FLowTriever for **A**cute **M**assive Pulmonary **E**mbolism **(FLAME)**

Device: FlowTriever® Retrieval/Aspiration System
Protocol Number: 20-001
Version: 3.0
December 6, 2020

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 subject information (e.g., source documents) and all other information collected during the study, in accordance with local and national regulations.

Investigator's Signature	Date

SYNOPSIS

Protocol Number	20-001
Study Title	**FL**owTriever for **A**cute **M**assive Pulmonary **E**mbolism
Study Device	FlowTriever Retrieval/Aspiration System
Regulatory Status	The FlowTriever System is cleared for the treatment of Pulmonary Embolism under 510(k) number K180466. 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
Study Objective	The primary objective of this observational study is to evaluate treatment outcomes of patients diagnosed with high-risk (massive) pulmonary embolism who have received treatment with the FlowTriever System compared to an established performance goal (literature-based goal). In addition to the primary objective, outcomes of patients diagnosed with high-risk (massive) pulmonary embolism who have received treatment with other (non-FlowTriever) therapies will also be analyzed.
Study Population	**FlowTriever Arm:** Up to 71 subjects will be enrolled in the FlowTriever Arm. FlowTriever Arm subjects are defined as those subjects where FlowTriever is used as the primary treatment for high-risk pulmonary embolism. Patients presenting with low /intermediate-risk PE and treated with anticoagulation alone who subsequently progress to high-risk PE and are treated front-line with FlowTriever will be enrolled in the FlowTriever Arm. An interim analysis will be performed on the first 50 subjects enrolled in the FlowTriever Arm, at which time enrollment may be closed based on the results of the interim analysis. **Context Arm:** Subjects with high-risk (massive) pulmonary embolism who are treated with non-FlowTriever therapies (as the primary treatment for high-risk PE) will be enrolled in the Context Arm concurrently with subjects in the FlowTriever Arm. Subjects presenting with low/intermediate-risk PE who are initially treated with anticoagulation and subsequently progress to high-risk PE should be enrolled in the Context Arm if not treated front-line by FlowTriever at this time. The Context Arm will enroll concurrently with the FlowTriever Arm until FlowTriever enrollment is completed, with a minimum enrollment of 1:1 subjects in both the FlowTriever and Context arms, and a maximum enrollment of 2:1 Context Arm to FlowTriever Arm subjects. Subjects enrolled in the Context Arm will be analyzed separately from the endpoint analysis utilizing descriptive methods.

	Prior Therapy Arm: Subjects presenting with low/intermediate-risk PE who receive advanced therapy during their hospital stay but subsequently progress to high-risk PE should be enrolled in the Prior Therapy Arm. Enrollment in the Prior Therapy Arm will be concurrent with the FlowTriever Arm of the study, and enrollment in this arm will cease when enrollment in the FlowTriever Arm is complete. Data collection for Prior Therapy Arm subjects will include information surrounding the PE treatment, progression to High-Risk PE, and patient course through hospital discharge. Safety data will be collected, but not CEC adjudicated or analyzed as outlined for the FlowTriever and Context Arm subjects. Subjects receiving prior advanced treatment for low/intermediate-risk PE in the same hospital setting as a second treatment for high-risk PE likely have a different profile than those receiving advanced care for the first time after diagnosis of high-risk PE, and therefore should be looked at separately. In the spirit of the AHA guidelines for trial design in this patient population, data will be collected to ensure representation of this smaller yet significant group of high-risk PE patients. **Concurrent Enrollment in All Arms:** Sites participating in the FLAME study will enroll all subjects presenting with high-risk (massive) PE over the course of the study, regardless of their primary thrombus removal strategy or prior therapy to ensure enrollment of all-comers to the study. Subjects will be enrolled in each arm as described above.
Number of Sites	The FLAME Study will be conducted at up to 20 sites in the United States.
Study Design	Prospective, multicenter, non-randomized, parallel group, observational study of subjects concurrently enrolled in the FlowTriever, Context, and Prior Therapy Arms.
Primary Endpoint	In-hospital composite endpoint of: • All-cause mortality • Bailout to an alternative thrombus removal strategy • Clinical deterioration • Major bleeding, BARC 3b/3c/5a/5b definition
Secondary Endpoints	**<u>Secondary Safety Endpoints</u>** • Frequency of each primary endpoint composite component • Frequency of Stroke (ischemic or hemorrhagic) • Frequency of device-related complications • Access site injury requiring intervention, both venous and arterial **<u>Utility Measures</u>** • Length of hospital stay • Length of ICU stay • Use of ECMO, including either pre- or post-treatment initiation and duration • Time to extubation, if intubated • Discharge location

Inclusion Criteria	High-risk pulmonary embolism (PE) subjects must meet each of the following criteria to be eligible for enrollment:
	
	• ≥18 years of age
	• Treatment team determines pulmonary embolism is the cause of shock
	• One or more of the following:
	  ○ Systolic blood pressure <90 mmHg for at least 15 minutes or drop of >40 mmHg in systolic blood pressure for at least 15 minutes, and/or
	  ○ Need for vasopressor support, and/or
	  ○ Resuscitation after cardiac arrest with <30 minutes of CPR and Glasgow Coma Scale >8.	

Exclusion Criteria	High-risk pulmonary embolism (PE) subjects will be excluded from the study for any of the following criteria: • Out of hospital cardiac arrest with Glasgow Coma Scale of ≤8 • Witnessed cardiac arrest with ongoing CPR >30 minutes • Contraindication to anticoagulants, i.e. heparin or alternative • Hematocrit <28% • Platelets <25,000/µL • INR >8 • Intracardiac thrombus and/or intracardiac clot in transit • Known anaphylactic sensitivity to radiographic agents that cannot be pre-treated • History of pulmonary hypertension with systolic pulmonary arterial pressure >70 mmHg • Presence of chronic medical conditions with estimated < 90 days life expectancy per physician discretion (should not consider the current pulmonary embolism and its treatment) • Current participation in another drug or device treatment study that, in the Investigator's opinion, would interfere with participation in this study • Patient is known to be COVID-19 positive at hospital admission (patient has active COVID-19)	
Primary Endpoint Definitions All events contributing to the Primary Endpoint will be adjudicated by the CEC for the FlowTriever and	Bailout to an alternate thrombus removal strategy	Need for mechanical circulatory support or another thrombus removal strategy after the primary treatment strategy was initiated. The additional treatment strategy was not an a priori part of the original treatment plan (conceived beforehand).
	Clinical Deterioration	• Need for CPR • Need to start IV vasopressors to keep systolic blood pressure > 90 mmHg in a previously normotensive patient • Need for mechanical ventilation in a previously spontaneously breathing patient

Context Arm Subjects		• Need for noninvasive positive pressure ventilation in a patient previously on nasal cannula
	Major Bleeding, BARC 3b/3c/5a/5b	• 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents • 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. • 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
Study Schedule	Subjects will be followed through hospital discharge from the Primary High-Risk PE treatment procedure.	
Safety Monitoring	Safety events for the FlowTriever and Context Arm subjects will be adjudicated by an external Clinical Events Committee (CEC).	
National Principal Co-Investigators	Mitchell Silver, DO James Horowitz, MD	

ABBREVIATIONS

Abbreviation	Term
AC	Anticoagulation
ADaM	Analysis data model
AE	Adverse event
AGC	Aspiration guide catheter
AHA	American Heart Association
BARC	Bleeding Academic Research Consortium
BNP	B-type natriuretic peptide
CDISC	Clinical Data Interchange Standards Consortium
CDT	Catheter-directed thrombolysis
CEC	Clinical Events Committee
CPR	Cardiopulmonary resuscitation
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
EDC	Electronic data capture
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FLARE	FlowTriever Clinical Embolectomy Clinical Study
FLAME	FlowTriever for Acute Massive Pulmonary Embolism
FLASH	FlowTriever All-Comer Registry for Patient Safety and Hemodynamics
FT	FlowTriever
GLM	Generalized linear models
H-FABP	Heart type fatty acid binding
ICU	Intensive care unit
IFU	Instructions for use
INR	International normalized ratio
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intent to treat
LV	Left ventricle
MAE	Major adverse events
NT-proBNP	N-terminal pro B-type natriuretic peptide
PE	Pulmonary embolism
PERT	Pulmonary Embolism Response Team
PESI	Pulmonary Embolism Severity Index

Abbreviation	Term
PHI	Protected Health Information
rt-PA	Recombinant tissue plasminogen activator
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
SAE	Serious adverse event
SIV	Site initiation visit
sPESI	Simplified Pulmonary Embolism Severity Index
TLF	Tables, lists, and figures
TNK	Tenecteplase
TTE	Transthoracic echocardiogram
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 deep vein thrombosis (DVT) and PE. PE occur 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 death. Some PEs 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."

High-risk PE carries a significantly high mortality rate. Even after intervention, the morbidity and mortality of this disease process is profound.[1-4] Medical treatment paradigms for high-risk PE also pose risk, with many of these possible therapies utilizing anticoagulants and thrombolytics.[5] Surgical thrombectomy for high-risk PE has been performed with some success if treated before the development of cardiogenic shock but again poses risk of significant morbidity and mortality.[6] Systemic thrombolysis has long been a treatment option for high-risk PE patients, although the treatment is associated with significant bleeding risks. Rates of major bleeding spanning from approximately 10%-50% have been reported, with rates of intercranial hemorrhage of approximately 3%-4%.[2, 3, 7-10] Accordingly, a non-surgical treatment modality obviating the need for thrombolysis would be an optimal addition to the treatment armamentarium.

1.1 INCIDENCE AND FATALITY RATE FOR INTERMEDIATE RISK PE AND HIGH-RISK PE

Estimates of VTE incidence range from 75 and 269 cases per 100,000 population.[11] While the actual incidence of reported VTE differs by global geography, the rate of 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 in the world (**Figure 1**).

Data from the Nationwide Inpatient Sample from 1993-2012 showed that US hospital admissions for PE rose from 23 per 100,000 in 1993 to 65 per 100,000 in 2012.[12] Interestingly, over the same time period there was a decrease in admissions for high-risk PE (2.8 to 1.5 per 100,000).[12] The rise in detection of PE is likely due to better diagnosis with the increased use of computed tomographic pulmonary angiography (CTPA) over the years of study. All-cause mortality in PE patients decreased from 7.1% in 1993 to 3.2% in 2012.[12] A study in China also showed a drop in the fatality rate, 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.[13] However, a recent multicenter U.S. study on Pulmonary Embolism Response Teams (PERTs) found the 30-day mortality rate among the centers ranged from 9% to 44% (with a mean of 16%) for patients with PE.[14] Not surprisingly, the mortality rate for patients with high-risk PE is higher compared to intermediate-risk patients. A fivefold increase in mortality has been reported for high-risk PE as compared to intermediate-risk patients.[8]

In a study published in Circulation, according to Kucher et al., the incidence of high-risk PE was 4.5%.[15] Of patients with PE, a recent report on PERTs in the U.S. found that 12.3% of PE patients were in the high-risk PE category.[14] Of all patients presenting with PE, the most significant variables that distinguished high-risk PE from non-massive PE were systolic blood pressure, heart rate, days from symptom onset to diagnosis, syncope, right ventricular hypokinesis, decreased left ventricular ejection fraction, concomitant deep vein thrombosis, congestive heart failure, and elevated serum creatinine.

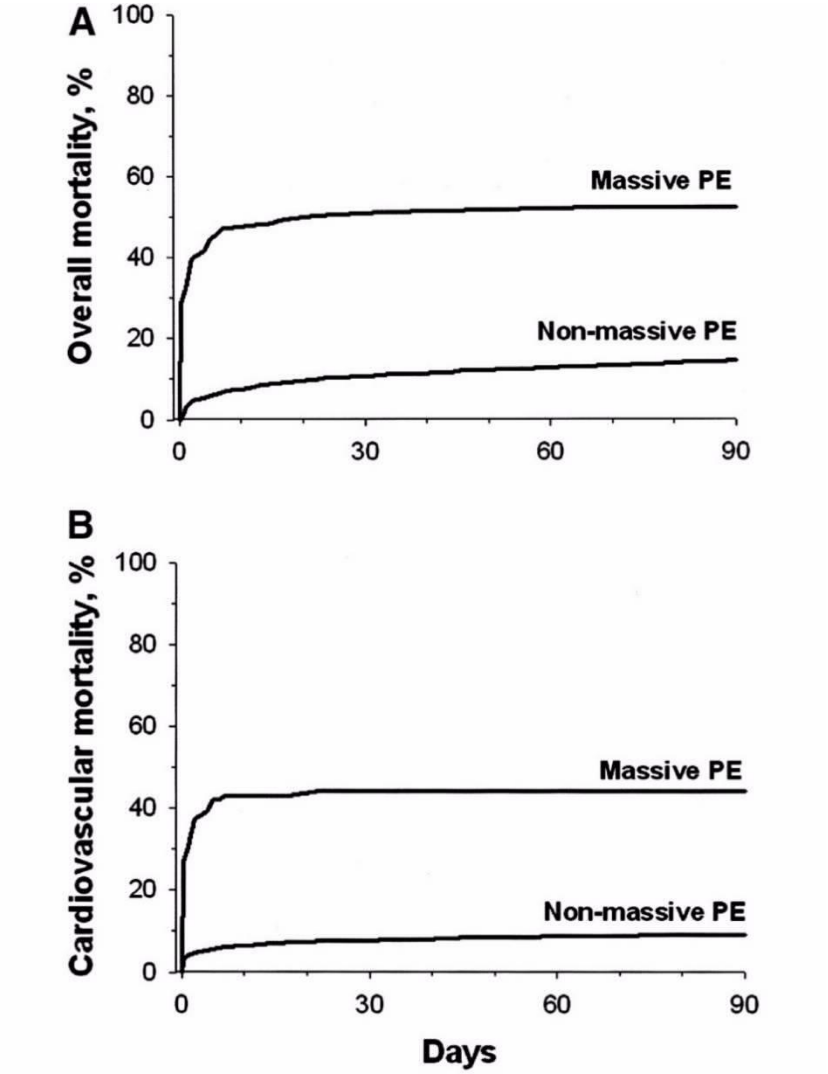


Figure 1. Incidence and Case-Fatality Rate for Massive vs non-Massive Pulmonary Embolism[11]

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.

CTPA imaging is performed in most centers today.[16] 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.[17] As well, CTPA can over-diagnose small, subsegmental emboli of little clinical consequence.[18] 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.[17,19] The terminology of massive pulmonary embolism correlates to the "high-risk" pulmonary embolus as defined by the European Society of cardiology (ESC).[20, 21]

The diagnosis of high-risk PE is typically made clinically using the following criteria: Acute PE with sustained hypotension (defined as a systolic blood pressure <90 mm Hg, for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).[20, 21] Other prognostic factors include; right ventricle (RV) dilation, hypokinesis, and ischemia/infarction. RV dilation leads to reduced filling of the left ventricle (LV), and an increase in short-term mortality is observed with an RV/LV ratio of greater than 0.9 at computed tomography (CT).[22-24] There is a 2.4 fold increase in mortality associated with RV dysfunction observed at echocardiography.[25] Increased mortality is also observed with elevated troponin and brain natriuretic peptides, which are associated with a four- to eight-fold risk and a six-fold risk, respectively.[25-27]

1.3 Pulmonary Embolism Treatment & Risk Stratification

The treatment of PE depends on its severity. The severity is defined by the risk of death; a risk tightly correlated with the hemodynamic consequences of the embolism, namely, acute right ventricular (RV) dysfunction. RV dysfunction is the principal determinant of a patient's clinical course.[21, 28] 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 death. 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.[29] 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.[30-32] 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.[31] 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. The FLAME Protocol will allow enrollment of only high-risk PE that would typically carry an overall mortality rate of approximately 50%, and cardiovascular mortality rate of nearly 40% at 30 days.[1-3]

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.[20] The AHA document included definitions for each category. Massive (high-risk) 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 specified combinations of clinical presentation, imaging, biomarkers to better risk-classify patients (**Figure 2**).[21] 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.

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

Figure 2. European Society of Cardiology Risk Stratification

From Konstantinides et al.[21]
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 : 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.
[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-IIor an sPESI of 0. 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.[26] 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.[20] 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.[33]

1.5 RISK-BASED TREATMENT OF PULMONARY EMBOLISM

High-risk PE is defined 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.[34]

The treatment of high-risk PE patients is clear; definitive intervention is indicated, up to and including open surgical thrombectomy with or without ECMO.[35] Once a diagnosis of high-risk PE is made, expeditious intervention is warranted in order to optimize outcome. Pharmacomechanical, ECMO, and open thrombectomy require anticoagulants and often thrombolytic therapy, with the possibility of concomitant morbidity secondary to bleeding.[8] Patients with high-risk PE have an increased risk or mortality and morbidity with treatment. A systematic review on the use of ECMO in high-risk PE showed that patients who were in cardiorespiratory arrest when ECMO was initiated had a higher risk of death.[36] In a study by Secemsky et al. there was a 2.28-fold increase in major bleeding in patients with high-risk PE compared to patients with submassive PE.[8]

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 is used followed by 3 months of oral vitamin K antagonists such as warfarin.[37] Longer treatment with oral agents has been controversial, but individualized therapy must balance the risk of hemorrhage and VTE recurrence.[37-39]

Some investigators have studied low molecular weight heparin in place of unfractionated heparin and Warfarin, with satisfactory results.[40] More recently, direct oral anticoagulants (DOACs) have been

employed as alternatives to Warfarin in the setting of PE.[41-43] However, with high-risk PE a more aggressive approach must be attempted, as anticoagulation alone will rarely restore pulmonary artery flow, and the patient will remain hemodynamically compromised.[5, 33, 44]

1.6.2 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 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,[47] 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 intermediate-risk and high-risk PE.[48-53] 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.[33, 54, 55] 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.[56] 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 in the treatment of intermediate and high-risk patients.[7,57] A study comparing catheter-directed thrombolysis to systemic thrombolysis in a group of intermediate and high-risk patients showed bleeding was higher in the catheter directed group, while in-hospital mortality was lower compared to the systematic thrombolysis group.[57]

1.6.3 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 intermediate-risk and high-risk 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 intermediate-risk PE.[58] UAT was more effective than anticoagulation in normalizing RV function in intermediate-risk PE patients. No intracranial bleeding was observed. The SEATTLE-II trial evaluated differing doses of rt-PA PAT infused over varying timeframes in 150 subjects with intermediate-risk and high-risk PE.[59] These studies concluded that catheter-directed pulmonary artery thrombolysis with rt-PA was safe and effective in the treatment of 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.[60] The review, however, documented a trend toward improved survival with UAT; 4% vs. 9% in the UAT and standard thrombolytic subjects, respectively. No device has been identified as superior in the treatment of high-risk PE subjects, opening the medical opportunity to augment the non-surgical armamentarium in the treatment of high-risk PE.

1.6.4 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.[45] Open surgical thromboembolectomy can result in rapid, life-saving hemodynamic improvement in patients with significant PE.[35, 46] 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 PE 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.[20, 21] 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 death is likely to occur before thrombolytic therapies can improve the patient's hemodynamic state.

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 a 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 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.[61] After that, other technologies were attempted, including fragmentation of proximal emboli,[62, 63] rheolytic thrombectomy,[64-68] and the use of various pulmonary artery thromboembolectomy devices.[69-71] 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.

2 THE FLOWTRIEVER SYSTEM

Noting the need for rapid restoration of pulmonary arterial flow after pulmonary embolism, Inari developed the FlowTriever Retrieval/Aspiration System (FlowTriever System) to extract pulmonary arterial thromboembolism without an obligatory need for thrombolytic agents.[72, 73]

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 for the treatment of pulmonary embolism. It is expected that the use of the FlowTriever System will augment effectiveness in the treatment of high-risk PE. Due to the high risk of mortality with current treatments for high-risk PE, with reported in-hospital mortality rates ranging from approximately 17% to 50%, it is expected that FlowTriever will also have a safety benefit in this patient group.[8, 74-78].

2.1 FLOWTRIEVER SYSTEM

The FlowTriever System will be used in the FlowTriever Arm of this study. The System is a catheter-based mechanical thrombectomy device for percutaneous endovascular retrieval of emboli and is intended for use in the proximal pulmonary arterial system. The FlowTriever System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in the setting of acute pulmonary embolism.

2.2 REGULATORY STATUS

The FlowTriever System was cleared for the treatment of pulmonary embolism under 510(k) number K180466, May 17, 2018.

2.3 INTENDED USE OF THE DEVICE

The FlowTriever System is a Class II device, intended for use in the peripheral vasculature and for the treatment of pulmonary embolism.

2.4 DEVICE DESCRIPTION

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 system is composed of two main components: the Triever Catheter and the FlowTriever Catheter.

The Triever Catheter is a large-bore catheter used primarily for controlled aspiration of thromboemboli. After being positioned adjacent to thrombus, a vacuum is applied to the catheter side port via a 60 mL custom large-bore syringe. Opening the side port valve produces an abrupt, high-flow suction to extract thrombus through the Triever catheter and into the syringe, while limiting blood loss to 60 mL per aspiration.

The FlowTriever Catheter, often delivered into the body through the Triever Catheter, consists of a flexible shaft attached to distal self-expanding nitinol disk(s). It is used to macerate and deliver

thrombus to the Triever Catheter for removal via aspiration and is often used for more chronic, wall-adherent thrombus.

A complete description of the FlowTriever System is provided in the Instructions for Use.

2.5 RATIONALE FOR THE USE OF THE FLOWTRIEVER SYSTEM

The use of thrombectomy for PE offers the opportunity to reduce the pulmonary arterial thrombus burden rapidly. As well, there are subpopulations where FlowTriever thrombectomy may be the only interventional option; for instance, in patients for whom pharmacologic thrombolysis is contraindicated. The effectiveness of the FlowTriever System does not rely on the use of obligatory adjunctive pharmacologic therapy. While some may choose to employ thrombolysis during or after FlowTriever thrombectomy, the use of thrombolytic agents is not required.

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.

Following FDA clearance for the FlowTriever System, a subsequent study (FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH)) was designed and is being conducted 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 is being assessed in a real-world population, and enrollment in the study is ongoing.

3.1 FLARE Study Design and Summary of Results

3.1.1 FLARE Study Design

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 a primary effectiveness performance goals were used in the study. For the safety Performance Goal, 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 death, 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 Performance Goal was chosen as the upper 95% confidence limit rounded down to two digits, for a safety Performance Goal of 25%.

The primary effectiveness performance goal was the change in RV/LV ratio from baseline to 48 hours. The Performance Goal 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 Performance Goal 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.

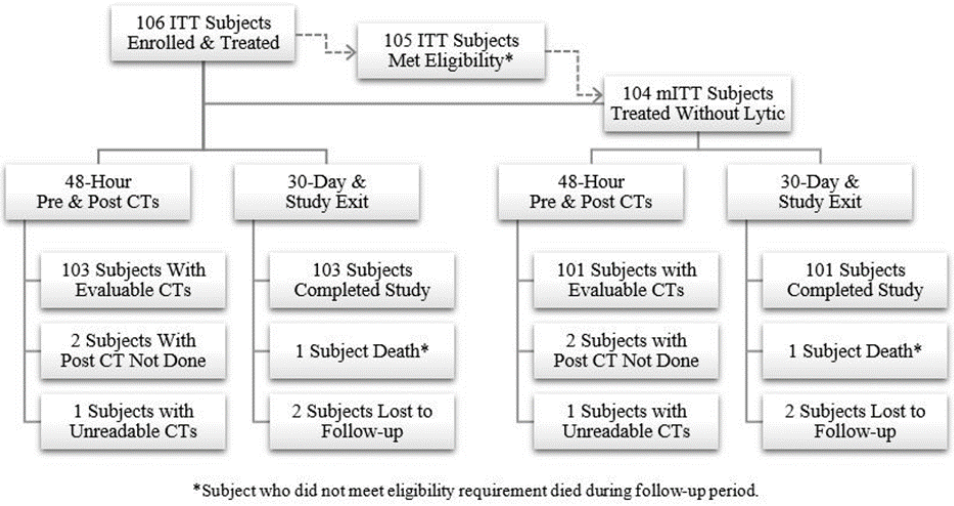
The sample size for safety was based on the Performance Goal of 25% for the composite endpoint. The true composite endpoint rate for the FlowTriever was expected to be about 13%, according to data from the historical studies used for the Performance Goal estimation. Additionally, rates of 15% and 17%

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.

3.1.2 FLARE 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 System 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.

For the primary safety endpoint, 4 subjects (3.8%) in the modified intention to treat population (all patients with treatment attempted and no thrombolytics were administered) 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%. None of the MAEs reported were device related.

[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.

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.

3.2 FLASH STUDY DESIGN AND STUDY STATUS

As described previously, the primary study objective of FLASH 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 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 study of the FlowTriever System for intermediate (submassive) and high-risk (massive) PE. Up to 500 subjects will be enrolled at up to 50 registry sites in the United States. Enrollment in the FLASH registry is ongoing.

4 FLAME STUDY OBJECTIVE

The primary objective of this observational study is to evaluate treatment outcomes of patients diagnosed with high-risk (massive) pulmonary embolism who have received treatment with the FlowTriever System compared to an established performance goal (literature-based goal).

5 FLAME STUDY DESIGN

The FLAME study is a prospective, multicenter, non-randomized, parallel group, observational study of subjects with high-risk pulmonary embolism concurrently enrolled in the FlowTriever, Context, and Prior Therapy Arms. FlowTriever Arm subjects will be the primary population utilized to evaluate the study Primary and Secondary Endpoints for study success. Subjects enrolled in the Context Arm will be analyzed separately from the endpoint analysis utilizing descriptive methods.

Data collection for Prior Therapy Arm subjects will include information surrounding the PE treatment, progression to High-Risk PE, and patient course through hospital discharge. Safety data will be collected, but not CEC adjudicated or analyzed as outlined for the FlowTriever and Context Arm subjects. Subjects receiving prior advanced treatment for low/intermediate-risk PE in the same hospital setting as a second treatment for high-risk PE likely have a different profile than those receiving advanced care for the first time after diagnosis of high-risk PE, and therefore should be looked at separately. In the spirit of the AHA guidelines for trial design in this patient population, data will be collected to ensure representation of this smaller yet significant group of high-risk PE patients.

5.1 ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the in-hospital composite endpoint of all-cause mortality, bailout to an alternative thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b definition). This will be assessed in the FlowTriever Arm compared to a performance goal. A description of the analysis methods is provided in **Section 7**. Definitions of each component of the composite primary endpoint are provided in **Table 1** below.

Subjects enrolled in the Context Arm will be analyzed separately from the endpoint analysis utilizing descriptive methods.

Table 1: Primary Endpoint Definitions

Primary Endpoint Definitions	Bailout to an alternate thrombus removal strategy	Need for mechanical circulatory support or another thrombus removal strategy after the primary treatment strategy was initiated. The additional treatment strategy was not an a priori part of the original treatment plan (conceived beforehand). All bailout events will be adjudicated by the CEC.
	Clinical Deterioration	• Need for CPR

		• Need to start IV vasopressors to keep systolic blood pressure > 90 mmHg in a previously normotensive patient • Need for mechanical ventilation in a previously spontaneously breathing patient • Need for noninvasive positive pressure ventilation in a patient previously on nasal cannula
	Major Bleeding, BARC 3b/3c/5a/5b	• 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents • 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. • 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

5.1.2 Secondary Endpoints

Secondary endpoints include safety endpoints as well as utility measures which will be assessed in the FlowTriever Arm. Details of the secondary endpoints are provided in **Table 2** below.

Subjects enrolled in the Context Arm will be analyzed separately from the endpoint analysis utilizing descriptive methods.

Table 2: Secondary Endpoint Definitions

Secondary Endpoints	**Secondary Safety Endpoints** • Frequency of each primary endpoint composite component • Frequency of stroke (ischemic or hemorrhagic) • Frequency of device-related complications • Access site injury requiring intervention, both venous and arterial **Utility Measures** • Length of hospital stay • Length of ICU stay • Use of ECMO, including either pre- or post-treatment initiation and duration • Time to extubation, if intubated • Discharge location

5.2 STUDY POPULATION AND ENROLLMENT

Patients diagnosed with high-risk pulmonary embolism will be enrolled in this study. Subjects will be enrolled into one of three arms: the FlowTriever, Context, or Prior Therapy Arm. Sites participating in the FLAME study will enroll all subjects presenting with high-risk PE over the course of the study, regardless of their primary thrombus removal strategy, to ensure enrollment of all-comers to the study. Subjects will be concurrently enrolled in all arms as described below.

Enrollment in the Context Arm will continue until FlowTriever enrollment is completed, with a minimum enrollment of 1:1 subjects in each arm, and a maximum enrollment of 2:1 Context Arm to FlowTriever Arm subjects. Enrollment in the Prior Therapy Arm will be concurrent with the FlowTriever Arm of the study, and enrollment in this arm will cease when enrollment in the FlowTriever Arm is complete.

Individual sites will be limited to no more than 25% enrollment (maximum enrollment of 17 subjects) in the FlowTriever Arm of the study.

5.2.1 FlowTriever Arm Enrollment

Up to 71 subjects will be enrolled in the FlowTriever Arm. FlowTriever Arm subjects are defined as those subjects where FlowTriever is used as the Primary Treatment for pulmonary embolism.

An interim analysis is planned for the first 50 subjects enrolled into the FlowTriever Arm. Based upon the interim analysis (as described in **Section 7.4.3**), a decision will be made whether to continue enrollment.

5.2.2 Context Arm Enrollment

Subjects with high-risk pulmonary embolism who are treated with non-FlowTriever therapies (as the primary treatment for high-risk PE) will be enrolled concurrently with subjects in the FlowTriever Arm (this includes subjects initially presenting with low/intermediate-risk PE who are initially treated with anticoagulation alone and subsequently progress to high-risk PE. Enrollment in the Context Arm will continue until FlowTriever enrollment is completed, with a minimum enrollment of 1:1 subjects in each arm, and a maximum enrollment of 2:1 Context Arm to FlowTriever Arm subjects.

Context-Arm therapies may include but are not limited to; thrombolysis (either systemic or catheter directed), anticoagulation, surgical thrombectomy, and non-FlowTriever percutaneous thrombectomy.

5.2.3 Prior Therapy Arm Enrollment

Subjects presenting with low/intermediate-risk PE who receive advanced therapy but subsequently progress to high-risk PE in the same hospital setting/admission should be enrolled in the Prior Therapy Arm. Enrollment in the Prior Therapy Arm will be concurrent with the FlowTriever Arm of the study, and enrollment in this arm will cease when enrollment in the FlowTriever Arm is complete.

For the purposes of this study, advanced therapy for low/intermediate-risk PE is considered therapy beyond anticoagulation alone, including: thrombolysis (either systemic or catheter directed), surgical thrombectomy, and percutaneous thrombectomy.

5.3 STUDY SITES

The FLAME Study will be conducted at up to 20 sites in the United States. Sites are 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 subjects. The criteria used for determination will be documented.

Once activated to enroll in the FLAME study, sites should enroll **all** high-risk pulmonary embolism subjects into FLAME, regardless of the primary thrombus removal strategy. This will help ensure an unbiased enrollment of all-comers into the study.

5.4 ELIGIBILITY CRITERIA

5.4.1 Inclusion Criteria

High-risk pulmonary embolism subjects must meet each of the following criteria to be eligible for enrollment:

- Age ≥ 18 years
- Treatment team determines pulmonary embolism is the cause of shock
- One or more of the following:
    - Systolic blood pressure <90 mmHg for at least 15 minutes, or drop of >40 mmHg in systolic blood pressure for at least 15 minutes, and/or
    - Need for vasopressor support, and/or
    - Resuscitation after cardiac arrest with <30 minutes of CPR and Glasgow Coma Scale >8.

5.4.2 Exclusion Criteria

High-risk pulmonary embolism subjects will be excluded from the study for any of the following criteria:

- Out of hospital cardiac arrest with Glasgow Coma Scale of ≤8
- Witnessed cardiac arrest with ongoing CPR >30 minutes
- Contraindication to anticoagulants, i.e. heparin or alternative
- Hematocrit <28%
- Platelets <25,000/μL
- INR >8
- Intracardiac thrombus and/or intracardiac clot in transit
- Known anaphylactic sensitivity to radiographic agents that cannot be pre-treated
- History of pulmonary hypertension with systolic pulmonary arterial pressure >70 mmHg
- Presence of chronic medical conditions with estimated life expectancy < 90 days (life-expectancy should not include the current pulmonary embolism and its treatment)
- Current participation in another drug or device treatment study that, in the Investigator's opinion, would interfere with participation in this study
- Subject is known to be COVID-19 positive at hospital admission (subject has active COVID-19)

6 FLAME STUDY CONDUCT

6.1 ENROLLMENT, STUDY ASSESSMENTS, AND PROCEDURES

6.1.1 Enrollment Logistics

Beginning at the point of site activation (approval to begin enrollment), all patients presenting to the hospital/ER with PE or who incidentally develop PE while in the hospital should first be reviewed to see if they have high-risk PE, and then assessed for eligibility for enrollment in the FLAME study. **This will require a regular (approximately daily/weekly) chart and/or database review by site study personnel to ensure that all presenting high-risk PE subjects meeting criteria are enrolled.**

Subjects who meet eligibility criteria for the study and have a primary thrombus removal strategy initiated, will be considered enrolled. The time of enrollment will be the initiation of the Primary Treatment Strategy for high-risk PE (the time of enrollment for patients in the Prior Therapy Arm will be the time of high-risk PE diagnosis).

Subjects who do not meet eligibility criteria or die before any anticoagulation or other thrombus removal strategy could be initiated will not be enrolled and will be considered screen failures. As such, screen failures will not be assigned a subject ID and will not be entered into the electronic data capture system (EDC, study database).

6.1.2 Patient Flow and Schedule of Assessments

Patient enrollment by study Arm study is provided in the **Figure 4** flowchart. The Schedule of Assessments is included in **Table 3**.

Figure 4: Patient Enrollment Flowchart by Study Arm

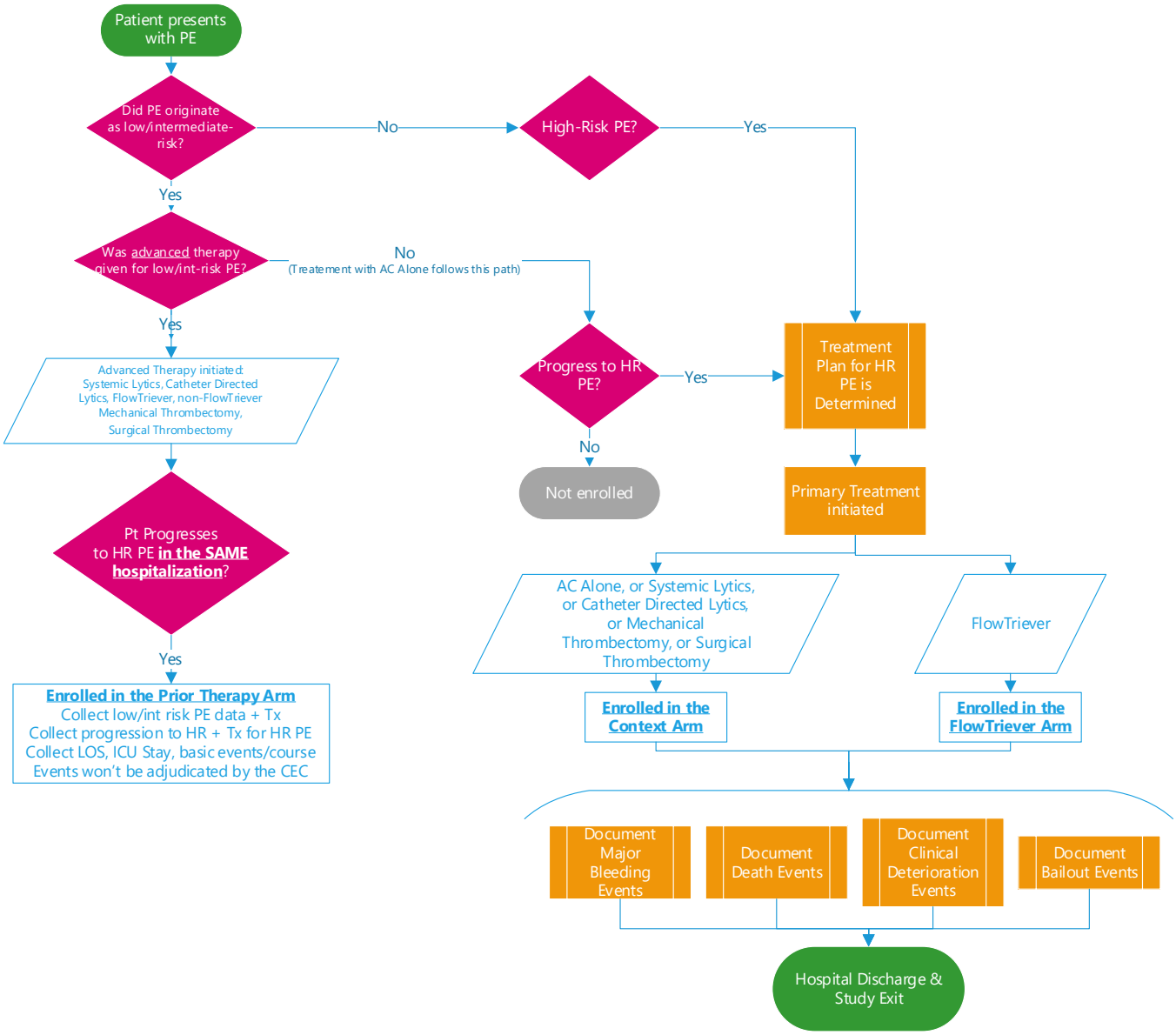


Table 3: Schedule of Assessments

Assessment	Baseline	Procedure	Post-procedure through Hospital Discharge
Eligibility[1]	X		
Medical History[2]	X		
Pre-procedure presentation and status[3]	X		
Anticoagulation[4]	X	X	X
Thrombolytic Therapy[4]	X	X	X
Primary Treatment Plan Decision for high-risk PE[5]	X		
Primary Treatment Initiated for high-risk PE[6]		X	
Bailout therapies for high-risk PE[7]		X	X
Clinical Deterioration[8]		X	X
Major Bleeding Events[8]		X	X
Adverse Events[9]		X	X
Discharge details			X

[1]Data used to determine eligibility include pre-treatment data only.
[2]Data collected for subject Medical History include pre-treatment data only.
[3]Signs and symptoms of high-risk PE beginning should be reviewed for eligibility. Data should also be collected for subjects first presenting with low/intermediate-risk PE who progress to high-risk PE in the same hospital setting/admission, including any treatment given to treat the low/intermediate-risk PE.
[4]Anticoagulation and thrombolytic therapy administration are not required, but if administered, detailed data will be collected including drug name, dosage, start and stop dates/times, route, and reason for administration.
[5]The Primary Treatment plan for treating the high-risk PE will be documented including the date and time that the Primary Treatment plan was decided.
[6]The date and time the Primary Treatment for thrombus removal is initiated will be documented. The patient is considered enrolled at the time the Primary Treatment for high-risk PE is initiated (the time of enrollment for patients in the Prior Therapy Arm will be the time of high-risk PE diagnosis).
[7]Any bailout therapies for thrombus removal applied after initiation of the Primary Treatment therapy through hospital discharge will be documented and subsequently adjudicated by the CEC. See Section 6.1.4.1 for details.
[8]Clinical deterioration occurring after initiation of the Primary Treatment therapy through hospital discharge will be documented and subsequently adjudicated by the CEC. See Section 6.1.4.2 for details.
[8]Major bleeding events occurring from the time of initiation of the Primary Treatment therapy through hospital discharge will be documented as adverse events and subsequently adjudicated by the CEC. See Section 6.1.4.3 for details.
[9]Only Adverse Events (AEs) related to the subject's PE condition and its treatment should be reported in the FLAME study.

6.1.3 Baseline

6.1.3.1 Waiver of Informed Consent in Emergency Research

Patients with high-risk pulmonary embolism are, by definition, unstable with a life-threatening condition and require emergent treatment. Currently, patients with high-risk pulmonary embolism suffer from 30-40% acute mortality [1-3], necessitating the analysis of current treatments for this high-risk patient population.

The FLAME registry study will not dictate use of any specific therapy for the pulmonary embolism. Treatment will be at the discretion of the physician caring for the patient, utilizing standard of care treatment, and the data surrounding the treatment decision and patient outcomes through hospital discharge will be collected via retrospective chart review in the FLAME registry.

Per the Department of Health and Human Services criteria for a waiver of consent in research for non-FDA regulated studies (45 CFR 46.116(d)), the FLAME study will include a waiver of consent for the following reasons (as listed in the regulation):

1. **The research involves no more than minimal risk to the participants.**

   The FLAME observational registry will not dictate use of any specific therapy for the pulmonary embolism. Treatment will be at the discretion of the physician caring for the patient, utilizing all available standard of care therapies for pulmonary embolism, and the data surrounding the treatment decision and patient outcomes through hospital discharge will be retrospectively collected in the FLAME registry, **therefore additional risks are not introduced specific to the study**.

   The only known risk to participants is the possible loss of confidentiality which has been guarded against by the following:

   - Data surrounding the treatment and patient outcomes through hospital discharge will be anonymized, re-identified with a study-specific subject ID, and collected for analysis.
   - Only the study site (Investigators and research staff) will have access PHI, providing an acceptable risk/benefit ratio for data collection and analysis activities performed for the study.
   - Access to the study database where anonymized data is entered is password protected and compliant with 21 CFR 11, Electronic Records.
   - Access to study data will be limited to hospital research and Sponsor personnel.

   Evaluating subject records fits the definition of minimal risk.

2. **The research could not practicably be carried out without the waiver or alteration.**

   As noted above, patients in this high-risk population suffer from 30-40% acute mortality, and treatment of these patients would occur regardless of the research. In order to carry-out credible and representative research in this population, all patients presenting with high-risk pulmonary embolism should be included in the results, including those who expire in the acute period following their pulmonary embolism. This research could not be practicably carried out **without** the waiver of consent to ensure proper accounting for patient mortality.

   This study is a non-interventional, data collection registry. As described above, patients with high-risk pulmonary embolism are, by definition, unstable with a life-threatening condition requiring emergent treatment. Patients with high-risk pulmonary embolism are unable to consent for data collection due to their medical condition. There is no reasonable way to prospectively identify potential eligible subjects and the data surrounding the treatment decision and patient outcomes will be collected in the FLAME registry via retrospective chart review by site research staff.

3. **If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;**

Identifiable private information **will not** be collected in the FLAME study. As described above, data surrounding the treatment and patient outcomes through hospital discharge will be anonymized, re-identified with a study-specific subject ID, and collected for analysis. Only the study site (Investigators and research staff) will have access PHI, providing an acceptable risk/benefit ratio for data collection and analysis activities performed for the FLAME study.

4. **The waiver or alteration will not adversely affect the rights and welfare of the participants.**

   As the study is collecting de-identified real-world treatment data after the patients have already left the hospital, and the study is not prescribing the intervention or therapy, the FLAME study will not adversely affect the rights and welfare of the participants.

5. **Whenever appropriate, the participants will be provided with additional pertinent information after participation.**

   This study is non-interventional and thus providing information to patients is not likely. However, if there were information that needed to be provided to the subject, we would work with the IRB to approve the correspondence to be provided to the subject.

6.1.3.2 Eligibility

Subjects will be enrolled by retrospective chart review. This is especially important for subjects enrolled in the Context and Prior Therapy Arms, to help eliminate the potential for enrollment bias. Once a site is activated to enroll in the FLAME study, ALL patients presenting with suspected PE should be assessed for high-risk PE status, and potential enrollment into the FLAME study.

All inclusion criteria must be met, and none of the exclusion criteria can be met for enrollment into the study (for all arms). All eligibility criteria are listed in **Section 5.4**. Subjects will be considered enrolled when the Primary Treatment for thrombus removal is initiated for high-risk PE (the time of enrollment for patients in the Prior Therapy Arm will be the time of high-risk PE diagnosis).

Patients not meeting eligibility criteria for the study will be considered Screen Failures, will not be enrolled, and are not entered into the EDC system.

6.1.4 Treatment

The treating physician should document what the intended initial treatment strategy was for high-risk PE (referred to as the Primary Treatment). Subjects with the Primary Treatment being FlowTriever will be enrolled into the FlowTriever Arm of the study. Subjects with the Primary Treatment being non-FlowTriever therapy will be enrolled into the Context Arm of the study. Subjects presenting with low/intermediate-risk PE who receive advanced therapy but subsequently progress to high-risk PE in the same hospital setting/admission should be enrolled in the Prior Therapy Arm.

Details of the treatment of PE (Primary Treatment, Bailout measures, Clinical Deterioration, and Major Bleeding) will be collected.

6.1.4.1 Bailout to an Alternate Thrombus Removal Strategy

If, during treatment of the high-risk PE, the subject requires additional thrombus removal therapy other than the Primary Treatment initiated, the additional therapy should be documented. The Clinical Events Committee (CEC, **Section 6.3**), will determine if the additional therapy meets the definition of Bailout for the purposes of analyzing the Primary Endpoint of the study. Definitions for Bailout are provided in **Table 4** below:

Table 4: Bailout Definitions

Initial Treatment Strategy/Primary Treatment:	Bailout to an Alternate Thrombus Removal Strategy Definition[1]:
Thrombolysis (systemic or catheter directed)	A bailout would be defined as the need for mechanical circulatory support or a different thrombus removal strategy at any time after the initial thrombolytic strategy was initiated. Applies when thrombolytic therapy alone was the original treatment plan (**conceived beforehand).** Note: if catheter directed thrombolysis (CDT) was the original treatment plan and emergent/clinically driven systemic thrombolytic administration (≥ 10 mg tPA or 5 mg TNK) was required after CDT was initiated, this would be considered a bailout. (Note: If the length of tPA or TNK administration is simply extended and is not emergent or clinically driven, this would not necessarily qualify as a bailout).
Anticoagulation (includes anticoagulation + ECMO)	A bailout would be defined as the need for thrombolytic therapy, mechanical circulatory support (if this was not part of the planned primary treatment), or a different thrombus removal strategy (for example, mechanical thrombectomy, open embolectomy, etc.) at any time after the initial anticoagulation strategy was initiated. Anticoagulation alone was the original treatment plan (**conceived beforehand).**
Surgical Thrombectomy	A bailout would be defined as the need for a different thrombus removal strategy or the addition of mechanical circulatory support once a surgical approach was initiated. Surgical thrombectomy alone was the original treatment plan (**conceived beforehand).**
Mechanical Thrombectomy (Includes FlowTriever and non-FlowTriever thrombectomy)	A bailout would be defined as the need for a different thrombus removal strategy, the addition of mechanical circulatory support, or surgical thrombectomy once a percutaneous mechanical thrombectomy approach was initiated. Low-dose catheter directed **adjunctive** thrombolytic therapy (less than 10 mg tPA or 5 mg TNK) that is administered intra-procedurally or post-procedurally will be discouraged but not considered a bailout. Note: • Completion of the FlowTriever procedure will be defined as the final removal of the FlowTriever catheter from the patient. • If mechanical circulatory support **was placed before mechanical thrombectomy was initiated as part of the planned treatment strategy, this is not considered a bailout**. If, however; mechanical

	circulatory support was not planned as part of the initial thrombus treatment strategy, and mechanical thrombectomy is initiated but mechanical circulatory support later becomes necessary, this will be recorded as a bailout.

[1]Bailout measures will be reviewed and adjudicated by the Clinical Events Committee for the purposes of analyzing the Primary Endpoint.

6.1.4.2 Clinical Deterioration

Subject clinical status will be monitored and recorded in the study records. Signs of clinical deterioration observed from the time of initiation of the Primary Treatment for high-risk PE through hospital discharge will be recorded by the site and adjudicated by the Clinical Events Committee (CEC, **Section 6.3**), and is defined in **Table 5** below.

Table 5: Clinical Deterioration Definition

Clinical Deterioration[1], defined as:
• Need for CPR after primary treatment initiation, or • Need to start IV vasopressors to keep systolic blood pressure > 90 mmHg in a previously normotensive patient after primary treatment initiation, or • Need for mechanical ventilation after primary treatment initiation in a previously spontaneously breathing patient, or • Need for noninvasive positive pressure ventilation after primary treatment initiation in a patient previously on nasal cannula

[1]Clinical Deterioration will be reviewed and adjudicated by the Clinical Events Committee for the purposes of analyzing the Primary Endpoint.

6.1.4.3 Major Bleeding

All bleeding events related to the patient's high-risk pulmonary embolism or its treatment should be recorded as adverse events by study sites. The CEC will review and adjudicate bleeding events for the purposes of analyzing the primary endpoint. Bleeding events which meet the BARC 3b/3c/5a/5b definition of Major Bleeding will be included in the Primary Endpoint analysis. The BARC 3b/3c/5a/5b Major Bleeding Definition is provided in Table 6 below:

Table 6: Major Bleeding, BARC 3b/3c/5a/5b Definition

Major Bleeding (BARC 3b/3c/5a/5b)[1], defined as:
• 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents • 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision.

- 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

[1]Major bleeding events will be reviewed and adjudicated by the Clinical Events Committee for the purposes of analyzing the Primary Endpoint.

6.1.5 Hospital Discharge

Subjects data will be collected through discharge from the hospital from their index-treatment for high-risk PE. Utility measures will be collected including, but not limited to:

- Length of hospital stay
- Length of ICU stay
- Use of ECMO, including either pre- or post-treatment initiation and duration
- Time to extubation, if intubated
- Discharge location

6.1.6 Study Exit

Subjects may be exited from the study if they are deceased prior to discharge. As this study is only looking at outcomes through hospital discharge, it is not expected that subjects will be lost to follow-up. Subjects who remain in-hospital (from the index hospitalization for high-risk PE) for ≥ 45 days after the Primary Treatment for high-risk PE will be exited from the study at that time, as the study is considering acute outcomes for the treatment of high-risk pulmonary embolism.

Study Exit for all subjects, regardless of reason, will be documented on a Study Exit form in the study record.

6.2 Safety Data Handling and Reporting

6.2.1 Adverse Event Definition and Assessment

An Adverse Event (AE) is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to enrollment in the study. AEs are assessed for severity, seriousness, and relationship to treatment devices and procedures, as defined in **Table 7**.

The study will only capture AEs related to the subject's PE condition and treatment. Reportable AEs include all events considered in the safety analyses, all thrombus removal therapy/device- and/or procedure-related AEs, as well as events resulting in death.

Table 7: Site Assessment of Adverse Events

AE Assessment	Categories and Definitions
Severity:	**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
Seriousness:	Serious Adverse Event (SAE): An AE which is 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
Relatedness (assessed for any thrombus removal strategy or procedure):	**Not Related:** The clinical event is completely independent of thrombus removal therapy or procedure and/or evidence exists that the event is related to another etiology.
	Related: The clinical event occurs in a plausible time relationship to the thrombus removal therapy or procedure and cannot be explained by any concurrent disease or other devices or procedures.
	Unknown: The relationship to the thrombus removal therapy or procedure is not known.

6.2.2 Site Reporting of Adverse Events

The study was designed to capture real world data regarding the clinical use of the FlowTriever System and other high-risk PE treatments. The study follows guidelines for Instructions for Use and physician discretion for PE treatment.

This is a data collection study only; there is nothing investigational or experimental in the subject's medical treatment and the subject will be treated per standard of care. **Therefore, the study will only capture AEs related to the subject's PE condition and treatment.** Reportable AEs include all events considered in the safety analyses, all thrombus removal therapy/device- and/or procedure-related AEs, as well as events resulting in death. The AEs will be captured on the AE CRF and should include, wherever possible, severity, duration, outcome, the Investigator's description the event, and its relationship to the thrombus removal therapy/device, to the thrombus removal procedure or any subsequent procedures, or to a thrombolytic agent or anticoagulant.

- 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.

6.3 CLINICAL EVENTS COMMITTEE (CEC)

A Clinical Events Committed (CEC) will be utilized in this study for the purposes of adjudicating the primary and secondary endpoints. Site-reported safety and outcome data will be provided to the CEC for review and adjudication of the following items for all FlowTriever and Context Arm subjects enrolled in the study:

- Classification as a Serious Adverse Event (SAE)
- Determination of relatedness
- Assessment of severity
- Assessment of endpoint criteria

Adjudication will be conducted according to the FLAME CEC Charter.

(Note that the primary endpoint will only be analyzed for subjects in the FlowTriever Arm of the study, but the CEC will adjudicate events for subjects enrolled in the Context Arm of the study as well)

6.4 PROTOCOL MODIFICATIONS

No changes from the final approved study protocol will be initiated at the site-level without the IRB's prior written approval of the amendment. Site Principal Investigators will acknowledge any protocol amendments by signing the associated Protocol Signature Page.

6.5 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.

Protocol deviations should be recorded in the study record and entered into the study database as soon as possible to ensure Sponsor oversite of the conduct of the study along with implementation of any corrective actions as necessary.

6.6 TRAINING FOR STUDY PERSONNEL

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

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.

6.6.1 Physician Device Training

Each physician selected to participate in this trial who will be enrolling in the FlowTriever Arm will be required to have experience treating pulmonary embolism using the FlowTriever device.

6.6.2 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 FLAME 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. 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.

6.7 SITE MONITORING VISITS

Interim monitoring 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 according to the study-specific monitoring plan.

The main responsibilities of the monitor are to ensure adherence to the protocol and to verify all data are correctly and completely recorded. The Investigator and assisting staff must agree to cooperate with the study monitor to resolve any study-related problems, errors, or possible misunderstandings concerning the findings detected during these monitoring visits or data review.

6.8 STUDY TERMINATION

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:

- As a result of the pre-specified Interim Analysis, or
- 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)

6.9 SITE CLOSE-OUT VISITS

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.

The close-out visit will be conducted when all subjects at the site have completed the study-specific follow-up, or after early termination as described in **Section 6.8**.

6.10 DATA COLLECTION AND MANAGEMENT

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

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.

6.10.1 Site Data Collection and Electronic Data Capture (EDC)

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. It is recommended a note be made in the subject's medical record that the subject is participating in the study.

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.

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.

6.10.2 Data Security and Integrity

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

The Investigator must maintain the primary records (source documents) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device label records, and worksheets that are used as the source.

7 STATISTICS & DATA ANALYSIS

7.1 SAMPLE SIZE

The sample size of the FlowTriever Arm is calculated using a two-stage group sequential design, where the FlowTriever Arm is expected to have a rate of in-hospital composite endpoint of all-cause mortality, bailout to an alternative thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b definition) of 18%. The rate of the FlowTriever Arm composite endpoint is compared with the historical performance goal of 32%, based on meta-analysis results shown in **Table 9**. A one-sided binomial proportion's test with normal approximation is used against the historical performance goal with a power of 80% and a one-sided $\alpha = 0.05$; O'Brien Fleming boundary was implemented where the first stage, or interim analysis, is planned at N = 50 subjects enrolled and consequently arriving at the second stage, or final analysis, with N = 71 subjects as shown in **Table 8**.

Table 8: Sample Size 2-stage Group Sequential Design

Analysis Stage	N	Z-score Threshold	P-value Threshold	FT Event proportion	Significant event number
Interim	50	-2.0311	0.0211	0.186	≤9.3
Final	71	-1.7116	0.0435	0.225	≤16.0

7.2 DERIVATION OF PERFORMANCE GOAL

The primary safety endpoint performance goal was derived from the following 22 studies, summarized in **Table 9**.

Table 9: Safety Performance Goal Literature Summary

First Author	Subjects	In-Hospital ACM	Bailout to Alternative Thrombus Removal Strategy	Clinical Deterioration (within 24 hours)	Major Bleeding (BARC3b/3c/5a/5b)
Avgerinos et al. 2017	90	15/90, 16.6%	NS	NS	24/90, 26.6%
Barrett et al. 2010	SE: 9	6/9, 66.6%	NS	NS	NS
	TL: 10	6/10, 60.0%			
	AC: 14	5/14, 35.7%			
Carvalho et al. 2010	16	7/16, 43.8%	NS	NS	NS
Cho et al. 2016	19	NS	4/19, 21.0%	NS	NS
	26		NS		
Corsi et al. 2017	17	NS	NS	NS	NS
de Winter et al. 2019	33	NS	8/33, 24.2%	NS	NS
George et al. 2018	32	15/32, 46.9%	NS	5/32, 15.6%	NS

First Author	Subjects	In-Hospital ACM	Bailout to Alternative Thrombus Removal Strategy	Clinical Deterioration (within 24 hours)	Major Bleeding (BARC3b/3c/5a/5b)
Hartman et al. 2015	24	NS	NS	NS	NS
Kuo et al. 2015	28	4/28, 14.3%	NS	NS	0/28, 0.0%
Minakawa et al. 2018	63	23/63, 36.5%*	NS	NS	NS
Moon et al. 2018	Without ECMO: 9	7/9, 77.8%	NS	NS	NS
	ECMO:14	8/14, 57.1%			7/14, 50.0%
Munakata et al. 2012	10	3/10, 30.0%†	NS	NS	2/10, 20.0%
Neely et al. 2015	49	5/49, 10.2%*	NS	NS	1/49, 2.0%
Niwa et al. 2012	289	NS	NS	NS	NS
Pasrija et al. 2018	Control: 27	5/27, 18.5%	NS	NS	3/27, 11.1%
	Protocol: 29	1/29, 3.4%			4/29, 13.8%
Roncon et al. 2018	47	NS	NS	NS	NS
	30				
Secemsky et al. 2019	46	15/46, 32.6%	NS	NS	11/46, 23.9%
Senturk et al. 2016	186	NS	NS	NS	10/186, 5.4%
Sharifi et al. 2016	23	2/23, 8.7%	NS	NS	0/23, 0.0%
Shiomi et al. 2017	31	4/31, 12.9%	NS	NS	NS
Ucar et al. 2013	107	18/107, 16.8%	NS	NS	4/107, 3.7%
Wang et al. 2010	20	NS	12/20, 60.0%	NS	NS
	20		4/20, 20.0%		
Total	**1,318**	**149/607**	**28/92**	**5/32**	**66/609**
Weighted Average [95% Confidence Intervals]	**NA**	**28.5% [20.6%, 37.9%]**	**30.3% [15.5%, 50.7%]**	**15.6% [6.7%, 32.5%]**	**11.5% [6.0%, 21.0%]**

AC, Anticoagulation; ACM, All-Cause Mortality; BARC, Bleeding Academic Research Consortium; ECMO, Extracorporeal Membrane Oxygenation; NA, Not Applicable; NS, Not Specified; SE, Surgical Embolectomy; TL, Thrombolytic Therapy
**Operative mortality was reported. Only patients in refractory shock were included in the analysis.*
†All patients died within 15 hours of the procedure.

The Performance Goal is a weighted average calculated from each individual component of the composite endpoint; each component is a result of a meta-analysis across previous publications using the random-effects model. The Performance Goal weighted average is 21.5%, and by using a 10% margin with rounding up to the nearest percent, the Performance Goal for the study is 32%.

7.3 ANALYTIC DATASETS

The CDISC process would be implemented to generate analytical datasets similar to the Analysis Data Model (ADaM) to be used for tables, lists, and figures (TLFs).

7.4 ENDPOINT ANALYSIS

7.4.1 PRIMARY ENDPOINT ANALYSIS

The primary endpoint is the in-hospital composite endpoint of all-cause mortality, bailout to an alternative thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b definition) from the FlowTriever Arm. The rate of the composite endpoint is expected to be 18% and compared with performance goal of 32%:

H_0: $P_S \geq$ Performance $Goal_S$ versus H_A: $P_S <$ Performance $Goal_S$

where P_s is the proportion of subjects with in-hospital composite endpoint and Performance $Goal_S$ is the performance goal of proportion of subjects with in-hospital composite endpoint derived from previous publications and expert opinions on subjects who were non-FlowTriever treatments.

The one-sided binomial's proportion test with normal approximation would be used at a one-sided $\alpha = 0.05$. Primary endpoint analysis can be carried out at interim analysis and/or final analysis stage.

7.4.2 SECONDARY ENDPOINT ANALYSIS

Secondary Endpoints include both Secondary Safety Endpoints and Utility Measures as listed below:

Secondary Safety Endpoints

- Frequency of each primary endpoint composite component
- Frequency of Stroke (ischemic or hemorrhagic)
- Frequency of device-related complications
- Access site injury requiring intervention, both venous and arterial

Utility Measures

- Length of hospital stay
- Length of ICU stay
- Use of ECMO, including either pre- or post-treatment initiation and duration
- Time to extubation, if intubated
- Discharge location

Descriptive statistics will be used for secondary endpoints for both the FlowTriever Arm and Context Arm populations. Continuous variable will report min, max, mean, SD, IQR, Q1, Q3 etc. as deemed appropriate. Categorical variable will report frequency counts and percentage. Time-to-event variable may be reported with Kaplan-Meier and/or Cox proportional hazards model estimates.

Additional exploratory analyses on secondary endpoints may include confounder adjustment in generalized linear models (GLMs).

7.4.3 INTERIM ANALYSIS

The interim analysis population will be N = 50 enrolled subjects in the FlowTriever Arm with adjudicated in-hospital composite endpoint. Primary endpoint analysis method in **Section 7.4.1** will be used on the interim analysis population to decide whether the study should be stopped early due to achieving early decision rule based on the primary endpoint. The $|z - score|$ threshold is 2.031, which translates to in-hospital composite endpoint proportion being ≤ 0.186. Therefore, having ≤ 9 in-hospital composite endpoint events out of N = 50 may qualify for stopping the study early and conclude achieving significant difference from performance goal = 32% (see **Table 9**).

Secondary endpoint analysis may be conducted in a descriptive fashion without hypothesis testing, therefore not spending any Type I error (α).

7.4.4 CONTEXT ARM ANALYSIS

The Context Arm may be analyzed with methods mentioned in primary and secondary endpoint analyses along with descriptive statistics and will not be used to determine study success.

7.4.5 PRIOR THERAPY ARM ANALYSIS

Data collection for Prior Therapy Arm subjects will include information surrounding the PE treatment, progression to High-Risk PE, and patient course through hospital discharge. Safety data will also be collected, but not CEC adjudicated or analyzed as outlined for the FlowTriever and Context Arm subjects. Subjects receiving prior advanced treatment for low/intermediate-risk PE in the same hospital setting as a second treatment for high-risk PE likely have a different profile than those receiving advanced care for the first time after diagnosis of high-risk PE, and therefore should be looked at separately. In the spirit of the AHA guidelines for trial design in this patient population, data will be collected to ensure representation of this smaller yet significant group of high-risk PE patients and will be reported in a descriptive manner

8 RISK ANALYSIS

8.1 RISKS TO SUBJECTS

The study involves the use and disclosure of health information. It collects only information relevant to the subject's PE condition and treatment. The information is for research, development, and educational purposes only. It does not specify how the physician will treat PE, and decisions regarding a subject's treatment are not influenced by the study.

Physicians participating in the study are expected to review the indications, contraindications, warnings, precautions, and safety events described in the IFU. As with any endovascular procedure, the treating physician is expected to counsel the subject on the risks and benefits specific to the planned treatment and to obtain the local, procedure-related informed consent per institutional policies and procedures.

8.2 MITIGATION OF RISKS

The study was designed to capture real world data regarding the treatment of high-risk PE. The risk of providing this health information is believed to be minimal, as information directly identifying the subject will not be collected in the study database.

8.3 STUDY JUSTIFICATION

The FlowTriever System offers an efficient treatment option for high-risk PE patients while obviating the need for thrombolytic drugs and their consequent high bleeding risk including intracranial hemorrhage. Furthermore, FlowTriever may offer quicker relief given the mechanical approach to clot removal versus a pharmacologic approach which can take several hours to have an effect. The current study is designed to assess high-risk PE outcomes in a real-world population that would be encountered in clinical practice.

9 ETHICS AND CONFIDENTIALITY

9.1 INSTITUTIONAL REVIEW BOARD

This study must be approved by an appropriate IRB representing each investigational 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 approval letter (or equivalent documentation) for the study protocol before the study can be started at that site.

The IRB and Sponsor must approve any significant changes to the protocol, as well as a change of the Principal Investigator. Documentation of IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in a Regulatory Binder or other appropriate repository and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study.

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

The IRB must receive notification of the completion of the study and final report after study completion or termination. 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, including a list of all reports and documents submitted.

9.2 STUDY SUBJECT CONFIDENTIALITY

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal health information, will be maintained at all times. Subjects will not be identified by their names in CRFs or other documents or image material submitted to the Sponsor or designee. Rather, the subject's unique identifier will be utilized.

A subject's Protected Health Information (PHI) will always be treated as confidential. PHI, however, may be reviewed by authorized study staff (e.g., the monitor) to verify data recorded in the eCRFs. The monitor may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities.

9.3 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 subject data at their site. The CRO will have read-only access and can post queries for potential data-related discrepancies.

9.4 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 subjects. The criteria used for determination will be documented.

9.4.1 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 subjects
- Ensuring that IRB 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)

10 TERMS AND DEFINITIONS

Table 10 contains categories, terms, and definitions that are utilized throughout the study and for reporting purposes.

Table 10: Terms and Definitions

Term or Phrase	Definition
Access site injury requiring intervention, both venous and arterial	An injury to an access site (both venous and arterial) utilized for treatment of PE which requires intervention in order to resolve. This includes for example, an arterial injury associated with ECMO support as part of PE treatment.
Advanced therapy for PE	For the purposes of this study, advanced therapy for low/intermediate- risk PE is considered therapy beyond anticoagulation alone, including: thrombolysis (either systemic or catheter directed), surgical thrombectomy, and percutaneous thrombectomy.
Adverse event (AE)	An Adverse Event (AE) is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to enrollment in the study. AEs are assessed for severity, seriousness, and relationship to thrombus removal therapies/devices/procedures. The study will only capture AEs related to the subject's PE condition and treatment. Reportable AEs include all events considered in the safety analyses, all thrombus removal therapy/device- and/or procedure-related AEs, as well as events resulting in death.
All-cause mortality	Mortality for any reason, does not need to be related to a device, treatment, or pulmonary embolism.
Bailout to an alternative thrombus removal strategy	New need for mechanical circulatory support or another thrombus removal strategy after the Primary Treatment strategy was initiated. The additional treatment strategy was not an a priori part of the original treatment plan (conceived beforehand). All bailout events will be adjudicated by the CEC. See **Table 4** for more guidance on bailout events.
Clinical Deterioration	Clinical deterioration is defined as: • Need for CPR • Need to start IV vasopressors to keep systolic blood pressure > 90 mmHg in a previously normotensive patient • Need for mechanical ventilation in a previously spontaneously breathing patient • Need for noninvasive positive pressure ventilation in a patient previously on nasal cannula Clinical deterioration occurring after initiation of the Primary Treatment therapy will be adjudicated by the CEC for analysis of the Primary Endpoint.
Context Arm	Context Arm subjects are defined as those subjects with PE who are treated with non-FlowTriever therapies (as the Primary Treatment for PE). Context-Arm therapies may include but are not limited to; thrombolysis (either systemic or catheter directed), anticoagulation, surgical thrombectomy, and non-FlowTriever thrombectomy. Endpoints will be evaluated in the Context Arm population in a descriptive manner and will not be used to determine study success.

Term or Phrase	Definition
Device-related complications	Complications related to devices used for thrombus removal. Complications related to Primary Treatment devices and bailout devices used will be adjudicated by the CEC. Note that complications related to ECMO should be included here where ECMO was part of the Primary Treatment strategy.
Discharge Location	The location where the patient is discharged from the hospital, may include but not limited to home, home with home healthcare, skilled nursing facility, hospice, etc.
FlowTriever Arm	FlowTriever Arm subjects are defined as those subjects where FlowTriever is used as the primary thrombus removal treatment for pulmonary embolism. FlowTriever Arm subjects will be the primary population utilized to evaluate the study Primary Endpoints for study success.
Glasgow Coma Scale	The Glasgow Coma Scale provides a practical method for assessment of impairment of conscious level in response to defined stimuli.
High-risk Pulmonary Embolism (PE)	Pulmonary embolism with the following signs/symptoms: ○ Systolic blood pressure <90 mmHg for at least 15 minutes or drop of >40 mmHg in systolic blood pressure for at least 15 minutes, and/or ○ Need for vasopressor support, and/or ○ Resuscitation after cardiac arrest with <30 minutes of CPR and Glasgow Coma Scale >8.
Length of Hospital Stay	Time from admission to the hospital for pulmonary embolism treatment until discharge from the hospital post-treatment. For subjects who do not survive until hospital discharge, the length of hospital stay will be from the time of admission until the time of death.
Length of ICU Stay	Time from admission to the ICU until time of discharge from the ICU. Multiple ICU stays within the same hospital admission (index hospitalization for high-risk PE) will be recorded.
Major Bleeding, BARC 3b/3c/5a/5b definition	• 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents • 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. • 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
Primary Endpoint	In-hospital composite endpoint of: • All-cause mortality • Bailout to an alternative thrombus removal strategy • Clinical deterioration • Major bleeding, BARC 3b/3c/5a/5b definition
Primary Treatment Strategy	The initial treatment strategy for thrombus removal (for the high-risk PE) determined by the treatment team prior to treatment initiation and documented.
Prior Therapy Arm	Subjects presenting with low/intermediate-risk PE who receive advanced therapy during their hospital stay but subsequently progress to high-risk PE in the same hospital stay should be enrolled in the Prior Therapy Arm.

Term or Phrase	Definition
Protocol Deviation	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.
Relatedness of Adverse Event	**Unrelated:** The clinical event is completely independent of study procedure/study device/study treatment and/or evidence exists that the event is related to another etiology. **Related:** The clinical event occurs in a plausible time relationship to study procedure/study device/treatment and cannot be explained by any concurrent disease or other devices, drugs or chemicals. **Unknown:** The relationship to the study procedure/study device/treatment is not known.
Screen Failure	Patients who do not meet eligibility criteria for enrollment in the study. Screen failure patients will not be entered into the study database/EDC system, and will not be assigned a study subject ID.
Serious Adverse Event (SAE)	Serious Adverse Event (SAE): An AE which is 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
Secondary Endpoints	**Secondary Safety Endpoints** • Frequency of each primary endpoint composite component • Frequency of Stroke (ischemic or hemorrhagic) • Frequency of device-related complications • Access site injury requiring intervention, both venous and arterial **Utility Measures** • Length of hospital stay • Length of ICU stay • Use of ECMO, including either pre- or post-treatment initiation and duration • Time to extubation, if intubated • Discharge location
Severity of Adverse Event:	**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
Site activation	The date the site receives approval from the Sponsor to begin enrolling in the study.

11 REFERENCES

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SIGNATURE APPROVAL PAGE

FLowTriever for **A**cute **M**assive Pulmonary **E**mbolism **(FLAME)**
Protocol Number: 20-001
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Signed: _____

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