56] and the use of various pulmonary artery thromboembolectomy devices.[57-59] 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.

2 STUDY DEVICE

2.1 OVERVIEW

The FlowTriever Retrieval/Aspiration System is a single-use over-the-wire catheter-based system for the minimally invasive treatment of thromboemboli in the peripheral vasculature and the treatment of pulmonary embolism. The device was cleared in the US under 510(k) number K180466, May 17, 2018, and CE Mark on December 30, 2020. The FlowTriever System is a Class II device in the US and a Class III device in Europe, intended for use in the peripheral vasculature and for the treatment of pulmonary embolism.

2.2 MANUFACTURER

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2.3 INDICATIONS FOR USE

The FlowTriever Retrieval/Aspiration System is a single-use over-the-wire catheter-based system for the minimally invasive treatment of thromboemboli in the peripheral vasculature and the treatment of pulmonary embolism. The FlowTriever System is indicated for the non-surgical removal of emboli and thrombi from blood vessels; the injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel. The completion of the FLARE prospective clinical trial resulted in FDA clearance and CE Mark for the treatment of pulmonary embolism.

3 PRIOR INVESTIGATIONS

The FlowTriever System was 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.

3.1 DESIGN OF THE FLARE STUDY

A maximum of 20 study sites were planned to participate in the study, and no single study site could enroll more than 25% of the total subjects. The study population comprised 106 subjects with acute submassive PE.

Primary safety and primary effectiveness performance goals (PG) were used in the study. For the safety PG, the results from seven studies with acute PE patients treated with a heparin control arm were used to develop a composite MAE rate. MAEs were defined when one or more of the following occurred within 48 hours: Device-related mortality, major bleeding, treatment-related clinical deterioration, treatment-related pulmonary vascular injury, or treatment-related cardiac injury. Combining these composite MAE rates yielded an estimate of 16% with a 95% confidence interval of 6.7% to 25.8% after adjusting for heterogeneity among studies. The PG was chosen as the upper 95% confidence limit rounded down to two digits, for a safety PG of 25%.

The primary effectiveness performance goal was the change in RV/LV ratio from baseline to 48 hours. The PG was based on heparin-treated subjects from four studies in which heparin was a control to an active pharmaceutical drug. Combining these results in a meta-analysis yielded a mean change from baseline of 12% with 95% confidence limits of 4% to 21% after adjusting for heterogeneity among studies, for an effectiveness PG of 12%.

Subjects were followed for 30 days post-procedure with CTPA at 48 hours and assessment of AEs through 30 days. The primary safety endpoint was assessed from the 48-hour MAE rate and the primary effectiveness endpoint from the change between the baseline and 48-hour CTPA imaging studies.

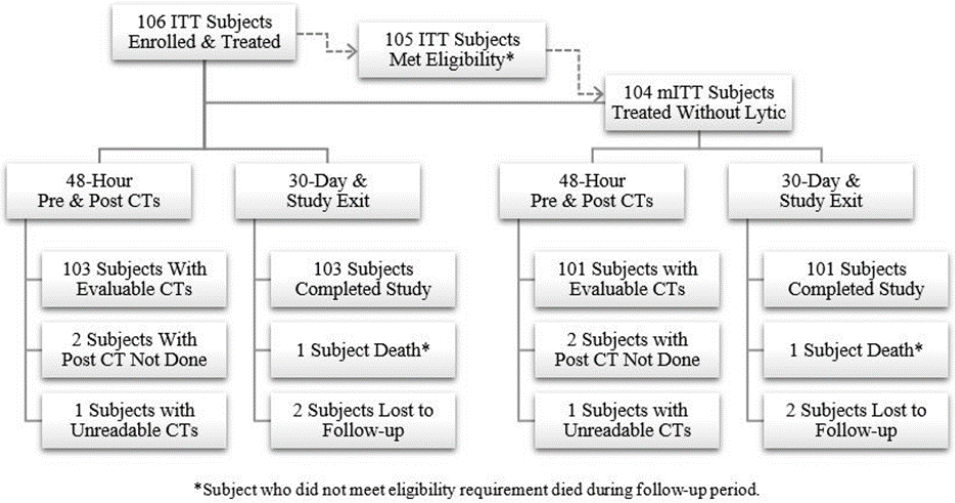
The sample size for effectiveness was computed based on an estimated RV/LV ratio change from baseline. For 80% power to detect an RV/LV ratio greater than 0.12 using a one-sided alpha = 0.025, the sample size needs to be at least 62, 38, or 26 assuming a true RV/LV ratio of 0.20, 0.225 or 0.25, respectively.

The sample size for safety was based on the PG of 25% for the composite endpoint. The true composite endpoint rate for the FlowTriever was expected to be about 13%, according to data from the historical studies used for the PG estimation. Additionally, rates of 15% and 17% were considered. For 80% power to detect a difference from the expected lower composite endpoint rates of 13%, 15%, and 17% compared to the performance goal with a one-sided alpha = 0.05, 70, 103, and 167 subjects would be needed if the true rates were 13%, 15%, and 17%, respectively. Since a conservative sample size for safety was calculated to be 103, 103 was used as the sample size for this study, not adjusted for subjects receiving thrombolytics. It was assumed that approximately 15% of the subjects would receive thrombolytics so that 103/0.85=121.2 or up to 122 subjects could be enrolled.

3.2 STUDY RESULTS

The disposition of subjects in the FLARE trial is depicted in **Figure 3**. 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 3. Disposition of Subjects in the FLARE Trial



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

[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.

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 sum, 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.

4 STUDY OBJECTIVE

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

5 OUTCOME VARIABLES

5.1 PRIMARY SAFETY ENDPOINT DEFINITION

The primary safety 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
- Intraprocedural device- or procedure-related adverse events, including:
    - Clinical deterioration defined by hemodynamic or respiratory worsening, or
    - Device-related pulmonary vascular injury, or
    - Device-related cardiac injury

The components of the composite MAE endpoint will be assessed by the independent Medical Monitor.

5.2 SECONDARY ENDPOINTS

The secondary endpoints of the study will assess safety, effectiveness, and utility measures, as follows.

5.2.1 Secondary Safety Endpoints

- Individual components of the MAE composite endpoint
- Major access site complications requiring open surgical or endovascular intervention or blood transfusion
- All-cause mortality within 30 days
- Device-related serious adverse events within 30 days

5.2.2 Secondary Effectiveness Endpoint

- Reduction in pulmonary artery pressures during the procedure
- Hemodynamic improvements during the procedure, including cardiac index (CI) and stroke volume index (SVI), right ventricular stroke work index (RVSWI), pulmonary artery pulsatility index (PAPi), and total pulmonary vascular resistance (TPVR)[b]
- Reduction in right-ventricular/left-ventricular (RV/LV) ratio from baseline to 30 days and 6 months; as measured by echocardiography

5.2.3 Utility Measures

- Fluoroscopy time
- Contrast used
- Estimated blood loss during the index procedure
- Thrombectomy Time
- Length of intensive care unit stay, if any
- Length of total hospital stay

6 STUDY DESIGN

The FLASH Registry study is a prospective, single-arm, multicenter analysis of the FlowTriever System for intermediate-risk (submassive) and high-risk (massive) PE. The Registry will collect data on demographics, comorbidities, details from the PE diagnosis and treatment, and clinical outcomes through 6-month follow-up.

Up to 1000 patients (up to 800 US, up to 200 Europe) with PE will be enrolled at up to 100 (up to 70 US, up to 30 Europe) Registry sites. All patients who sign consent and are treated with the FlowTriever System will comprise the analytic dataset.

Conservative Therapy Sub-study: (US Patients Only) Up to 300 additional patients with anticoagulation treatment as the initial planned primary treatment strategy for intermediate risk PE will be evaluated. Clinical assessments will be performed at Baseline, 48 hours, 30 days, and 6 months.

Conservative Therapy Sub-study: (US Patients Only) Approximately 150 of these patients should be considered intermediate-high risk. Enrollment will be limited to 60 patients per site. The Conservative Therapy Sub-study will

[b] The Fick Method will be utilized to estimate cardiac output. Measurement of pulmonary artery oxygen saturation, peripheral arterial oxygen saturation by pulse oximetry or arterial line, and the hemoglobin concentration is required. Body surface area (BSA) will be approximated with the modified DuBois formula; BSA = 0.007184 x (height in cm)$^{0.725}$ x (weight in kg)$^{0.425}$. O_2 consumption is approximated as body weight in kg x 3 ml/kg.

Cardiac output (CO) is estimated as the O_2 consumption divided by the product of arterial-mixed venous O_2 difference, hemoglobin concentration, and the constant 13.6. As an example, an 80 kg patient with a hemoglobin of 11 g/dL, a mixed venous (pulmonary artery) O_2 saturation of 60% and an arterial O_2 saturation of 97% would have an estimated cardiac output of (80 kg x 3 ml/kg) / [(.97 - .60] x 13.6 x 11 g/dL), or 210/ 53, or 4.34 L/min. If the BSA is 1.7, the cardiac index is 4.34/1.7, or 2.6. If the heart rate is 80, the SVI is 2,600 / 80 or 32.5 ml.

RVSWI is calculated as the (mean pulmonary artery pressure – right atrial pressure) x stroke volume index x 0.136.

PAPi is calculated as (pulmonary artery systolic – pulmonary artery diastolic) / right atrial pressure.

TPVR is calculated as the mean pulmonary artery pressure / cardiac output.

collect data on demographics, comorbidities, details from the PE diagnosis and treatment, and clinical outcomes through 6-month follow-up.

6.1 STUDY POPULATION

The study will consist of up to 1000 patients (up to 800 US, up to 200 Europe) with intermediate-risk and high-risk PE, who meet the eligibility criteria and are appropriate candidates for treatment with the FlowTriever System.

Conservative Therapy Sub-study (US Patients only): In addition to the up to 800 US patients enrolled who will receive treatment with the FlowTriever System, anticoagulation treatment will be evaluated on up to 300 patients diagnosed with intermediate-risk PE, who are not using mechanical thrombectomy as the primary treatment strategy. Approximately 150 of these patients should only be considered intermediate-low risk.

6.2 INFORMED CONSENT

Written, study-specific Informed Consent will be obtained from each patient 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 Informed Consent Form 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.

6.3 POINT OF ENROLLMENT

The FlowTriever System is not being used in an investigational manner and the patient will be treated with the device in the same manner regardless of whether the patient enrolls in the study. Therefore, the patient's consent for treatment is covered under the institution's internal procedures. To participate in the study, the patient must consent to share his/her de-identified personal health information (PHI) with the study sponsor. This allows sites to treat patients prospectively and consent patients after treatment. This can be helpful for sites when the research staff is unavailable to consent the patient prior to the index procedure (i.e., after hours, weekends, holidays). This practice is allowed provided there is no institutional prohibition against post-procedure consent.

Pre-procedure consents are the preferred consenting method and should be obtained ***within*** 48 hours of the scheduled index procedure. When the informed consents are obtained retrospectively to the Index procedure, the consent must be obtained ***after*** the patient gains full capacity from anesthesia ***and within*** 7 days of the index procedure unless approved by a Legal Authorized Representative (LAR).

If utilization of the FlowTriever System is planned, but the FlowTriever device does not enter the patient's vasculature, the patient is not enrolled and as such, his/her data is not entered into the database. The patient is considered enrolled when 1the patient consents to the study and the device enters the patient or 2) the device enters the patient and the patient consents within 7 days. The timing of the two events, index procedure and consent, are interchangeable.

Conservative Therapy Sub-study (US Patients Only): Point of enrollment will be defined as when 1) the patient is diagnosed with PE and the primary treatment strategy of anticoagulation is administered and 2) the patient consents to the study. The timing of treatment and consent are interchangeable.

6.4 INCLUSION CRITERIA

Patients must meet each of the following criteria to be included in the study:

1. Age ≥ 18 years

2. Clinical signs and symptoms consistent with acute PE
3. Echo, CTPA, or pulmonary angiographic evidence of proximal filling defect in at least one main or lobar pulmonary artery
4. Scheduled for PE treatment with the FlowTriever System per the Investigator's discretion*

*US Only Patients enrolled in the Conservative Therapy Sub-study are not required to meet this inclusion criterion but must instead be scheduled for primary anticoagulation therapy as the primary treatment strategy.

6.5 EXCLUSION CRITERIA

Patients will be excluded from the study for any of the following criteria:

1. Unable to anticoagulate with heparin or alternative
2. Diagnosed with a minor PE with less than a 0.9 RV/LV ratio
3. Known sensitivity to radiographic contrast agents that, in the Investigator's opinion, cannot be adequately pre-treated*
4. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the patient is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location or predominately chronic clot) *
5. Life expectancy < 30 days, as determined by the Investigator
6. Current participation in another investigational drug or device treatment study that, in the investigator's opinion, would interfere with participation in this study

*US Only Patients enrolled in the Conservative Therapy Sub-study are not required to meet these exclusion criteria.

7 ASSESSMENTS AND FOLLOW-UP SCHEDULE

7.1 SCHEDULE OF ASSESSMENTS

The assessments conducted will be according to normal instructions and care of patients. The Schedule of Assessments comprises recommended and required assessments. Any departures from the follow-up schedule will be documented as a protocol deviation. Required assessments include invasive hemodynamic measurements with HGB during the index procedure*; Echo at baseline, 30 days, and 6 months; dyspnea mMRC score at 48 hours, 30 days, and 6 months; and 6-minute walk test/PEmb QOL at 30 days and 6 months. Missing any of these elements will be documented as a protocol deviation.

**Invasive hemodynamic measurements are not required for patients in the Conservative Therapy Sub-study (US only)*

Wearables Assessment (US Patients Only): In addition to the follow-up schedule, approximately 100 patients receiving treatment with the FlowTriever System and approximately 100 patients receiving anticoagulation treatment will be asked to participate in ongoing data collection utilizing an Apple iWatch. Patients will be provided with a pre-configured Apple iWatch with cellular capabilities at the 48-hour visit. An iPhone is not required to participate. Patients who choose to participate will be expected to wear the Apple iWatch daily, with data collection occurring through their 6-month visit. Data to be collected will include but are not limited to blood oxygen saturation (Sp02), Heart Rate, and activity. Push notifications via SMS will also require the patient to respond to questions as applicable. Data collected via these means will not be provided to sites, routinely monitored, or used in the clinical decision-making process related to patient health.

Schedule of Assessments

Assessment	Baseline (≤ 48 hrs.)	Procedure* (Day 0)	48 Hours℘ (± 36 hrs.)	30 Days (± 15 days)	6 Months (± 90 days)
Inclusion/exclusion review	X				
Demographics	X				
Medical History and Risk Factors	X				
Clinical Diagnosis (CTEPH, CTED/Post PE Syndrome)	X			X	X
Current PE Condition	X				
Clinical Condition on Arrival to ED/Hospital	X				
Clinical Condition prior to treatment administration	X				
Anticoagulation regimen	X	X	X	X	X
Clinical Labs: HGB, CBC, Troponin, BNP, Lactate, INR, Creatinine, D-Dimer	X	X	X		
Echocardiogram (Required)	X			X	X
CTPA (Requested) †	X				
mMRC Dyspnea Score (Required)	X		X	X	X
Thrombectomy Time		X			
Vitals	X		X	X	X
Invasive hemodynamic measures with HGB, SvO2% (Required)		2X Δ			
Pulmonary angiograms		2X			
Bleeding measures		X	X		
FlowTriever Devices used		X			
Access Site information		X			
Procedure Summary (e.g. treatment location, EBL, Fluoro time, clot removal score, HR, pressures)		X			
Adjunctive therapy (thrombolysis and/or additional thrombectomy)	X**	X		X	
6-minute walk test (Required)				X	X
PEmb QOL (Required)				X	X
Adverse event assessment		X	X	X	X
Wearables assessment℺			X	X	X

* *Procedural assessments are not required nor will be captured for patients in the Conservative Therapy Sub-study.*

℘ *The time to assessment clock starts after TrieverCatheter is removed for the final time.*

† *CTPA imaging will be performed as per the local standard of care. If a CTPA is ordered, imaging data is requested.*

Δ *Invasive hemodynamic measures will include RA, RV, and PA pressures. From the tip of the pulmonary catheter, record the mixed venous PA sat (SvO2), RA pressure, and the PA pressures. Then, flush the catheter and draw the HGB sample from the PA and simultaneously record the heart rate, peripheral artery O2 sat (SaO2), and the oxygen level the patient is receiving. These measurements are obtained pre-FlowTriever insertion and at least 5 minutes after removing the FlowTriever for the final time.*

℺ *Data collection occurring from the 48-hour visit through the 6-month visit*

** *(US Patients Only) For Conservative Therapy Sub-study, collect if adjunctive therapy was used at Baseline*

NOTE: Consenting can be done 48hr pre-index procedure OR within 7 days post-index procedure. Enrollment occurs when consent is signed AND FlowTriever enters the body. For the Conservative Therapy Sub-study (US Patients Only), consenting can be done 48hr prior to the administration of anticoagulation therapy as the primary treatment strategy OR within 7 days after. Enrollment occurs when consent signed AND the primary treatment strategy to administer anticoagulation has commenced.

NOTE: Please collect COVID status at all visits as applicable on the supplemental EDC form

7.2 BASELINE ASSESSMENTS

An initial evaluation will be used to determine if a patient will be considered for enrollment. Assessments include diagnostic testing that would have been done as part of a patient's routine care. The following must be completed to evaluate for enrollment:

- Review inclusion/exclusion to ensure patient meets criteria
- Review of symptoms
- Confirm PE on echocardiogram or CTPA

If the consented patient meets all eligibility criteria and is scheduled for the thrombectomy procedure as the primary treatment strategy the patient will be enrolled in the study. If the patient consents within 7 days after the thrombectomy procedure and meets all eligibility criteria, the patient will be considered enrolled.

Patients (US Only) being treated with anticoagulation as the primary treatment strategy (instead of FlowTriever) may be invited to participate in the Conservative Therapy sub-study.

The following assessments will be performed at the Baseline Visit within 48 hours of the index procedure. All data must be recorded in the patient's case report forms (CRF):

- Demographic information
- Medical History and risk factors
- Current PE condition
- Clinical condition on arrival to ED/Hospital
- Clinical condition prior to procedure
- Anticoagulation regimen

Clinical laboratory tests are expected to be performed at this visit to establish baseline levels. The panel of tests (including: HGB, CBC, Troponin, BNP, Lactate, INR, Creatinine, D-Dimer) standardly performed at the institution for patients with similar conditions related to PE should be considered.

7.3 INDEX PROCEDURE*

Thrombectomy using the FlowTriever System is considered the index procedure and the treatment phase of the study. The procedure is conducted under fluoroscopic/angiographic guidance. Refer to the Instructions for Use (IFU) for techniques and methods for device deployment. The following data are to be recorded on the patient's Procedure CRF.

- Thrombectomy Time
- Number of FlowTriever devices used, with lot numbers
- Pre- and post-procedure hemodynamics (Invasive hemodynamic measures will include RA, RV, and PA pressures. From the tip of the pulmonary catheter, record the mixed venous PA sat (SvO2), RA pressure, and the PA pressures. Then, flush the catheter and draw the HGB sample from the PA and simultaneously record the heart rate, peripheral artery O2 sat (SaO2) and the oxygen level the patient is receiving. These measurements are obtained pre-FlowTriever insertion and at least 5 minutes after removing the FlowTriever for the final time.
- Pre- and post-procedure pulmonary angiograms

- Access site information
- Procedure Summary information (e.g. treatment location, EBL, Fluoro time, clot removal score)
- Procedure Bleeding Measures
- Adjunctive therapy (thrombolysis and/or additional thrombectomy)
- Anticoagulation regimen

All procedural angiograms will be uploaded/sent to the sites core laboratory.

7.4 BLEEDING MEASURES

Various bleeding scales have been used to assess hemorrhagic complications after treatment for PE. The current study will capture elements of the commonly-utilized scales.[62-65] This will allow comparisons of the rate of bleeding in the current study to that of other studies that have used a variety of bleeding scales. The elements that are included in several commonly employed bleeding scales are summarized in **Table 1**. Each element of each scale will be collected on the electronic case report forms (eCRFs) so that any of the bleeding scales can be retrospectively tabulated. Bleeding will be measured for 48 hours after conclusion of the index procedure.

Table 1. Elements of Various Bleeding Scales

Elements	Bleeding Scale					
	BARC	PEITHO	VARC	TIMI	GUSTO	ISTH/SSC
Clinically-overt bleeding				X		X
Hemoglobin drop (g/dL)[§]	X		X	X	X	X
Units of transfusion for bleeding[§]	X	X	X		X	X
Hemodynamic compromise		X			X	
Requires surgical intervention	X	X	X			
Life-threatening bleeding[*]	X	X	X			
Fatal bleeding				X		X
Intracranial hemorrhage	X	X	X	X	X	
Intraocular bleed, impairment vision	X					
Chest tube output	X					
Bleeding is actionable[†]	X		X	X		X
Bleeding is in a critical organ			X			X
Compartment syndrome						X

[*] Includes cardiac tamponade, intracranial bleeding, bleeding requiring intravenous vasoactive agents
[†] Defined by BARC as overt (clinically-evident or observed on imaging) bleeding that leads to discontinuation of a medication (e.g. antiplatelet or anticoagulant), local wound compression or other therapy, leads to hospitalization or prolonging of hospitalization, or to an unscheduled visit to a healthcare profession with laboratory or imaging assessment. Visits not prompting such assessments do not meet the criteria for BARC Type 2 bleeding. Defined by ISTH as hospital admission for bleeding, a physician-guided medical or surgical intervention for bleeding, or a change in antithrombotic therapy.
[§] The numerical hemoglobin drop and/or the number of units transfused will be recorded for all patients. However, neither will be captured as a complication unless they also meet the VARC-2 definition. Both will require a concurrent overt cause of bleeding AND either a ≥5g/dL Hgb drop or ≥2 units whole blood/RBC.

7.5 FOLLOW-UP ASSESSMENTS AND WINDOWS

Follow-up evaluation will be scheduled at 48 hours (±36 hours), 30 days (±15 days), and 6 months (±90 days) post-procedure (or post anticoagulation administration for patients enrolled in the Conservative Therapy Sub-study.

The following assessments and procedures will be performed at the 48-hour visit:

- Vitals
- Dyspnea mMRC
- Clinical Labs: HGB, CBC, Troponin, BNP, Lactate, INR, Creatinine, D-Dimer
- Anticoagulation regimen
- Bleeding Measures
- AE observations that occurred since the last visit

The following assessments and procedures will be performed at the 30-day and 6-month visits:

- Vitals
- Clinical Diagnosis (CTEPH, CTED/Post PE Syndrome)
- Echocardiogram
- Dyspnea mMRC
- Anticoagulation regimen
- 6-Minute Walk Test
- PEmb QOL
- AE observations that occurred since the last visit

7.6 UNSCHEDULED FOLLOW-UP VISITS

This Registry study was designed to capture real-world data regarding the clinical use of the FlowTriever System and anticoagulation therapy. Therefore, the study will only record patient visits during the follow-up period that are related to the patient's PE condition and treatment. If a patient returns to the site between scheduled follow-up visits for matters related to the study, the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the Investigator*. CRF pages are provided for unscheduled visits with appropriate assessments and reason for the visit.

* *(US Only Patients) If a patient enrolled in the Conservative Therapy Sub-study requires an unscheduled visit for mechanical thrombectomy utilizing the FlowTriever System, pre-and post-hemodynamic measurements are required to be captured on the Unscheduled Visit CRF.*

7.7 WITHDRAWALS AND LOST TO FOLLOW-UP

Participation is completely voluntary, and each patient is free to withdraw from the study at any time. An investigator also has the right to withdraw the patient from the study in the event of reasons concerning the health or well-being of the patient, or in the case of lack of cooperation. Should a patient decide to withdraw for any reason, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal must be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

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.

If the FlowTriever procedure is aborted after entering the vasculature, the patient does not need to complete the follow-up assessments, however, patients who require conversion to open surgery due to incomplete FlowTriever

procedure will be followed for safety through 30 days, or until any treatment-related adverse events resolve, whichever is later. Then the patient will be exited from the study.

All efforts will be made to return patients for all follow-up visits. Due diligence in reaching the patient must be made by two documented telephone contact attempts, emails, or regular postal mail letters. After the above attempts are made, if no response is obtained, the final evaluation of the patient and study exit will be dated on the last visit at which study-related assessments were performed. The Study Exit CRF page will be completed, and communication attempts will be documented.

7.8 COVID-19 Effect on Research

This Registry study was designed to capture real-world data regarding the clinical use of the FlowTriever System (and anticoagulation treatment in the Conservative Therapy Sub-study). As a result of the COVID-19 pandemic, clinic practice patterns may have been affected and patient visits may have been postponed or eliminated. In addition, some data may be collected from patients over the phone. Our goal is to collect as much real-world data as possible while protecting everyone's safety.

8 RISK ANALYSIS

8.1 Risks to Patients

The FLASH Registry involves the use and disclosure of deidentified health information. It collects only information relevant to the patient's PE condition and treatment.

The Registry study involves the collection of specific information for research and educational purposes only. It does not specify how the FlowTriever System or anticoagulation will be used to treat PE, and decisions regarding a patient's treatment are not influenced by the Registry study. Physicians participating in the Registry study are expected to review the indications, contraindications, warnings, precautions, and safety events described in the IFUs. As with any endovascular procedure or anticoagulation regimen, the treating physician is expected to counsel the patient on the risks and benefits specific to the planned treatment and to obtain the local, procedure-related, or treatment-related informed consent per institutional policies and procedures.

8.2 Risk Mitigation

The Registry study was designed to capture real world data regarding the clinical use of the FlowTriever System (and anticoagulation treatment in the US Conservative Therapy Sub-study). The risks of providing this personal health information have been mitigated, as no personal information directly identifying the patient will not be collected for the Registry database. At the time of participation, each participant will be assigned a unique study identification number. This number will be used in the database to identify the patient. . All data handling will be in accordance with GDPR and HIPAA requirements and only de-identified information will be entered.

9 SAFETY ASSESSMENT

9.1 Defining Adverse Events

An AE is any untoward medical occurrence or exacerbation of an existing medical condition subsequent to treatment with the FlowTriever. AEs are classified in several ways, including severity, relationship, and seriousness.

- Severity (mild, moderate, severe)

- ***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 mortality.

- Relationships (unrelated, device-related, procedure-related, drug-related, or relationship unknown) are defined below.

  Unrelated**:** The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.
  Device-related: The event is directly related to the study device itself, as defined by its intended use. AEs will be considered unrelated to the device if the complication could have occurred if the device functioned entirely within its specifications.
  Procedure-related: Procedure-related events include all AEs that occur at any time of patient participation that was directly related to the procedure. The exception to this rule is an event that is device-related; such events should not also be classified as procedure-related.
  Drug-related: Event is attributable to thrombolytic or anticoagulant therapy. These events may occur from inadequate (thrombosis) or excessive therapy (bleeding). A drug-related AE cannot also be classified as device-related, but many will be classified as procedure-related, since the drug may be part and parcel of the index procedure or the event may have occurred within 30 days.
  Relationship unknown: The relationship to the study procedure/study device is not known.

  A ***Serious Adverse Event (SAE)*** is an event that meets at least one of the following:

  - Is fatal
  - Is life-threatening
  - Results in persistent or significant disability/incapacity
  - Results in permanent impairment of a body function or permanent damage to a body structure
  - Results in hospitalization or prolongs a hospitalization
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
  - Results in a congenital anomaly or birth defect
  - Serious deterioration of the health of the patient that resulted in chronic disease

9.2 REPORTING OF EVENTS

The FLASH Registry study was designed to capture real-world data regarding the clinical use of the FlowTriever System (and anticoagulation treatment in the Conservative Therapy Sub-study) and involves the collection of specific information for research and educational purposes only. It does not specify how the FlowTriever System or anticoagulation will be used to treat PE, and decisions regarding a patient's treatment are not influenced by the study. This is a data collection study only; there is nothing investigational or experimental in the patient's medical treatment.

Therefore, the study will only capture AEs related to the patient's PE condition and its treatment. Reportable AEs include all events considered in the safety analyses (e.g., major bleeding[c]), all device- and/or procedure-related AEs, as well as any event resulting in mortality.

The AEs will be captured on the Adverse Event CRF and should include, wherever possible, severity, duration, outcome, the Investigator's description of the event, and his/her medical judgment as to the relationship of the AE (i.e., not related, related, or relationship unknown) to the study device, to the index procedure or any subsequent procedure(s), to a thrombolytic agent or anticoagulant, or underlying disease.

- Non-serious reportable AEs are to be submitted via the electronic data capture system (EDC) in a timely fashion.
- Reportable SAEs must be reported to the Sponsor within 5 business days of the Investigator's knowledge of the event. The event is reported in the EDC.

Appendix 1 includes a list of possible SAEs associated with thrombectomy, including those events considered major device-related events and major morbidity. These events are considered reportable at all time points throughout the study and require submission to the Sponsor and the IRB/EC and regulatory authorities, as required.

10 STATISTICS & DATA ANALYSIS

10.1 SAMPLE SIZE

The sample size of up to 1000 patients (up to 800 US and up to 200 Europe) for the FlowTreiver System and up to an additional 300 patients for anticoagulation treatment reflects an adequate size to accrue data on real-world use, as assessed in up to 100 (up to 70 US, up to 30 Europe) registry sites.

10.2 STATISTICAL METHODOLOGY

This is an observational study and as such is not hypothesis-driven. The endpoints will be assessed for patients receiving treatment with the FlowTriever System with descriptive statistics. Continuous variables will report any combination of mean, median, Q1, Q3, IQR, minimum and maximum while the categorical variables will report frequency count and percentages (%). Additional ad-hoc and exploratory analyses for both the main study and US Conservative Therapy Sub-study will be separately defined in the Statistical Analysis Plans.

11 STUDY MANAGEMENT CONSIDERATIONS

11.1 DATA MANAGEMENT AND COLLECTION OF CLINICAL DATA

The Sponsor and/or designee will be responsible for the processing and quality control of the data. All source data, CRFs, copies of protocols and protocol amendments, correspondence, patient identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after study completion or closure.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator prior to the conclusion of the retention period. 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.

[c] For the purposes of this study, mild to moderate pain or ecchymosis at the access site do not require reporting as adverse events.

11.2 PROTOCOL MODIFICATIONS

No changes from the final approved study protocol will be initiated without the IRB/EC prior written approval of the amendment. The Principal Investigator will acknowledge the amendment by signing the Protocol Signature Page.

11.3 PROTOCOL DEVIATIONS

A protocol deviation is the non-adherence to or divergence from the protocol-required study procedures. For example, the inclusion and exclusion criteria, improper or lack of consent, and lack of IRB/EC approval would all be considered protocol deviations. Non-compliance with required assessments or out of window visits will result in a protocol deviation.

The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

11.4 INFORMATION FOR STUDY PERSONNEL

The Sponsor or designee is responsible for explaining the protocol to all study staff, including the Investigator, and for ensuring their compliance with the protocol throughout the study. Additional information will be made available during the study when new staff become involved in the study, and as otherwise agreed upon with either the Investigator or the Sponsor or designee.

The Investigator is responsible for giving information about the study to all staff members involved in the study or any element of patient management, both before starting the study and during the study (e.g., when new staff become involved). The Investigator must ensure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

12 STUDY ADMINISTRATION

12.1 SITE INITIATION

A Site Initiation Visit (SIV) may be conducted by the Sponsor or designee in-person or via teleconference to ensure proper training of the Investigator and study staff members regarding the study protocol and data collection, as well as to ensure regulatory requirements are fulfilled prior to enrollment of the first study patient at a site.

12.2 SITE MONITORING VISITS

Interim monitoring visits may be conducted by the Sponsor or designee in-person or remotely to ensure compliance with the protocol, and other written instructions and regulatory guidelines according to a study-specific monitoring plan.

The main responsibilities of the Monitor or designee are to ensure adherence to the protocol; to verify all data are correctly and completely recorded and reported; confirm that informed consent is obtained and recorded for each patient before any medical record or personal health information is shared with any study representatives. The Investigator and assisting staff must agree to cooperate with the Monitor or Sponsor representative to resolve any study-related action items, errors, or possible misunderstandings concerning the findings detected during these monitoring visits or data review.

12.3 STUDY TERMINATION

Inari Medical and applicable regulatory authorities have the right to terminate the entire study or a specific study site at any time. Situations that could 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
- Insufficient patient enrollment rates
- Recurrent protocol deviations or other non-compliances
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis
- 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)

12.4 DATA HANDLING AND RECORDKEEPING

12.4.1 Completing, Signing and Archiving Case Report Forms

Clinical study data will be collected using electronic case report forms (eCRFs). A web-based electronic data capture (EDC) database will be used to record and manage study data. eCRF completion guidelines and instructions for electronic data-entry will be developed in conjunction with the Sponsor and/or EDC vendor. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the patients participating in the study.

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.

It is important to have proper data collection in a timely manner (approximately 5 business days of the study visit/assessment). When the Sponsor or designee requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily in a timely manner.

12.4.2 Data Management and Archiving

The Sponsor or designee will be responsible for the processing and quality control of the data. All imaging and wearable data collected for the study, eCRFs, copies of protocols and protocol amendments, correspondence, patient identification lists (kept by the Investigator), informed consent forms, and other essential documents must be retained for a period of at least 2 years after the study completion or closure.

No study document or image 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.

12.4.3 Direct Access to Source Data/Documentation

The Investigator must maintain, at all times, the primary records (i.e., the original source of the data/source documents) of each patient's data. Examples of source documents are hospital records, office visit records, examining physician's findings or progress notes, consultant's written opinion or notes, laboratory reports, imaging data, and worksheets that are used as the source.

The Investigator must keep a separate patient identification list showing enrollment numbers and names to allow unambiguous identification of each patient included in the study.

The Sponsor, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical chart/records, laboratory test results, images) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

13 ETHICS AND CONFIDENTIALITY

13.1 INFORMED CONSENT

Written informed consent will be obtained from each patient prior to the patient's medical record or personal health information being shared with any study representative. The patient's willingness to participate in the study will be documented in writing in a study-specific Informed Consent Form, which will be signed and dated by the patient or Legally Authorized Representative. The Investigator will keep the original consent form and a copy will be given to the patient. It will be explained to the patients 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. Patients will be consented for the duration of the patient's participation in the study.

13.2 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC)

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 ISO 14155-1 and FDA regulations (21 CFR Part 56), prior to starting the study.

The Sponsor must receive a copy of the IRB/EC approval letter (or equivalent documentation) for the study protocol and Informed Consent Form before the study can be started at that site.

The IRB/EC and Sponsor must approve any changes to the protocol, as well as a change of Principal Investigator. Documentation of IRB/EC approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Study File/ Regulatory Binder and are patient to inspection by the Sponsor (or designee) or regulatory authority during or after completion of the study.

The Investigator must notify the IRB/EC, as per their reporting guidelines, and the Sponsor when they deviate from the protocol. The Sponsor must be notified of all relevant action taken by the IRB/EC and must receive a copy of all study-related correspondence between the Investigator and the IRB/EC.

The IRB/EC must receive notification of study completion and a final report upon study completion or closure. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB/EC.

13.3 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 or image material submitted to the Sponsor, 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) and General Data Protection Regulation (GDPR).

13.4 Independent Medical Monitor

An independent Medical Monitor, an independent physician who is not a participant in the study, will review AEs that occur throughout the course of the study. The activities of the Medical Monitor will be guided by the Safety Manual. The Medical Monitor will be responsible for classifying events by severity, relationship, and seriousness, as well as whether they meet MAE criteria related to the primary safety endpoint. For the Primary Endpoint, the Medical Monitor AE assessments will supersede those of the Investigators when there are differences.

13.5 Core Laboratory and Image Transfer

A core laboratory may be utilized in the study. The core laboratory will independently evaluate selected images collected at participating institutions.

Irrespective of whether a core laboratory is utilized for pulmonary angiogram measurements of anatomic endpoints, de-identified, electronic pulmonary angiograms, echocardiographs, and CTPA images will be sent via secure electronic transfer to a **secured** imaging repository per US FDA/EU GDPR regulations. Where an electronic submission is not possible, deidentified images will be sent by other secure means per US FDA/EU GDPR regulations. Copies of images will be securely stored for a minimum of 2 years after the study has ended.

13.6 Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential patients. The criteria used for determination will be documented.

13.7 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., ISO 14155-1, 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)

14 ELECTRONIC DATA

Electronic data will only be accessible to authorized personnel with a unique user identifier and password for the EDC. Passwords will be set to expire periodically. Access to electronic study data will be provided to research

personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and patient data at their site. The Sponsor and designee will have read-only access and can post queries for potential data-related discrepancies.

(US Patients Only) Wearables: Electronic data collected via the Apple iWatch will be uploaded into a CFR Part 11 compliant database daily via cellular data transfer. Data will only be accessible to authorized personnel with a unique user identifier and password.

15 TERMS AND DEFINITIONS

Term	Definition
Primary Safety Endpoint Definitions	

Major adverse event (MAE)	A composite endpoint triggered when one or more of the following events occur:
	• Device-related mortality within 48 hours, *or*
	• Major bleeding within 48 hours, *or*
	• Intraprocedural Device or procedure-related adverse events, including:
	  ○ Clinical deterioration defined by hemodynamic or respiratory worsening, *or*
	  ○ Device-related pulmonary vascular injury, *or*
	  ○ Device-related cardiac injury.

Intraprocedural	Events occurring during the procedure or within 30 minutes of the FlowTriever Catheter being removed from the patient.
MAE: Major Bleeding (≤48 hours)	Fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 5 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.
MAE: Clinical Deterioration (Intraprocedural)	Clinical deterioration is defined when new (not present at the start of the index procedure) hemodynamic or respiratory deterioration occurs.
MAE: Hemodynamic Deterioration (Intraprocedural)	When one or more of the following is *definitely documented*, with relation to both the severity *and* the duration of the event: • Hypotension with systolic blood pressure <90 mm Hg lasting at least 30 minutes, unresponsive to fluid resuscitation, and requiring the addition of or increased dose of vasopressors • Fall in systolic blood pressure by 40 mm Hg or more, lasting at least 30 minutes, and accompanied end-organ hypoperfusion (such as oliguria, mental status changes, ischemic extremities) • Cardiac arrest requiring cardiopulmonary resuscitation • Bradycardia lasting more than 10 minutes, accompanied by hypotension, and requiring pharmacologic intervention or insertion of a pacemaker • Ventricular tachycardia or fibrillation requiring pharmacologic intervention or defibrillation
MAE: Respiratory Deterioration (Intraprocedural)	A significant decline in respiratory function with one or more of the following is *definitely documented* with respect to the severity *and* the duration of the event:

Term	Definition
	• Requirement for an increase in fraction of inspired oxygen requirements 0.20 or greater, lasting longer than 30 minutes (e.g. from 0.21 to 0.41) • Need for intubation in a previously non-intubated subject
MAE: Pulmonary Vascular Injury (Intraprocedural)	Perforation or injury of a major pulmonary arterial branch requiring intervention to avoid permanent injury.
MAE: Cardiac Injury (Intraprocedural)	Any damage to the heart requiring intervention to avoid permanent injury.

Additional Safety Definitions	
Adverse event (AE)	An AE is any untoward medical occurrence or exacerbation of an existing medical condition subsequent to treatment with the FlowTriever.
Device-related event	The event is directly related to the study device itself, as defined by its intended use. AEs will be considered unrelated to the device if the complication could have occurred if the device functioned entirely within its specifications.
Drug-related event	Event is attributable to thrombolytic or anticoagulant therapy. These events may occur from inadequate (thrombosis) or excessive therapy (bleeding). A drug-related AE cannot also be classified as device related, but many will be classified as procedure-related, since the drug may be part and parcel of the index procedure or the event may have occurred within 30 days.
Minor bleeding	All non-major bleeds will be considered minor bleeds.
Procedure-related event	Procedure-related events include all AEs that occur at any time of subject participation that was directly related to the procedure. The exception to this rule is an event that is device-related; such events should not also be classified as procedure-related.
Reportable adverse event	Reportable AEs include all events considered in the safety analyses, all device- and/or procedure-related AEs, as well as any event resulting in mortality.
Serious adverse event (SAE)	An adverse event that meets at least one of the following: is fatal; is life-threatening; results in persistent or significant disability/incapacity; results in permanent impairment of a body function or permanent damage to a body structure; results in hospitalization or prolongs a hospitalization; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; results in congenital anomaly or birth defect; results in chronic disease
Other Definitions	
Asymptomatic PE	Pulmonary embolism detected on an imagining study in a patient without clinical symptoms.
CTED/Post PE Syndrome	Chronic thromboembolic Disease: Per 2019 ESC Guidelines, some patients may present with normal pulmonary hemodynamics at rest despite symptomatic disease. If other causes of exercise limitation are excluded, these patients are considered as having chronic thromboembolic disease (CTED). From Respiratory medicine journal on PE, (CTED) is characterized by similar symptoms and imaging findings to CTEPH but without pulmonary hypertension at rest.

CTEPH	Chronic thromboembolic pulmonary hypertension: Per 2019 ESC Guidelines, CTEPH is a disease caused by the persistent obstruction of pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodeling of the pulmonary microvascular bed. The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation, to distinguish this condition from acute PE. The diagnosis requires a mean PAP of ≥25 mmHg along with a pulmonary arterial wedge pressure of ≤ 15 mmHg, documented at right heart catheterization in a patient with mismatched perfusion defects on V/Q lung scan.
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.
Proven PE	Pulmonary embolism proven by a positive pulmonary angiogram, an unequivocally positive CT scan, a high-probability ventilation-perfusion scan, or autopsy.
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 independent Medical Monitor.
Suspected PE	Pulmonary embolism suspected based on clinical symptoms and/or signs but for which definitive diagnosis has not been made by imaging or autopsy.
Symptomatic PE	Clinical pulmonary embolism symptoms and/or signs such as chest pain, dyspnea, hemoptysis, palpitations, or tachycardia.
Wearable Technology (Wearables) US Patients Only	From Dictionary.com, Wearable technology is a small computer or advanced electronic device that is worn or carried on the body. For purposes of this study, the wearable technology being used is the Apple iWatch, which collects health metrics.

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APPENDIX 1 KNOWN RISKS OF THROMBECTOMY

Event Category	Event
Cardiac	Myocardial infarction
	Congestive heart failure
	Arrhythmia
	Hypertension
	Hypotension
Wound	Wound infection
	Wound pain
	Wound dehiscence
	Serous wound drainage
	Lymphorrhea
	Hematoma
	Ecchymosis
Peripheral vascular	Vessel perforation
	False aneurysm formation
	Arterial dissection
	Mural thrombus formation
	Vessel occlusion
	Arteriovenous fistula
	Distal embolization
Venous	Deep venous thrombosis
	Pulmonary embolism
	Paradoxical embolization
Cerebrovascular	Transient ischemic attack
	Stroke
	Intracranial hemorrhage
Pulmonary	Exacerbation of chronic lung disease
	Respiratory failure
Miscellaneous	Sepsis
	Mortality

SIGNATURE APPROVAL PAGE

FLowTriever **A**ll-Comer Registry for Patient **S**afety and **H**emodynamics **(FLASH)**
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Signed: 

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