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PEERLESS Study

Protocol v. 4.0

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PEERLESS Study

A prospective, multicenter, randomized controlled trial of the FlowTriever System compared to Catheter-Directed Thrombolysis (CDT) for use in the treatment of acute pulmonary embolism. The trial includes a non-randomized cohort of subjects with an absolute contraindication to thrombolysis.

Devices: FlowTriever® Retrieval/Aspiration System and CDT
Protocol Number: 21-002
Version: 4.0
August 23, 2023

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PROTOCOL SIGNATURE PAGE

Investigator Name	Title
Site Name	Site Number

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

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

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

Investigator's Signature	Date

SYNOPSIS

Protocol Number	21-002
Study Title	PEERLESS Study
Study Devices	FlowTriever Retrieval/Aspiration System and any commercially available Catheter-Directed Thrombolysis (CDT) System
Regulatory Status	The FlowTriever System is FDA-cleared in the United States for the treatment of Pulmonary Embolism under 510(k) number K211013 and CE Marked for distribution in Europe. The FlowTriever Retrieval/Aspiration System is indicated for: • The non-surgical removal of emboli and thrombi from blood vessels. • Injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel. The FlowTriever Retrieval/Aspiration System is intended for use in the peripheral vasculature and for the treatment of pulmonary embolism. Triever Catheters (Triever 16, Triever 20, Triever 20 Curve, and Triever 24) are also intended for use in treating clot in transit in the right atrium but not in conjunction with FlowTriever Catheters. The study will allow any market cleared CDT systems to be used per local regulations. These products may include: • Cragg-McNamara™ Micro Therapeutics Infusion Catheter (Medtronic) • Uni-Fuse™ (AngioDynamics) • EkoSonic (EKOS™) Endovascular System (Boston Scientific)
Sponsor	Inari Medical Inc. 6001 Oak Canyon, Suite 100 Irvine, CA 92618 (USA) European Office Inari Medical Europe GmbH St. Jacob-Strasse 7 4052 Basel Switzerland
Study Objective	The primary study objective is to compare the clinical outcomes of patients treated with the FlowTriever System versus Catheter-Directed Thrombolysis (CDT) for use in the treatment of acute pulmonary embolism (PE).

Study Population	RCT Cohort: Up to 550 subjects with acute PE will be enrolled and randomized at up to 60 study sites. All subjects who sign informed consent and who meet all of the baseline inclusion criteria and none of the exclusion criteria will be randomized (1:1, FlowTriever or CDT). • One-to-one (1:1) randomization will be stratified by bleeding risk, as measured by the VTE-BLEED score[3]. • Stratification by the VTE-BLEED algorithm will occur automatically in the Electronic Data Capture (EDC) system upon data entry, and randomization will be assigned accordingly. Contraindication Cohort: Up to 150 additional subjects who meet study eligibility criteria and who have an absolute contraindication to thrombolytics, whose initial planned primary treatment strategy includes FlowTriever, will be evaluated as part of the Contraindication Cohort. The same RCT Cohort clinical assessments and follow up schedule will be administered in this Contraindication Cohort.
Number of Sites	This study will be conducted at up to 60 study sites (locations in US, UK, and/or Europe).
Study Design	This study is a prospective, multicenter, randomized controlled trial of the FlowTriever System compared to CDT for acute PE, and includes a non-randomized cohort for subjects with an absolute contraindication to thrombolytics. The study will collect data on demographics, comorbidities, details from the PE diagnosis and treatment, and clinical outcomes through 30-day follow up. **Randomized Controlled Trial Cohort (RCT Cohort):** This study is a prospective, multicenter, randomized controlled trial of the FlowTriever System compared to Catheter-Directed Thrombolysis (CDT) for treatment of acute PE. **Non-Randomized Absolute Contraindication to Thrombolytics Cohort (Contraindication Cohort):** Subjects who meet study eligibility criteria and who have an absolute contraindication to thrombolytics, whose initial planned primary treatment strategy includes FlowTriever, will be evaluated as part of the Contraindication Cohort. The same RCT Cohort clinical assessments and follow up schedule will be administered in this Contraindication Cohort.

Primary Endpoint	The primary endpoint is a composite clinical endpoint constructed as a win ratio, a hierarchy of the following, assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner: 1. All-cause mortality, or 2. Intracranial hemorrhage (ICH), or 3. Major bleeding per ISTH definition[4], or 4. Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy, or 5. ICU admission and ICU length-of-stay during the index hospitalization and following the index procedure.

Secondary Endpoints	The secondary endpoints of the study will assess safety, effectiveness, and utility measures, as follows:
	
	• Composite clinical endpoint constructed as a win ratio hierarchy of the following four components, assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner:
	  ○ All-cause mortality, or
	  ○ Intracranial hemorrhage (ICH), or
	  ○ Major bleeding per ISTH definition[4], or
	  ○ Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy
	• Individual components of the win ratio composite endpoint, assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner:
	  ○ All-cause mortality
	  ○ Intracranial hemorrhage (ICH)
	  ○ Major bleeding per ISTH[4] definition
	  ○ Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy
	  ○ ICU admission and ICU length of stay during the index hospitalization and following the index procedure
	• All-cause mortality within 30 days from index procedure
	• PE-related and all-cause readmission within 30 days from index procedure
	• Device and drug-related serious adverse events through the 30 day visit
	• Clinically Relevant Non-Major (CRNM) and Minor bleeding events through hospital discharge or at 7 days after the index procedure, whichever is sooner
	• Change in right-ventricular/left-ventricular (RV/LV) ratio from baseline to 24 hour visit, as measured by echocardiography or CT
	• mMRC Dyspnea score at 24 hour visit and 30 day visit
	• Length of total hospital stay and post-index-procedure hospital stay (to a maximum of 30 days)
	• Disease-specific and general health-related quality of life at the 30 day visit (PEmb-QoL and EQ-5D-5L)

Inclusion Criteria	Subjects must meet each of the following criteria to be included in the study: 1. Age ≥ 18 years 2. Echo, computed tomographic pulmonary angiography (CTPA), or pulmonary angiographic evidence of any proximal filling defect in at least one main or lobar pulmonary artery 3. Including ALL of the following: a. Clinical signs and symptoms consistent with acute PE, or PESI class III-V, or sPESI ≥1 AND b. Hemodynamically stable AND c. RV dysfunction on echocardiography or CT AND d. Any one or more of the following present at the time of diagnosis: i. Elevated cardiac troponin levels ii. History of heart failure iii. History of chronic lung disease iv. Heart rate ≥110 beats per minute v. SBP <100mmHg vi. Respiratory rate ≥30 breaths per minute vii. O2 saturation <90% viii. Syncope related to PE ix. Elevated lactate 4. Intervention planned to begin within 72 hours of the later of either a. Confirmed PE diagnosis OR b. If transferring from another hospital, arrival at the treating hospital 5. Symptom onset within 14 days of confirmed PE diagnosis
Exclusion Criteria	Subjects will be excluded from the study for any of the following criteria: 1. Unable to anticoagulate with heparin, enoxaparin or other parenteral antithrombin 2. Index presentation with hemodynamic instability that are part of the high-risk PE definition in the ESC Guidelines 2019[1], including ANY of the following: a. Cardiac arrest OR b. Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status, AND end-organ hypoperfusion OR c. Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis 3. Known sensitivity to radiographic contrast agents that, in the Investigator's opinion, cannot be adequately pre-treated

	4. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the patient is not appropriate for catheter-based intervention (e.g., inability to navigate to target location, clot limited to segmental/subsegmental distribution, predominately chronic clot) 5. Patient has right heart clot in transit identified at baseline screening 6. Life expectancy < 30 days (e.g., stage 4 cancer or severe COVID-19 infection), as determined by the Investigator 7. Current participation in another drug or device study that, in the Investigator's opinion, would interfere with participation in this study 8. Current or history of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis, per ESC 2019 guidelines[1] 9. Invasive systolic PA pressure ≥70 mmHg prior to study device entering the body 10. Administration of bolus or drip/infusion thrombolytic therapy or mechanical thrombectomy for the index PE event within 48 hours prior to enrollment 11. Ventricular arrhythmias refractory to treatment at the time of enrollment 12. Known to have heparin-induced thrombocytopenia (HIT) 13. Subject has any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being or that could prevent, limit, or confound the protocol-specified assessments). This includes a contraindication to use of FlowTriever or CDT System (for example, EKOS System) per local approved labeling 14. Subject has previously completed or withdrawn from this study 15. Patient unwilling or unable to conduct the follow up visits per protocol.
Follow Up Schedule	Subjects will have follow-up evaluations after the Index Procedure at: • 24 hours (24 hours ±8 hours) • Hospital discharge • 30 days (30 days +15 days)
Safety Monitoring: Clinical Events Committee (CEC)	A Clinical Events Committee (CEC) will be utilized in this study for the purposes of adjudicating safety-related primary and secondary endpoints. Site-reported safety and outcome data will be provided to the CEC for review and adjudicated for all subjects enrolled in the study.
Global Principal Investigators	Wissam Jaber, M.D. and Carin Gonsalves, M.D.
European Principal Investigator	Stefan Stortecky, M.D., MPH FESC

ABBREVIATIONS

Abbreviation	Term
AC	Anticoagulation
ADE	Adverse device effect
AE	Adverse event
AHA	American Heart Association
ASADE	Anticipated serious adverse device effect
CCU	Coronary care unit
CDT	Catheter-directed thrombolysis
CEC	Clinical Events Committee
CI	Cardiac Index
CRNM	Clinically Relevant Non-Major
CT	Computed Tomography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
DD	Device deficiency
DVT	Deep venous thrombosis
EBL	Estimated Blood Loss
ECMO	Extracorporeal membrane oxygenation
eCRFs	Electronic case report forms
ED	Emergency Department
EKOS	EkoSonic catheter system
ESC	European Society of Cardiology
EC	Ethics Committee

Abbreviation	Term
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FLAME	FlowTriever for Acute Massive Pulmonary Embolism
FLARE	FlowTriever Clinical Embolectomy Clinical Study
FLASH	FlowTriever All-Comer Registry for Patient Safety and Hemodynamics
FT	FlowTriever
GDPR	General Data Protection Regulation 2016/679
H-FABP	Heart type fatty acid binding
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-induced thrombocytopenia
ICF	Informed consent form
ICH	Intracranial hemorrhage
ICU	Intensive Care Unit
IFU	Instructions for use
IRB	Institutional review board
ISTH	International Society on Thrombosis and Haemostasis
LMWH	Low molecular weight heparin
LOS	Length of stay
LV	Left ventricle
MAE	Major adverse events
MEC	Medical Ethics Committee
mMRC	Modified Medical Research Council Dyspnea Scale
PA	Pulmonary Artery

Abbreviation	Term
PAP	Pulmonary Artery Pressure
PAPi	Pulmonary Artery Pulsatility Index
PE	Pulmonary Embolism
PEmb-QOL	Pulmonary Embolism Quality of Life
PESI	Pulmonary Embolism Severity Index
PHI	Protected Health Information
QOL	Quality of life
RA	Right Atrial
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
RVSWI	Right ventricular stroke work index
SAE	Serious adverse event
SADE	Serious adverse device effect
SIV	Site initiation visit
sPAP	Systolic Pulmonary Artery Pressure
sPESI	Simplified Pulmonary Embolism Severity Index
SVI	Stroke volume index
tPA	Tissue plasminogen activator
TPVR	Total pulmonary vascular resistance
TTE	Transthoracic echocardiography
UADE	Unanticipated adverse device effect
UAT	Ultrasound-accelerated thrombolysis
USADE	Unanticipated serious adverse device effect
USAT	Ultrasound-assisted thrombolysis

Abbreviation	Term
VTE	Venous thromboembolism

1. INTRODUCTION AND BACKGROUND

Pulmonary embolism (PE) is a debilitating and potentially lethal disease, leading to an estimated 300,000 hospitalizations per year in the US, and over 400,000 PE events in Europe in 2004 with 10-30% mortality.[5-7] PE and deep vein thrombosis (DVT) are the 2 main clinical consequences of venous thromboembolism (VTE), which together lead to over 500,000 annual hospitalizations in the US, and a similar number in Europe.[5, 7] 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.[8] While a reduction in mortality was seen over that time period, mortality in 2012 still ranged from 1.6% to 39.1%, depending on the severity of the disease.[8] VTE is also the leading cause of preventable in-hospital death.[9, 10]

PE occurs when venous thrombi travel from the peripheral veins, through the right heart, and lodge in the pulmonary arterial system. The emboli often arise from existing DVTs of the legs, but they may also initiate within the large veins of the upper extremities. While small PEs may remain asymptomatic and go unnoticed, larger emboli can result in significant pulmonary artery obstruction, leading to right heart decompensation and mortality. In fact, because VTE may remain undetected in the initial stages, sudden death is the first symptom of PE in up to 25% of cases.[6] PE may also occur in a repeated fashion, 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 (CTEPH). Due to high mortality and debilitating long-term outcomes, better treatment options that provide rapid hemodynamic relief and reduction in acute mortality, as well as improved long-term functional outcomes, are clearly needed.

DIAGNOSIS OF PULMONARY EMBOLISM

Clinical signs of PE tend to be non-specific, and include dyspnea, chest pain, elevated heart rate, and syncope. Because of the non-specific nature of PE symptoms, assessment of predisposing factors for VTE becomes an important component of the clinical work-up. These factors include recent trauma or surgery, prolonged inactivity, active cancer, and previous VTE. Several predictive scores have been developed to help diagnosis and prediction of disease severity, including the Wells[1] and Geneva[11] scores, but studies suggest the predictive value of these scores fared no better than empirical clinical evidence, or clinical "gestalt".[12, 13]

Once PE is suspected based on clinical signs and predisposing factors, a more definitive diagnosis as well as assessment of severity can be obtained by imaging. The most informative approach is computed tomography pulmonary angiography (CTPA), which is now readily available at most clinical sites with rapid acquisition time. The Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II study demonstrated a sensitivity of 83% and a specificity of 96% for CTPA in diagnosing PE.[14] CTPA can reveal right ventricle (RV) dilatation and provide an RV/left ventricle (LV) ratio, which is an independent predictor of an adverse outcome when RV/LV ≥ 0.9.[15] In addition, it provides visualization of both location and size of emboli within the pulmonary arterial system down to the subsegmental level.

Transthoracic echocardiography (TTE) can be effective at detecting right heart dysfunction and RV dilatation associated with PE, along with other parameters, including estimated right atrial (RA) pressure and RV systolic pressure. It can also detect RA clot-in-transit, which if left untreated, may result in acute PE.

Laboratory biomarkers can contribute to both the diagnosis and the risk assessment of PE patients. Plasma D-dimer concentration can be elevated in patients with acute thrombosis, and it has a high negative predictive value

for PE.[1] However, its positive predictive value is low,[16] and elevated D-dimer is seen in other disease states, such as cancer or severe infection. Thus, a negative test safely excludes PE in patients with low clinical probability of the disease, but further imaging is necessary when the D-dimer test is positive.[1]

The guideline-recommended diagnosis and treatment of PE depends on its severity, which is defined by the risk of mortality. This risk is tightly correlated with the hemodynamic consequences of the embolism, namely, acute RV dysfunction. RV dysfunction is the principal determinant of a patient's clinical course.[17] The risk of hemodynamic compromise is related to the interplay between the size of the embolus and the baseline cardiorespiratory state of the patient. For instance, a PE of moderate size in a healthy patient may be unassociated with hemodynamic compromise while the same embolus in an elderly patient with preexisting cardiac disease may result in fulminant right heart decompensation and mortality. In this regard, the severity of pulmonary embolism is only partially represented by the presenting hemodynamic condition of the patient, and baseline comorbidities should be considered.

RISK STRATIFICATION OF PULMONARY EMBOLISM

Once the diagnosis of PE has been made, it becomes essential to identify those patients at highest risk for mortality in order to triage them to advanced therapies that can quickly reduce the right heart strain and thus the risk of mortality. A variety of indices have been used to predict outcomes following PE. The Pulmonary Embolism Severity Index (PESI) has been well-validated.[18] 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.[19-21] Patients with an sPESI score of 0 have a very low risk of early adverse outcome. Adding a negative cardiac troponin further increases the negative predictive value of the scores.[20] 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.

Approximately 30-60% of acute PE patients have elevated cardiac troponins I or T[22, 23] and elevated troponin is associated with an increased risk in mortality, even in patients who initially present as hemodynamically stable.[24] In addition, B-type natriuretic peptide (BNP) and N-terminal (NT) proBNP have low positive predictive value for mortality in normotensive PE patients but have a high sensitivity and a negative predictive value for ruling out PE.[25] Additional biomarkers, such as heart-type fatty acid-binding protein (H-FABP) and lactate, have been studied and shown to have some utility in the diagnosis of PE, risk assessment, or both,[26, 27] but these have not yet become routinely used.

There are several well-established guidelines for classifying the mortality risk and PE severity for affected patients. The most recent and widely used of these are the American Heart Association Scientific Statement on Interventional Therapies for Acute Pulmonary Embolism[28] and the European Society of Cardiology Guidelines for Diagnosis and Management of Acute Pulmonary Embolism.[1]

American Heart Association. The 2019 American Heart Association (AHA) Scientific Statement on Interventional Therapies for Acute Pulmonary Embolism reiterates the established classification of PE into three traditional categories utilized in the literature: massive, submassive, and low-risk.[28]

- Massive PE is defined as hypotension with systolic blood pressure < 90 mm Hg, a drop of > 40 mmHg for at least 15 minutes or requiring vasopressor support. Mortality is ~30% within 1 month.

- Submassive PE is defined as RV strain without hypotension, with RV strain identified by either RV dysfunction on CTPA or myocardial necrosis as measured by elevated troponins or BNPs. Mortality varies widely in published studies, ranging between 3 - 15% over 7 - 90 days.

- 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. Mortality at one month is ~1% in this group.

While these categories correlate roughly with the risk of mortality, the AHA statement stresses that concurrent comorbidities must be accounted for in the prediction of mortality and the decision for treatment options. While most low-risk patients do well on anti-coagulation (AC) alone, advanced therapies should be increasingly considered as the mortality/risk stratification level increases, with the possible treatment risks weighed against the PE severity and mortality risk. As such, the development of new therapies with lower risk profiles could allow these advanced therapies to be a compelling option for more than just the highest risk patients. Potential but unproven benefits of treating intermediate-risk (sub-massive) PE patients beyond the immediate hemodynamic relief and mortality benefit seen when treating high-risk patients may be improved long-term functional outcomes and prevention of CTEPH.

European Society of Cardiology. The 2019 European Society of Cardiology (ESC) Guidelines for Diagnosis and Management of Acute Pulmonary Embolism specified risk stratification using combinations of hemodynamic instability, clinical parameters of PE severity and/or co-morbidity, RV dysfunction by imaging, and cardiac troponin levels (**Figure 1**).[1] This risk stratification differs slightly from the AHA stratification in the definition, and further stratification, of the sub-massive (AHA), or intermediate-risk (ESC) category into intermediate-high and intermediate-low categories, resulting in four risk levels.

High-risk PE patients present with acute hemodynamic instability and imaging evidence of RV dysfunction, analogous to the massive category in the AHA guidelines. These patients present in shock and have PESI scores III or greater or sPESI scores greater than 0 (if assessed) and positive cardiac troponins indicative of myocardial necrosis (if assessed). An intermediate-risk category is defined by the ESC guidelines, analogous to the submassive category in the literature and AHA guidelines. The intermediate-risk subgroup is further divided into intermediate-high-risk and intermediate-low-risk subcategories, depending on whether both RV dysfunction and elevated cardiac troponin levels are present (intermediate-high-risk) or only one or neither of the two are present (intermediate-low-risk). The last category is the low-risk group and is similar to the AHA low-risk category. These patients present without hemodynamic compromise, have low PESI/sPESI scores, and normal RV imaging or laboratory assessments when they are performed.

Figure 1 European Society of Cardiology Risk Stratification

From Konstantinides et al.[1]

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

[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_II or an sPESI of 0.[2] Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

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

RISK-BASED TREATMENT OPTIONS FOR PULMONARY EMBOLISM

Anticoagulation (AC)

AC is the mainstay of therapy for VTE, directed at decreasing the risk of recurrent embolic events and propagation of existing thrombi. Upon suspicion of PE, AC should be started immediately with either subcutaneous

administration of low-molecular weight heparin or fondaparinux, with a Class 1C recommendation in the ESC guidelines.[1] For low-risk patients, AC therapy on an outpatient basis may be sufficient if proper outpatient care and medication compliance can be assured (Class IIa-A recommendation, ESC guidelines).[1]

Open Surgical Thrombectomy

Open surgical thrombectomy was perhaps the first definitive interventional treatment for PE. Open surgical thrombectomy can result in rapid, life-saving hemodynamic improvement in patients with significant PE.[29, 30] However, it is a major invasive procedure, fraught with complications in unstable patients. The in-hospital mortality rate is more than 25%, although this figure must be considered in the context of alternative therapies in this high-risk group. No randomized trials have been performed to compare the outcome with alternate therapies in similar patient populations. For these reasons, AHA and ESC guidelines suggest that open surgical intervention be reserved for hemodynamically-unstable patients with contraindications to thrombolysis.[1, 28] However, selected indications remain appropriate for open thrombectomy; for example, emboli in transit such as within the right heart or a patent foramen ovale. In this regard, the American College of Chest Physicians advocates open surgical intervention for patients who are severely compromised such that mortality is likely to occur before thrombolytic therapies can improve the patient's hemodynamic state.[31]

Thrombolysis

While anticoagulation is effective in preventing formation of new thrombus and thus reducing recurrent PE, it does little to treat existing thrombus. Pharmacologic lysis of the obstructive pulmonary artery thromboembolism has the potential to provide rapid relief of right heart strain, and thus reduce mortality risk, in patients with intermediate-risk (submassive) and high-risk (massive) PE, where normalization of right heart function is critical to reduce mortality. For this reason, systemic infusion of thrombolytic drugs was evaluated in order to more directly reduce the burden of existing thrombus. These thrombolytic drugs consisted of various early-generation plasminogen activators, such as urokinase and streptokinase. These enzymatic pharmacologic agents target the breakdown of fibrin within acute thrombi. After initial anecdotal success with intravenous urokinase for PE reported in 1968 by Sasahara,[32] the landmark randomized clinical trials upon which the initial US Food and Drug Administration (FDA) approval for urokinase was based demonstrated improved outcome with thrombolysis versus anticoagulation for submassive and massive PE.[33-38] 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, lysis of pulmonary artery thrombus was demonstrated to be safe, effective, and appeared advantageous compared to anticoagulation alone.

Systemic Thrombolysis: 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.[39-41] These findings remained unchanged despite the use of newer modern thrombolytic agents and better periprocedural patient management over the years.

Catheter-Directed Thrombolysis (CDT): Noting the hemorrhagic complications associated with systemic thrombolysis for PE, lower-dose, CDT approaches were studied in which catheters were maneuvered into the pulmonary arteries to selectively deliver thrombolytics directly to the location of the obstructing thrombus. Catheter-directed thrombolysis for PE was the subject of a meta-analysis published in 2009.[42] In summary, catheter-directed thrombolysis appeared effective and probably safer than the systemic approach. The authors recommended that catheter-directed thrombolysis be considered as a first-line therapy for acute, massive PE. However, recent work suggests that even a catheter-directed approach may be associated with significant bleeding complications,[43] although possibly at a lower rate than with systemic treatment.[44]

Ultrasound-Accelerated Thrombolysis: To further enhance the efficacy of CDT, ultrasound technology was incorporated into the CDT catheter to accelerate the lytic process by thinning and separating the fibrin strands within the thrombus, which led to the development of the EkoSonic catheter system (EKOS™). This ultrasound-assisted thrombolysis (USAT) approach was evaluated for submassive and massive PE in two multicenter, prospective studies, ULTIMA and SEATTLE-II. ULTIMA was a randomized analysis of USAT vs. anticoagulation alone in 59 subjects with submassive PE.[45] USAT was found to be more effective than anticoagulation in normalizing RV function. No intracranial bleeding was observed. The SEATTLE-II trial evaluated 24mg of tissue plasminogen activator (tPA[a]), infused over 24hr in one catheter, or over 12 hours in two catheters, in 150 subjects with submassive and massive PE.[46] Further refinement of the lytic dose and infusion duration using EKOS was conducted in the OPTALYSE PE trial, which contained four study arms with tPA dose from 4 to 12 mg per lung and infusion duration from 2-6 hours.[47] These studies concluded that catheter-directed pulmonary artery thrombolysis with tPA was safe and effective in the treatment of submassive (intermediate-risk) PE, at least with respect to reductions in RV/LV ratio, and suggested that lower doses and infusion durations were associated with significant RV/LV improvements and clot burden reduction at 48 hours. These conclusions, however, have not been without controversy. A 2017 review of 23 studies and 700 subjects found no difference in the rate of bleeding complications between USAT and conventional, catheter-directed thrombolysis, 12% with USAT vs. 10% with conventional catheter-directed thrombolysis.[48] The review, however, documented a trend toward improved survival with USAT; mortality rates of 4% vs. 9% in the USAT and conventional thrombolytic subjects, respectively. A more recent prospective, randomized controlled trial (SUNSET PE) comparing USAT to CDT demonstrated no benefit of USAT compared to CDT.[49] It should be noted that use of thrombolytics, whether by conventional or USAT approach, typically requires the patient be admitted to the Intensive Care Unit (ICU), due to the elevated bleeding risk, for the duration of the perfusion, which can last up to 48 hours.

Percutaneous Pulmonary Artery Thrombectomy

Pulmonary artery thrombectomy involves the mechanical removal of the thrombus from the vasculature, either through aspiration (suction) or through entrapment of the thrombus in mechanical tools that are then retracted after capturing the thrombus. Interest in this purely mechanical approach grew as it offers a rapid treatment option in contrast to the relatively slow thrombolytic treatment, without the inherent risk of bleeding complications seen with pharmacologic thrombolysis. In addition, percutaneous thrombectomy can be performed in the catheterization lab without the need for the ICU stay required during thrombolytic infusion. The lack of ICU requirement has been particularly attractive in the time of the Covid-19 pandemic with ICU bed shortages. Mechanical thrombectomy also provides a much-needed treatment option for the up-to-50% of PE patients who are contraindicated for thrombolytics. This treatment option may also be more effective at removing older thrombus, in which much of the fibrin has been replaced with collagen, against which thrombolytic drugs are ineffective. Direct pulmonary arterial thrombectomy thus offers the opportunity for rapid removal of thrombus in the catheterization lab for a broader range of PE patients without thrombolytic-related bleeding complications. Multiple mechanical thrombectomy devices with slightly differing approaches have been developed, although none to date have been evaluated in a head-to-head comparison of other treatment options in a randomized trial.

Treatment Recommendations Based on Risk Stratification

The risk stratification strategies of both the 2019 AHA Scientific Statement and the 2019 ESC PE Guidelines provide a data-driven clinical decision strategy for optimal treatment of PE based on clinical presentation. Treatment of low-risk PE patients with no serious co-morbidities or aggravating conditions is straightforward, with data supporting early discharge and the use of AC for at least 3 months after diagnosis, with a Class IIa-A recommendation in the ESC guidelines.

[a] Authors of this study refer to the thrombolytic agent as 'tPA,' which is presumably alteplase but not specified.

Early, aggressive treatment beyond AC therapy is necessary for the massive, or high-risk, PE patient to prevent the rapid, downhill spiral that culminates in a patient's demise. Based on existing clinical data at the time of publication, the 2019 ESC guidelines recommend systemic thrombolysis as the treatment choice for high-risk PE, with a Class IB recommendation. Surgical pulmonary embolectomy or percutaneous CDT as alternative treatments in patients in whom thrombolysis is contraindicated or has failed is given a Class IIa-C recommendation. Of note, extracorporeal membrane oxygenation (ECMO) may be considered with any of these treatments to provide hemodynamic support in patients with refractory circulatory collapse or cardiac arrest until stabilization is achieved.

More controversial and less well-defined is the treatment of intermediate-risk patients. There has been recent enthusiasm for endovascular interventional treatment modalities utilizing catheter-directed thrombolysis, ultrasound-accelerated thrombolysis, or mechanical thrombectomy.[48, 50-53] Currently, however, there is scant data on which to base therapeutic decisions for the intermediate-risk group, as randomized control trials comparing the different therapy options is lacking. Based on the current data available, thrombolytic treatment is recommended for those submassive, or intermediate-risk, patients with hemodynamic deterioration (Class I-B), but not for routine use in all intermediate- or low-risk patients. Surgical or percutaneous thrombectomy is given a "may also be considered in these patients" Class IIa-C recommendation.

LIMITATIONS OF CURRENTLY AVAILABLE THERAPY

Generally, the AHA Scientific Statement and ESC guidelines agree that the mainstay of treatment for massive and submassive PE is anticoagulation and that thrombolysis should be offered to unstable patients.[1, 28] They further suggest that thrombolytics not be routinely used to treat submassive PE but should instead be considered on a per patient basis. The choice between treating the PE patient with standard AC alone versus advanced therapy, as well as which advanced therapy to use, should be based on clinical evidence, much of which to date is derived from clinical trials and meta-analyses of studies of systemic thrombolysis. While some trials have shown benefit of using either systemic or catheter-directed thrombolysis compared to AC alone,[39] that benefit is typically offset by an increase in major bleeding risk. For this reason, and because many PE patients are contraindicated for thrombolytics, advanced treatment options that do not involve a thrombolytic component, such as mechanical thrombectomy, are being pursued, but clinical data are lacking.

While a treatment's impact on acute hemodynamic parameters is critical for reducing mortality, understanding the long-term outcomes and potential impact of unresolved, residual thrombus post-treatment is critically important to the long-term morbidity and quality of life of the PE patient. Residual thrombus can lead to post-PE syndrome and/or CTEPH in up to 50% of PE patients, with long-term, debilitating impact on functional status and quality of life.[54-56] Data on residual thrombus post-treatment as well as the incidence of post-PE syndrome and CTEPH following the different treatment options is also lacking.

The goal of a successful interventional procedure is to restore RV outflow through the pulmonary artery, thereby disrupting the potentially lethal cascade towards hemodynamic collapse. However, there remains a strong clinical need to develop a reliable, rapid, percutaneous method of thrombus removal for the treatment of clinically significant acute PE. The need is especially strong for a mechanical method that does not rely on the use of thrombolytics, as physicians are reluctant to administer thrombolytics given the high bleeding risk and because many patients cannot tolerate lytics. Once the immediate thrombus burden is removed, blood flow is restored and the acute physiological effects from pressure overload should begin to dissipate. The FlowTriever System was developed to meet this need to rapidly restore blood flow through the pulmonary vasculature in patients experiencing acute submassive or massive pulmonary embolism. However, clinical data from prospective, randomized control trials are still lacking for FlowTriever and other advanced therapies. The 2019 AHA document urges the pursuit of such studies, and suggests several components for these future trials, including patient-centric functional quality of life (QOL) outcomes in addition to the traditional outcomes of mortality and hemodynamic decompensation.[28]

2. STUDY DEVICES

Subjects enrolled in this study will undergo PE treatment with either the FlowTriever System or standard commercially available CDT devices, depending on each patient's randomization assignment (or inclusion into the Contraindication Cohort). These study devices are reviewed briefly in the following sections. Future commercially available FlowTriever system components or commercially available CDT systems may be included in the study but may not be listed here due to current regulatory approval status.

FLOWTRIEVER SYSTEM

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 for the treatment of pulmonary embolism. The system is comprised of two main components packaged separately:

- Triever Catheters (available in 3 sizes: 16, 20 (and 20 Curved) and 24 Fr)
- FlowTriever Catheters (available in 4 sizes: 6-10 mm, 11-14 mm, 15-18 mm, and 19-25 mm)

Triever Catheters (Triever 16, Triever 20, Triever 20 Curve, and Triever 24) are inserted and advanced to the thrombus over a pre-placed 0.035" guidewire. After removal of its dilator, thrombus may be removed by aspiration with the provided 60 cc VacLok Vacuum syringe. After the procedure is complete, the Triever Catheter is removed from the patient.

Regulatory Status

The FlowTriever System is FDA-cleared in the United States for the treatment of Pulmonary Embolism under 510(k) number K211013 and CE Marked for distribution in Europe.

Manufacturer

The FlowTriever System is manufactured by Inari Medical, Inc. The manufacturer location:

Inari Medical, Inc.

6001 Oak Canyon, Suite #100

Irvine, CA 92618 (USA)

Indications for Use and Intended Use

The FlowTriever Retrieval/Aspiration System is indicated for:

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

The FlowTriever Retrieval/Aspiration System is intended for use in the peripheral vasculature and for the treatment of pulmonary embolism.

Triever Catheters (Triever 16, Triever 20, Triever 20 Curve, and Triever 24) are also intended for use in treating clot in transit in the right atrium but not in conjunction with FlowTriever Catheters.

Device Description

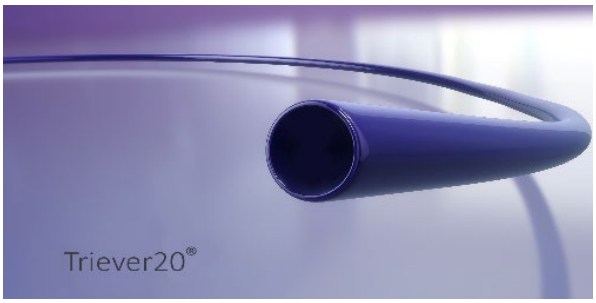
The FlowTriever System is a single-use over-the-wire catheter-based system for the minimally invasive treatment of thromboemboli in the peripheral vasculature and the treatment of pulmonary embolism. The FlowTriever System is composed of two main components: the Triever aspiration catheter and the FlowTriever catheter. The FlowTriever System can be used in conjunction with the FlowSaver™ Blood Return System, which is a separate product for filtering and reintroducing blood aspirated by the FlowTriever System. Each of these devices is described below.

Triever™ Aspiration Catheters

The Triever Aspiration Catheter is a large-bore catheter used primarily for controlled aspiration of thromboemboli (Fig. 2A). The catheters are available in 16, 20, and 24Fr diameters, which are referred to as the Triever16™ (T16), Triever20™ (T20), and Triever24™ (T24) catheters, respectively. The Triever20 Curve™ (T20 Curve) pre-shaped catheter is designed with a bend of up to 260° to provide access to challenging anatomy (Fig. 2B) and must be used coaxially with the T24 catheter. After the distal end of the Triever catheter is positioned adjacent to thrombus, a vacuum is applied to the closed catheter side port via a 60 mL custom large-bore syringe (Fig. 3). 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.

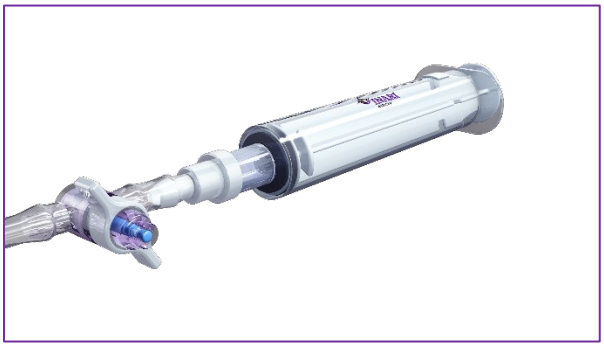
Figure 2 Triever Catheters

A



B

Figure 3 Large Bore Syringe

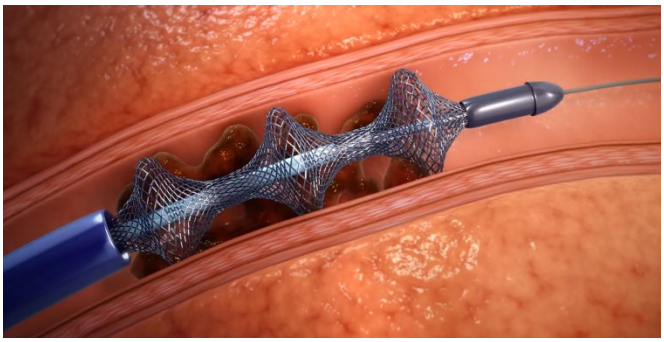


FlowTriever™ Catheter

The FlowTriever catheter, which is designed to be deployed coaxially through the Triever Catheter, consists of a flexible shaft attached to distal self-expanding nitinol disks. 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. The

FlowTriever catheter is available in multiple configurations. One representative version of the FlowTriever catheter consists of 3 disks (Fig. 4) that are available in four sizes ranging in disk diameters from 12.5 to 28.0mm.

Figure 4 FlowTriever Catheter (3-disk Configuration Shown)



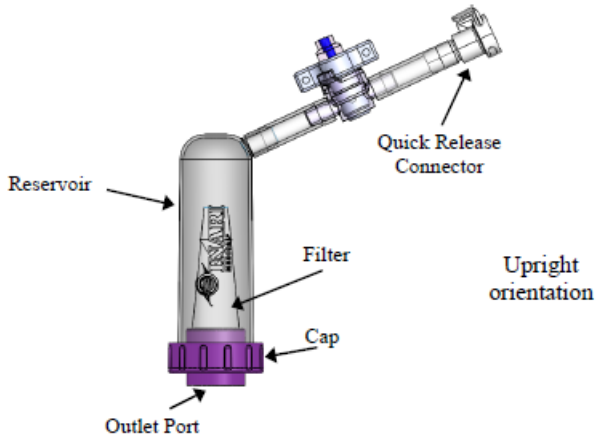
Additional FlowTriever catheters that have different nitinol disk configurations may be used during the course of this study depending on the status of regulatory clearances local to each geographic region in which the study is conducted. All FlowTriever catheter configurations have the same function to macerate and deliver thrombus to the Triever catheter for aspiration.

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

FlowSaver™ Blood Return System

The FlowSaver Blood Return System is used to filter the aspirated contents of the Large Bore Syringe from a FlowTriever System procedure. The provided 60cc syringe is connected to the outlet port and used to aspirate blood through the 40 µm filter (Fig. 5). The filtered blood is then re-introduced to the patient through a sheath or catheter. It is indicated to be used with the Triever Catheters for autologous blood transfusion.

Figure 5 The FlowSaver Blood Return System



A complete description of the FlowSaver System is provided in the Instructions for Use (FlowSaver is FDA-cleared in the United States under 510(k) number K210176).

CATHETER-DIRECTED THROMBOLYSIS (CDT)

Catheter-directed thrombolysis devices are catheters introduced endovascularly and placed at the site of the thrombus for localized infusion of thrombolytic drugs, such as various tissue plasminogen activators (tPA), which are infused through side holes in the catheter to enhance thrombus dissolution. Due to the bleeding risks associated with thrombolytic drugs, patients undergoing CDT are typically admitted to the ICU and immobilized during the infusion, then returned to the catheterization lab to assess the degree of thrombus dissolution following treatment. Additional thrombolytic infusions may be attempted if the initial infusion resulted in insufficient thrombus dissolution.

Various commercially available endovascular catheters may be used for CDT purposes, including both conventional CDT catheters and ultrasound-assisted CDT catheters. These two categories of CDT devices are described briefly in the following sections.

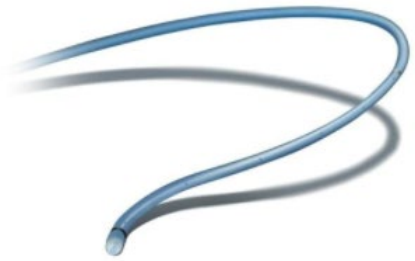
Conventional CDT Catheters

Conventional CDT catheters rely on their side hole designs to deliver targeted thrombolytic drugs to the local vicinity of the thrombus via a simple 'drip' infusion approach. Two types of catheters commonly used for conventional CDT in the setting of PE treatment are the Cragg-McNamara infusion catheter and the Uni-Fuse infusion catheter, though other similar catheters may be used depending on the standard of care at the particular clinical facility. Both these conventional CDT systems are market cleared in the geographies for this study.

Cragg-McNamara™ Micro Therapeutics Infusion Catheter

The Cragg-McNamara Micro Therapeutics Infusion Catheter (Fig. 6; Medtronic, Dublin, Ireland) is intended to be used for the controlled selective infusion of physician-specified pharmacologic agents or contrast into the general vasculature. It comes in 4 and 5 French (F) sizes with a valved-tip, single-lumen catheter designed to be used without a guidewire.

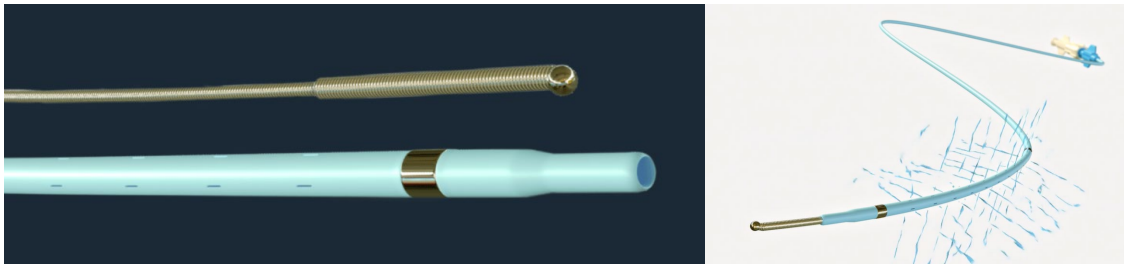
Figure 6 Cragg-McNamara Infusion Catheter



Uni-Fuse™

The Uni-Fuse infusion catheters (Fig. 7; AngioDynamics, Latham, NY) are indicated for the administration of fluids, including thrombolytic agents and contrast media in the peripheral and pulmonary artery vasculature. The catheter system includes a 4 or 5 F catheter with an occluding ball wire. When inserted into the catheter, the occluding ball wire provides force, activating pressure response outlets (slits) and resulting in the consistent distribution of thrombolytic agent to an area of thrombus.

Figure 7 Uni-Fuse Infusion Catheters



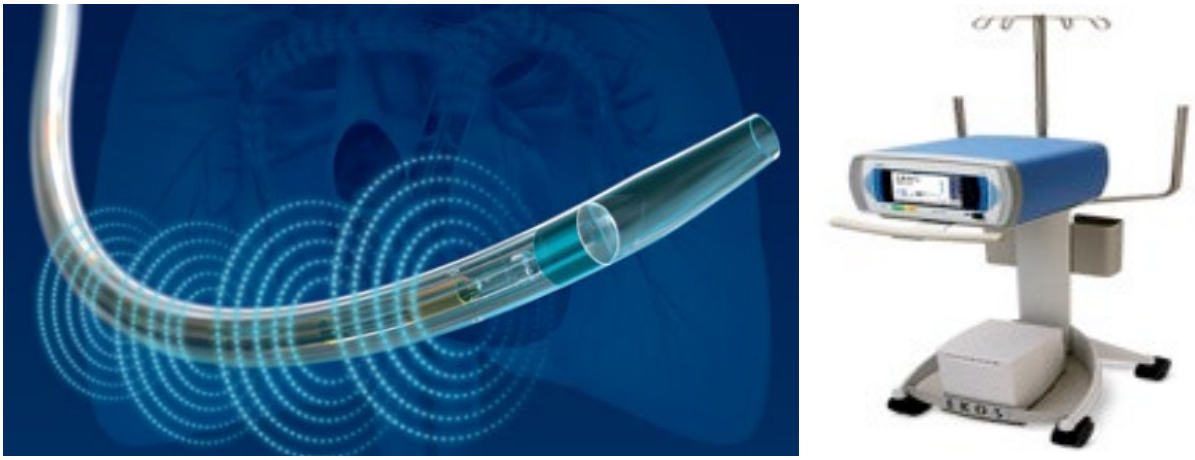
Ultrasound-Assisted CDT Catheters

Ultrasound-assisted thrombolysis (USAT) catheters are a specialized subset of CDT catheters that include miniature ultrasound transducers embedded within the distal portion of the catheter. Currently, these specialized catheters are available only in the EkoSonic (EKOS™) Endovascular System (Boston Scientific, Marlborough, MA). Like the conventional CDT catheters described above, the EKOS catheter is designed to deliver the thrombolytic agent to the location of the thrombus; however, in addition, this type of catheter actively emits controlled ultrasonic energy to theoretically enhance drug penetration. The EKOS system is market cleared in the geographies for this study.

EkoSonic (EKOS™) Endovascular System

The EKOS Endovascular System (Fig. 8; Boston Scientific, Marlborough, MA) consists of a 5.4 F multi-side-hole catheter indicated for ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism. It is also indicated for the infusion of solutions into the pulmonary arteries, and the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. The emission of ultrasonic waves is thought to thin and separate the fibrin strands to facilitate thrombolytic drug infusion into the thrombus.

Figure 8 EKOS Endovascular System



3. PRIOR INVESTIGATIONS

FLOWTRIEVER SYSTEM

The FlowTriever System was first evaluated for PE treatment in a US pivotal Investigational Device Exemption trial, the FlowTriever Pulmonary Embolectomy Clinical Study (FLARE) trial, 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. This study provided the data allowing FDA clearance for the FlowTriever System for use in treatment of PE.

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

In addition, a second post-market registry (FlowTriever for Acute Massive Pulmonary Embolism (FLAME)) was recently initiated. 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). These three Inari-sponsored studies (FLARE, FLASH, and FLAME) are summarized below, along with key published literature reporting outcomes from FlowTriever use in clinical practice.

FLARE Study Design and Summary of Results

FLARE Study Design

The FLARE study was designed as a US pivotal Investigational Device Exemption trial, 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. A maximum of 20 study sites were planned to participate in the study, and no single study site could enroll more than 25% of the total subjects. The study population comprised 106 subjects with acute submassive PE.

Primary safety and primary effectiveness performance goals were used in the study. To establish the safety performance goal, the results from seven studies published in the medical literature in which acute PE patients were treated with a heparin control arm were used to develop a composite Major Adverse Event (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 safety performance goal was chosen as the upper 95% confidence limit rounded down to two digits, for a safety performance goal of 25%.

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

Subjects were followed for 30 days post-procedure with computed tomography pulmonary angiography (CTPA) at 48 hours and assessment of Adverse Events (AEs) through 30 days. The primary safety endpoint was assessed from

the 48-hour MAE rate and the primary effectiveness endpoint from the change in RV/LV ratio between the baseline and 48-hour CTPA imaging studies. Powering considerations for detecting results exceeding the established performance goals led to a final sample size of 106 enrolled subjects.

FLARE Study Results

In all, 106 subjects were enrolled and treated with the FlowTriever System in FLARE, and 104 of these did not receive 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-treatment RV/LV ratio for comparison. For these paired subjects, the mean change (reduction) in RV/LV ratio from pre- to post-treatment 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 (25.1%, $P < 0.0001$), indicating that the null hypothesis was rejected and the FlowTriever System met the performance goal.[b]

For the primary safety endpoint, 4 subjects (3.8%) in the modified intention to treat population (all subjects with treatment attempted and no thrombolytics administered) experienced one or more MAEs. The composite endpoint of 3.8% was statistically lower than the performance goal of 25% ($P < 0.0001$), with an upper one-sided 95% confidence limit of 8.6%. None of the MAEs reported were device related.[57]

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 FlowTriever System for PE treatment in May 2018.

FLASH Study Design, Status, and Results

FLASH Study Design

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

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

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

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

[b] 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.

- Device-related pulmonary vascular injury, or
- Device-related cardiac injury

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

FLASH Interim Results

An interim analysis of outcomes out to 30 days on the first 230 subjects was presented at the 2021 Society for Interventional Radiology Annual Conference in March, 2021, with the abstract from this conference published in the Journal of Vascular and Interventional Radiology, as well as earlier conferences.[58-60] These subjects (60.7 ± 13.9 years, 52.2% male) were enrolled across 17 sites, with 93.0% having intermediate-risk PE and 7.0% high-risk PE. The average baseline RV/LV ratio was 1.6 ± 0.5 and sPESI was 1.6 ± 1.1. 96.3% of subjects had elevated biomarkers, and 69.7% of subjects had concomitant DVT. The primary endpoint of composite MAEs occurred in three (1.3%) subjects, all of which were non-ICH major bleeds, and no deaths occurred within 48 hours.

In-hospital outcomes demonstrated significant improvements across several acute parameters. Subjects experienced significant on-table hemodynamic improvements, including a 21.9% decrease in mean pulmonary artery pressure (32.0 mmHg to 25.0 mmHg, $P < 0.0001$) and a 20.1% decrease in heart rate (pre-procedural high of 113.2 bpm to 90.5 bpm immediately post-procedure, $P < 0.0001$). There was only one (0.4%) access site complication. The median post-procedure hospital length of stay was 3.0 [2.0 – 5.1] days and ICU length of stay was 0.0 [0.0 – 1.1] days.

30-day follow up data was available for 201 subjects in this analysis. In this population, there was one death (0.5% mortality), which was unrelated to the device, and there were ten hospital readmissions, one of which was related to the procedure. The average RV/LV ratio improved by 33.2% at a median follow up of 30 days ($P < 0.0001$) and subjects with confirmed baseline dyspnea had a significant improvement from baseline to 30 days (Modified Medical Research Council Dyspnea Scale, 3.0 ± 1.0 to 1.4 ± 1.3, $P < 0.0001$).

These results of the FLASH all-comer registry demonstrate both safety and efficacy of the FlowTriever System, with a low all-cause mortality rate (0.0% at 48 hours, 0.5% at 30 days; no device-related deaths), along with significant and immediate hemodynamic improvements and continued improvements in RV/LV ratio and dyspnea out to 30 days.

FLAME Study Design and Status

The primary study objective of FLAME is to evaluate treatment outcomes of subjects 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 subjects diagnosed with high-risk (massive) pulmonary embolism who have received treatment with other (non-FlowTriever) therapies will also be analyzed. It is expected that 250 subjects will be enrolled across all therapies utilized in the study. The study will be conducted at up to 20 US sites.

The primary endpoint of this study will be an in-hospital composite endpoint of:

- All-cause mortality
- Bailout to an alternative thrombus removal strategy
- Clinical deterioration

- Major bleeding

Additional secondary endpoints and utility measures will be collected and analyzed as well. Safety events will be adjudicated by an external Clinical Events Committee (CEC).

Enrollment is currently ongoing, and no interim data have been reported to date.

Additional Published Results

Several analyses of FlowTriever outcomes from single-center clinical experiences have been published for PE patients who are not part of the FLASH registry.[61-63] Toma, et al., reported results from a multicenter retrospective analysis of 34 high-risk or very sick submassive PE patients, demonstrating significant improvements in cardiac index and mean pulmonary artery pressure, with low procedural failure rate (2/34, 5.9%) and low mortality (1/34, 2.9%).[62] A more recent single-center retrospective analysis from Buckley and Wible compared outcomes in intermediate-high and high-risk PE patients treated with FlowTriever to those who receive routine care (AC alone, AC + CDT, or systemic thrombolysis). Results demonstrate significantly lower in-hospital mortality (3.6% vs 23.3%, $P < 0.001$) and length of hospital stay (2.1 ± 1.2 days vs 6.1 ± 8.6 days, $P < 0.001$) for FlowTriever patients than those receiving routine care.[64] Additional single-center retrospective studies demonstrate similar results, with 0% mortality and 0-4% major complicate rate, as well as significant improvements in acute hemodynamic measurements.[61, 63] FlowTriever System has also recently been used to effectively remove thrombus from intermediate- to high-risk PE patients experiencing a "thrombotic storm"-like response to COVID-19.[65] Taken together with the data from FLARE and FLASH, these data demonstrate the safe and effective treatment of intermediate- and high-risk PE patients, even for those patients contraindicated to thrombolysis, with the FlowTriever System. Comparative data assessing these outcomes in a randomized trial including other advanced therapies is still lacking and will be the focus of this study.

CATHETER-DIRECTED THROMBOLYSIS

Conventional Catheter-Directed Thrombolysis (CDT)

Due to the elevated bleeding risk noted with systemic thrombolysis, the use of CDT to deliver thrombolytics locally rather than systemically has increased. While many mostly retrospective studies have been published on CDT outcomes, randomized studies comparing systemic to catheter-directed thrombolytics administration have been lacking. To address this, Kuo, et al., published a systematic review and meta-analysis comparing the two treatment options using data collected from 594 patients across 35 studies.[42] Results demonstrate an 86.5% clinical success rate, with minor and major procedural complications of 7.9% and 2.4%, respectively, which compared favorably to the 22% major bleeding rate published in the ICOPER study for systemic thrombolysis.[66]

Avgerinos, et al., published a retrospective review of patients receiving CDT versus AC alone.[43] While RV/LV ratios showed a non-significant trend towards greater improvement in the CDT group, these patients still experienced significantly higher bleeding complications than those on AC alone (4 vs 3 major bleeds, and 7 vs 0 minor bleeds for CDT and AC ($P = 0.028$), respectively). A propensity-matched retrospective analysis of data from the National Readmission Database compared outcomes of patients treated with CDT and systemic thrombolysis, with CDT patients matched 2:1 with systemic thrombolysis patients (N=4,426). Results demonstrate significantly lower in-hospital mortality (6.1% vs 14.9%, $P < 0.001$) and a lower composite measurement of mortality + gastrointestinal bleeding + intracranial hemorrhage in the CDT group (8.4% vs 18.3%, $P < 0.001$).

Ultrasound-assisted Catheter-Directed Thrombolysis (USAT)

USAT using the EkoSonic catheter system (EKOS) incorporates ultrasonic pulses, along with thrombolytic infusion, to purportedly accelerate the lytic process by thinning and separating the fibrin strands. This device has the most published clinical evidence of the advanced therapies available for PE, with several retrospective studies,[67-70] as

well as randomized controlled studies comparing EKOS outcomes to AC alone[45] or to CDT.[49] Two seminal multicenter, prospective studies, ULTIMA[45] and SEATTLE-II[46], evaluated the ultrasound-assisted thrombolysis (USAT) approach for submassive and massive PE.

The ULTIMA study compared EKOS to AC (heparin) alone in a total of 59 intermediate-risk PE patients across eight centers in Switzerland and Germany.[45] Results demonstrated a significantly greater reduction in RV/LV ratio, along with other echocardiographic right heart parameters, at 24 hours in EKOS patients compared to those treated with heparin. However, any significant difference in RV/LV ratios between EKOS and heparin was absent at 90 days.[45] There was no device-related mortality or major bleeding events related to either study treatment, but minor bleeding complications were observed in 10% and 3% of patients in the USAT and CDT arms, respectively (*P*=0.61).

The SEATTLE II study was a single-arm prospective study of 150 submassive and massive PE patients to further evaluate the safety and efficacy of EKOS, with a primary efficacy outcome of the change in RV/LV ratio within 48 hours of procedure initiation, and a primary safety outcome of major bleeding within 72 hours of procedure initiation. One hundred fifty submassive and massive PE patients each received 24mg of tPA, infused either in one catheter over 24hr, or in two catheters over 12 hours. Results demonstrated statistically significant improvements in RV/LV ratio, mean PAP, and thrombus burden as defined by the modified Miller Index score at 48 hours. One severe bleed and 16 moderate bleeding events in 15 patients (10%) occurred out to 72 hours.[46] Further refinement of the lytic dose and infusion duration using EKOS was conducted in the OPTALYSE PE trial, a multicenter, prospective study with 101 intermediate-risk PE patients randomized to 1 of 4 study arms in which both tPA dose and infusion duration were varied.[47] It is notable that randomization and enrollment into the study arm using 12mg (unilateral)-24mg (bilateral) of tPA over 6 hours was stopped after an ICH developed that was considered probably related to thrombolytic therapy and anticoagulation by the safety monitor. Results indicated that lower-dose tPA (as low as 4 mg per lung) and infusion duration as low as 2 hours was as effective as 6mg or 12mg doses infused up to 6 hours.

Taken together, these studies demonstrate that USAT is effective relative to AC, and like conventional CDT, the local delivery of smaller doses of thrombolytics compared to systemic administration likely provides greater patient safety. However, the question remained whether the ultrasound technology provided significant improvement over conventional CDT. To address this, Tafur, et al., performed a systematic review and meta-analysis of 23 studies and 700 subjects to summarize the evidence on safety and efficacy for conventional CDT versus USAT.[49] Of the included studies, 18 evaluated CDT only, 6 evaluated USAT only, and only one study evaluated and compared both treatments. The meta-analysis found no difference in the rate of bleeding complications between USAT and conventional catheter-directed thrombolysis, (total bleeding: 12% USAT vs. 10% CDT; major bleeding: 4% USAT vs. 10% CDT).[48] The review, however, documented a trend toward improved survival with USAT; 4% vs. 9% mortality in the USAT and conventional CDT subjects, respectively. However, the methods used to evaluate efficacy varied amongst studies, preventing a pooled comparative analysis. The authors conclude, however, that while the bleeding risk appeared to be lower with USAT treatments, the heterogeneity of the studies and lack of comparative data prevented them from reaching a definitive conclusion. They point out that the calculated mortality rates (4% for USAT and 9% for CDT) highlight the continued critical need for further study in this area.

Results from a more recent prospective, randomized control trial (SUNSET sPE) comparing USAT to CDT were recently published.[49] Eighty-one submassive PE patients from three clinical US centers were randomized 1:1 to either USAT or CDT and followed up out to 90 days. Primary efficacy outcomes of reductions in both pulmonary obstruction index and score were not different between the two groups. The reduction in RV/LV ratio from pre-procedure to 48 hours was statistically greater in the CDT group (USAT: 0.37 ± 0.34; CDT: 0.59 ± 0.42; *P*=0.01), and the overall mean hospital stay was shorter in the CDT arm as well (USAT: 4.1 ± 8.8 days; CDT: 2.4 ± 1.2 days; *P*=0.03). Two major and three minor bleeding events and one in-hospital death were recorded, all in the USAT group. The conclusion of this publication is that USAT may not confer a benefit over CDT.[49]

EKOS is being further evaluated for safety and efficacy in the largest PE device registry to date, KNOCOUT, with 1,500 patients enrolled and a 1-year follow up planned.[71] No data has been published to date from this study. In addition, the recently-initiated HI-PEITHO study is a randomized controlled trial comparing EKOS to standard AC with a planned enrollment of 406 intermediate high-risk PE patients.[72]

4. STUDY OBJECTIVE

The primary study objective is to compare the clinical outcomes of patients treated with the FlowTriever System versus Catheter-Directed Thrombolysis (CDT) for use in the treatment of acute pulmonary embolism (PE).

5. OUTCOME VARIABLES

PRIMARY ENDPOINT DEFINITION

The primary endpoint is a composite clinical endpoint constructed as a win ratio, a hierarchy of the following, which are assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner:

1. All-cause mortality, or
2. Intracranial hemorrhage (ICH), or
3. Major bleeding per ISTH definition[4], or
4. Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy, or
5. ICU admission and ICU length-of-stay during the index hospitalization and following the index procedure.

Definition of Intracranial Hemorrhage

Intracranial hemorrhage (ICH) is defined as ANY bleeding involving the brain parenchyma, ventricular system, or subarachnoid, subdural, or epidural regions, as identified by CT scan or MRI, regardless of symptoms.

Definition of Major Bleeding

Major bleeding is defined according to the International Society for Thrombosis and Haemostasis (ISTH) definition of major bleeding in non-surgical subjects[4].

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Definitions of Clinical Deterioration and Bailout

Clinical deterioration is defined as documented objective hemodynamic or respiratory worsening that is new (i.e. not present at the time of enrollment).

Clinical deterioration is when one or more of the following is *definitively documented*, with relation to both the severity *and* the duration of the event:

- Hypotension with systolic blood pressure <90 mm Hg lasting at least 30 minutes, unresponsive to fluid resuscitation, and requiring the addition of or increased dose of vasopressors

- Fall in systolic blood pressure by 40 mm Hg or more, lasting at least 30 minutes, and accompanied end-organ hypoperfusion (such as oliguria, mental status changes, ischemic extremities)
- Cardiac arrest requiring cardiopulmonary resuscitation
- Bradycardia lasting more than 10 minutes, accompanied by hypotension, and requiring pharmacologic intervention or insertion of a pacemaker
- Ventricular tachycardia or fibrillation requiring pharmacologic intervention or defibrillation
- Requirement for an increase in fraction of inspired oxygen requirements 0.20 or greater, lasting longer than 30 minutes (e.g. from 0.21 to 0.41)
- Need for intubation in a previously non-intubated subject, or unplanned use of extracorporeal membrane oxygenation (ECMO)

Note that transient fluctuations in hemodynamic and/or respiratory function may be common during thrombectomy and thrombolysis procedures, and events not meeting both severity and duration requirements are not considered meeting the definition of Clinical Deterioration. Such changes may resolve spontaneously upon continuation of an existing treatment plan, and as such are unremarkable. Vagal episodes are also, in themselves, not considered Clinical Deterioration. Shorter term changes in hemodynamic or respiratory function, when accompanied by an unplanned escalation of therapeutic measures under the primary clinician's judgement to avoid overt deterioration, may be considered Bailout Therapy. Any such escalations of therapy will be documented in detail and adjudicated by a Clinical Events Committee (CEC).

Bailout Therapy is an unplanned escalation of therapeutic measures, taken when the patient's condition has not improved or is not improving according to expectations. Potential Bailout Therapy events will be adjudicated by a Clinical Events Committee, including when any of the following occur:

- Unplanned use of additional mechanical, pharmacomechanical, pharmacologic catheter-based therapies, or systemic thrombolytics, or changing from the assigned treatment strategy, after initial treatment strategy as assigned was initiated.
    - If catheter-directed thrombolysis (CDT) was the assigned treatment strategy and emergent/clinically driven systemic thrombolytic administration (e.g. ≥ 10 mg tPA) was required after CDT was initiated, this would be considered a bailout.
        - If the length of thrombolytic administration is simply extended and is not emergent or clinically driven, this would not qualify as a bailout.
    - If mechanical thrombectomy was the assigned treatment strategy, low-dose catheter-directed **adjunctive** thrombolytic therapy (less than 10 mg tPA) that is administered intra-procedurally or post-procedurally will be *strongly discouraged* but not considered a bailout
- Surgical thrombectomy

Before escalating to a Bailout Therapy, physicians are encouraged to consider the patient's condition and identify one or more reasons from the following list to justify the need for Bailout Therapy. These reason(s) will be documented in the study case report forms (CRFs).

- Persistent elevated respiratory rate
- Ongoing or increased requirement for supplemental oxygen
- Persistent or new-onset tachycardia
- Sustained or sudden bradycardia
- Sudden or persistent hypotension, not associated with a vagal episode, or signs of end-organ hypoperfusion
- Hemodynamic worsening or lack of hemodynamic improvement
- Lack of improved lung perfusion, or inadequate clot resolution
- New-onset, persistent, or worsening symptoms of PE

Any unplanned escalation of therapy adjudicated by the CEC to not meet clinical definitions for Bailout Therapies will be considered a protocol deviation.

Definition of ICU Admission and ICU Length of Stay

ICU Admission will be defined as admission or transfer to an Intensive Care Unit (ICU), Critical Care Unit (CCU), or similar high-acuity floor, collectively referred to as "ICU." For the purpose of the endpoint assessment, ICU Admission is met under the following conditions:

- Orders are entered for Subject to be admitted or transferred to the ICU after the end of the Index Procedure and before hospital discharge from the index hospitalization, up to a maximum of 7 days from the end of the Index Procedure, or
- Subject had been in the ICU leading up to the Index Procedure, with plans to return to the ICU immediately after the end of the Index Procedure, with or without a transfer to a PACU, recovery room, or similar temporary step-down unit according to local standard.

ICU Length of Stay (LOS) is the total number of hours a subject is medically required to be in the ICU, measured from the end of the Index Procedure or the time of ICU Admission, whichever is later, until the time of an *order to discharge* the subject from the ICU or transfer the subject to a standard or lower-acuity unit. If a subject remains physically located in the ICU due to hospital bed availability, transport delays, or other non-medical reasons instead of a need for high acuity of care, the time of the order for discharge or transfer, rather than the actual time a subject physically leaves the ICU, is used for assessing ICU LOS.

For subjects getting discharged from or transferred off the ICU and returning again during the index hospitalization, up to a maximum of 7 days after the Index Procedure, the total hours of all ICU admissions or transfers during that period (i.e., after the Index Procedure and until hospital discharge up to a maximum of 7 days) are used for assessing ICU LOS.

Subjects who had been in the ICU leading up to the Index Procedure, but *not* returning to the ICU after the end of the Index Procedure, are *not* considered to have had an ICU Admission per the endpoint definition.

For the win ratio primary endpoint, ICU admission and ICU LOS are characterized hierarchically as follows:

1. No ICU Admission
2. ICU Admission, lasting between 0 – 24 hours
3. ICU Admission, lasting longer than 24 hours

SECONDARY ENDPOINTS

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

- Composite clinical endpoint constructed as a win ratio hierarchy of the following four components, assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner:
    - All-cause mortality, or
    - Intracranial hemorrhage (ICH), or
    - Major bleeding per ISTH definition[4], or
    - Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy
- Individual components of the win ratio composite endpoint, assessed at hospital discharge or at 7 days after the index procedure, whichever is sooner:
    - All-cause mortality
    - Intracranial hemorrhage (ICH)

  - Major bleeding per ISTH[4] definition
  - Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy
  - ICU admission and ICU length of stay during the index hospitalization and following the index procedure
- All-cause mortality within 30 days from index procedure
- PE-related and all-cause readmission within 30 days from index procedure
- Device and drug-related serious adverse events through the 30 day visit
- Clinically Relevant Non-Major (CRNM) and Minor bleeding events through hospital discharge or at 7 days after the index procedure, whichever is sooner
- Change in right-ventricular/left-ventricular (RV/LV) ratio from baseline to 24 hour visit, as measured by echocardiography or CT
- mMRC Dyspnea score at 24 hour visit and 30 day visit
- Length of total hospital stay and post-index-procedure hospital stay (to a maximum of 30 days)
- Disease-specific and general health-related quality of life at the 30 day visit (PEmb-QoL and EQ-5D-5L)

6. STUDY DESIGN

This study is a prospective, multicenter, randomized controlled trial of the FlowTriever System compared to CDT for acute PE, and includes a non-randomized cohort for subjects with an absolute contraindication to thrombolytics. The study will collect data on demographics, comorbidities, details from the PE diagnosis and treatment, and clinical outcomes through 30-day follow up.

Randomized Controlled Trial Cohort (RCT Cohort):

This study is a prospective, multicenter, randomized controlled trial of the FlowTriever System compared to Catheter-Directed Thrombolysis (CDT) for treatment of acute PE.

Non-Randomized Absolute Contraindication to Thrombolytics Cohort (Contraindication Cohort):

Subjects who meet study eligibility criteria and who have an absolute contraindication to thrombolytics, whose initial planned primary treatment strategy includes FlowTriever, will be evaluated as part of the Contraindication Cohort. The same RCT Cohort clinical assessments and follow up schedule will be administered in this Contraindication Cohort.

STUDY POPULATION

RCT Cohort: Up to 550 subjects with acute PE will be enrolled and randomized at up to 60 study sites. All subjects who sign informed consent and who meet all of the inclusion criteria and none of the exclusion criteria will be randomized (1:1, FlowTriever or CDT).

- One-to-one (1:1) randomization will be stratified by bleeding risk, as measured by the VTE-BLEED score[3].

Table 1 VTE-BLEED Algorithm

Parameter	Points
Active cancer	2
Male patient with uncontrolled hypertension (≥140 mmHg)	1
Anemia	1.5
History of bleeding	1.5
Renal dysfunction (Cr clearance 30-60 ml/min)	1.5
Age ≥60 years	1.5
TOTAL ≥2 indicates higher risk of bleeding on stable AC vs <2	9

- Stratification by the VTE-BLEED algorithm will occur automatically in the Electronic Data Capture (EDC) system upon data entry, and randomization will be assigned accordingly.

Contraindication Cohort: Up to 150 additional subjects who meet study eligibility criteria and who have an absolute contraindication to thrombolytics, whose initial planned primary treatment strategy includes FlowTriever, will be evaluated as part of the Contraindication Cohort. The same RCT Cohort clinical assessments and follow up schedule will be administered in this Contraindication Cohort.

POINT OF ENROLLMENT

To participate in the study, the patient must sign the informed consent. If a subject signs the informed consent but is later deemed NOT to meet the invasive systolic PA pressure eligibility criteria, the subject would be considered a screen failure and not enrolled in either the RCT Cohort or the Contraindication Cohort. Screen failures will be tracked in the EDC system with rationale for the screen failure. The point of enrollment is when the subject meets all eligibility criteria and study device enters the subject's body.

Enrollment considerations in study design

Any patient with a documented ***absolute contraindication*** to thrombolytics will be excluded from the RCT Cohort but may be enrolled in the Contraindication Cohort if treated with FlowTriever. Absolute contraindications include (per ESC Guidelines 2019[1] and AHA Scientific Statements 2019):

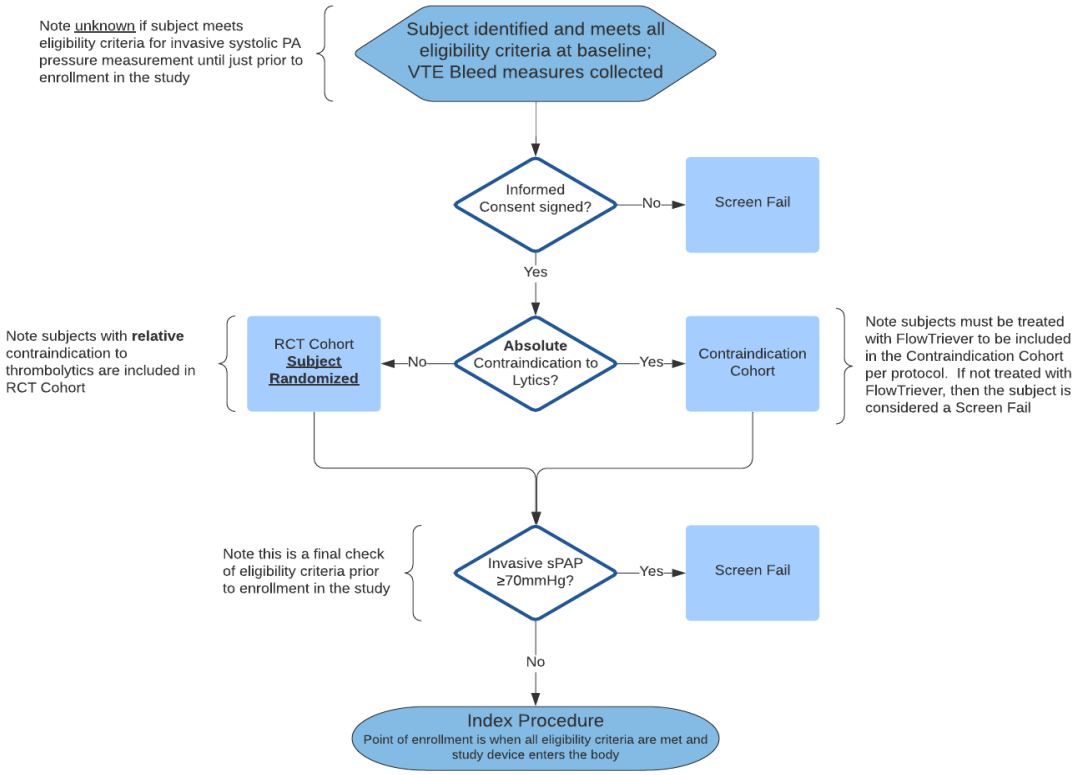
- History of hemorrhagic stroke or stroke of unknown origin
- Ischemic stroke in previous 6 months
- Presence of intracranial conditions that may increase the risk of bleeding, such as neoplasms, arteriovenous malformations, or aneurysms
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Bleeding diathesis
- Active internal bleeding, excluding menses
- Aortic dissection

- Severe uncontrolled hypertension
- Any other condition listed as an absolute contraindication on the product label for the thrombolytic agent planned for use by local standard and investigator discretion

Subjects with a ***relative contraindication*** to thrombolytics are eligible for the RCT Cohort per protocol. Subjects with *only* relative contraindication(s) to thrombolytics are *not* eligible for the Contraindication Cohort. Relative contraindications include:

- Transient ischemic attack in previous 6 months
- Oral anticoagulation, except for aspirin
- Therapeutic LMWH within 24 hours
- Pregnancy or first post-partum week
- Non-compressible puncture sites
- Traumatic resuscitation, defined as prolonged (>10 min) cardiopulmonary resuscitation
- Refractory hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg) on two confirmed measurements
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer
- Recent administration of glycoprotein (GP) IIb/IIIa inhibitors
- Anemia (e.g. hemoglobin <10 g/dL)

Figure 9 Subject Enrollment Flowchart



INCLUSION CRITERIA

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

1. Age ≥ 18 years
2. Echo, computed tomographic pulmonary angiography (CTPA), or pulmonary angiographic evidence of any proximal filling defect in at least one main or lobar pulmonary artery
3. Including ALL of the following:
    a. Clinical signs and symptoms consistent with acute PE, or PESI class III-V, or sPESI ≥1
    AND
    b. Hemodynamically stable
    AND
    c. RV dysfunction on echocardiography or CT
    AND
    d. Any one or more of the following present at the time of diagnosis:
        i. Elevated cardiac troponin levels
        ii. History of heart failure
        iii. History of chronic lung disease
        iv. Heart rate ≥110 beats per minute
        v. SBP <100mmHg
        vi. Respiratory rate ≥30 breaths per minute
        vii. O2 saturation <90%
        viii. Syncope related to PE
        ix. Elevated lactate
4. Intervention planned to begin within 72 hours of the later of either
    a. Confirmed PE diagnosis
    OR
    b. If transferring from another hospital, arrival at the treating hospital
5. Symptom onset within 14 days of confirmed PE diagnosis

EXCLUSION CRITERIA

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

1. Unable to anticoagulate with heparin, enoxaparin or other parenteral antithrombin
2. Index presentation with hemodynamic instability that are part of the high-risk PE definition in the ESC Guidelines 2019[1], including ANY of the following:
    a. Cardiac arrest
    OR
    b. Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status, AND end-organ hypoperfusion
    OR
    c. Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis
3. Known sensitivity to radiographic contrast agents that, in the Investigator's opinion, cannot be adequately pre-treated
4. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the patient is not appropriate for catheter-based intervention (e.g., inability to navigate to target location, clot limited to segmental/subsegmental distribution, predominately chronic clot)
5. Patient has right heart clot in transit identified at baseline screening
6. Life expectancy < 30 days (e.g., stage 4 cancer or severe COVID-19 infection), as determined by the Investigator

7. Current participation in another drug or device study that, in the investigator's opinion, would interfere with participation in this study
8. Current or history of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis, per ESC 2019 guidelines[1]
9. Invasive systolic PA pressure ≥70mmHg prior to study device entering the body
10. Administration of bolus or drip/infusion thrombolytic therapy or mechanical thrombectomy for the index PE event within 48 hours prior to enrollment
11. Ventricular arrhythmias refractory to treatment at the time of enrollment
12. Known to have heparin-induced thrombocytopenia (HIT)
13. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being or that could prevent, limit, or confound the protocol-specified assessments). This includes a contraindication to use of FlowTriever or CDT System (for example, EKOS System) per local approved labeling
14. Subject has previously completed or withdrawn from this study
15. Patient unwilling or unable to conduct the follow up visits per protocol.

7. ASSESSMENTS AND FOLLOW UP SCHEDULE

SCHEDULE OF ASSESSMENTS

The schedule of assessments comprises the assessments to be performed for all subjects enrolled in the study. Any departures from the follow up schedule will be documented as protocol deviations.

Schedule of Assessments

Assessment	Baseline (≤ 72 hrs)[a]	Index Procedure[h] (Day 0)	24 Hour Visit (24 hrs. ± 8 hrs.)	Hospital Discharge [e]	30 Day Visit (30 days + 15 days)	Unscheduled Visit
Informed Consent	X					
Inclusion/exclusion review	X					
Demographics	X					
Medical history, risk factors, and PE condition	X					
Anticoagulation regimen	X	X	X	X	X	X
Clinical labs (Hemoglobin, Troponin)	X					
Clinical labs (Hemoglobin, ACT, and PTT)		X				
Imaging (Echo or CT)[f]	X		X			
mMRC dyspnea score, Borg, and NYHA	X		X	X	X	
Oxygenation status		X [d]	X	X	X	
Invasive PA pressures (**required** Pre-Index Procedure)		X [b]				
Invasive PA pressures (**optional** Post-Index Procedure)		X [c]				
Bleeding measures		X	X	X		
Evaluation of primary endpoint components[g]				X		
PEmb-QoL and EQ-5D-5L					X	
Adverse event assessment		X	X	X	X	X

[a] Baseline assessment must be done ≤ 72 hours of Index Procedure

[b] Interventionalists will collect pulmonary artery pressures immediately before primary therapeutic catheter insertion.

[c] Trained interventionalists will collect pulmonary artery pressures at least 10 minutes after primary therapeutic catheter (for CDT) begins therapy, or after the primary therapeutic catheter (for FlowTriever) is removed for the last time. Additional PA pressures are requested to be collected in the CDT subjects 6 hours (± 2 hours) post procedure using the same technique.

[d] Collect oxygenation status just prior to index procedure

[e] Note that the Discharge Visit can be done at the same time as the 24-hour visit if applicable. However, if both visits are completed at the same time, both CRFs will need to be filled out. There are no windows from Index Procedure determining when the Discharge Visit must be completed. The Discharge Visit is completed when the patient is discharged from the hospital and the assessments are completed within the 12 hours prior to discharge. If the subject has not been discharged from the hospital by the 30-day visit, then the Discharge Visit is missed and the 30-day assessment (including evaluation of primary endpoint components) and patient exit is completed.

[f] Imaging can be either echo or CT, but needs to be the same modality within each patient at Baseline and 24-hour visit

[g] Note that the evaluation of endpoint considerations include All-cause mortality, ICH, Major bleeding, Clinical deterioration and/or escalation to a bailout therapy, and ICU admission and ICU length-of-stay. These are assessed at hospital discharge or 7 days after the index procedure, whichever is earlier. If a subject is still in the hospital and exits the study for any reason before the 30-day Visit, evaluation of primary endpoint components should be completed at the time of patient exit.

[h] The Index Procedure begins when access for treatment is obtained. The Index Procedure is considered complete upon exit from the procedure room. The time of exit from the procedure room is the time reference used for the subsequent visit windows including the 24-hour visit.

BASELINE ASSESSMENTS

The baseline assessments must be done ≤ 72 hours of Index Procedure including:

- Informed consent
- Inclusion/exclusion review
- Demographics
- Medical history, risk factors, and PE condition
- Anticoagulation regimen
- Clinical labs (Hemoglobin, Troponin)
- Cardiac imaging (Echo or CT)
    - Imaging can be either echo or CT, but needs to be the same modality within each patient at baseline and 24-hour visit.
- mMRC dyspnea score, Borg, and NYHA

ALLOCATION AND RANDOMIZATION

Upon the patient meeting baseline eligibility criteria and providing informed consent, a check against the list of absolute contraindications to thrombolytics is performed (see Figure 9: Patient Enrollment Flowchart). Subjects with one or more absolute contraindications to thrombolytics and whose initial treatment plan includes FlowTriever are allocated to the Contraindication Cohort. Subjects without any absolute contraindications (whether there are relative contraindications to thrombolytics or no contraindication to thrombolytics) are allocated to the RCT Cohort.

Study sites will receive the subject randomization assignment electronically in the electronic data capture (EDC) system upon completion of baseline information used to stratify randomization using the calculated VTE-BLEED score. Subjects will be randomized to and treated with (a) mechanical thrombectomy with FlowTriever or (b) catheter-directed thrombolysis per local practice standards.

INDEX PROCEDURE

The initial catheter-based intervention for acute PE is considered the Index Procedure. The procedure is conducted under fluoroscopic/angiographic guidance. Refer to the Instructions for Use (IFU) for techniques and methods for device deployment. The following assessments are collected during the index procedure including:

- Anticoagulation regimen
- Clinical labs (Hemoglobin, ACT, and PTT collected just prior to index procedure intervention)
- Oxygenation status collected just prior to index procedure
- Invasive PA pressures (**required** pre-index procedure)
    - Interventionalists will collect pulmonary artery pressures immediately before primary therapeutic catheter insertion.
- Invasive PA pressures (**optional** post-index procedure)
    - Trained interventionalists will collect pulmonary artery pressures at least 10 minutes after primary therapeutic catheter (for CDT) begins therapy, or after the primary therapeutic catheter (for FlowTriever) is removed for the last time. Additional PA pressures are requested to be collected in the CDT subjects 6 hours (± 2 hours) post procedure using the same technique.
- Bleeding measures
- Adverse event assessment

The Index Procedure begins when access for treatment is obtained. The Index Procedure is considered complete upon exit from the procedure room. The time of exit from the procedure room is the time reference used for the subsequent visit windows including the 24-hour visit. The 7-day maximum for in-hospital primary endpoint

assessment is defined as 168 hours from the end of the Index Procedure. The 30-day Visit window refers to 30 calendar days from the day the Index Procedure ends.

Recommendations for Anticoagulation Management and Thrombolytic Therapy

In order to approximate real-world practice, the use of pre-procedure, intra-procedure, and post-procedure anticoagulation should be guided by investigator discretion, local standard of care, and in accordance with IFU for the assigned therapy.

Similarly, dose and duration of thrombolytic agents in subjects assigned to CDT is guided by investigator discretion, local standard of care, and in accordance with IFU. Initial dosing strategy should be recorded in the corresponding CRF, along with any changes in dose throughout the infusion, including extended infusion times. Bolus thrombolytics that are part of initial treatment plan are not considered bailout, although bolus lytics are discouraged in subjects assigned to FlowTriever therapy.

Suggested PTT target to avoid bleeding during CDT, per SEATTLE-II, is PTT 40-60s.

FOLLOW UP ASSESSMENTS

Follow up evaluations will include the 24-hour visit (24 hrs ±8 hrs), hospital discharge, and the 30-day visit (30 days +15 days). All windows reference time from Index Procedure completion (defined as time of exit from the procedure room).

24-hour visit: The following assessments will be performed at the 24-hour visit:

- Anticoagulation regimen
- Cardiac imaging (Echo or CT required)
  - Imaging can be either echo or CT, but needs to be the same modality within each patient at baseline and 24-hour visit.
- Oxygenation status
- mMRC dyspnea score, Borg, and NYHA
- Bleeding measures
- Adverse event assessment

Note that the discharge visit can be done at the same time as the 24-hour visit if applicable. However, if both visits are completed at the same time, both CRFs will need to be filled out.

Discharge visit: The following assessments will be performed at the discharge visit:

- Anticoagulation regimen
- mMRC dyspnea score, Borg, and NYHA
- Oxygenation status
- Bleeding Measures
- Evaluation of primary endpoint components including all-cause mortality, ICH, major bleeding, clinical deterioration and/or escalation to a bailout therapy, and ICU admission and ICU length-of-stay
- Adverse event assessment

Note that the Discharge Visit can be done at the same time as the 24-hour visit or the 30-day visit, if applicable. However, if two visits are completed on the same day, both CRFs will need to be filled out. There are no windows from Index Procedure determining when the Discharge Visit must be completed. Rather, the Discharge Visit is

completed when the patient is discharged from the hospital and the assessments are completed within the 12 hours prior to discharge. If the subject has not been discharged from the hospital by the 30-day visit, then the Discharge Visit is missed and the 30-day assessment (including evaluation of primary endpoint components) and patient exit is completed.

Note that the evaluation of endpoint considerations include All-cause mortality, ICH, Major bleeding, Clinical deterioration and/or escalation to a bailout therapy, and ICU admission and ICU length-of-stay. These are assessed at hospital discharge or 7 days after the index procedure, whichever is earlier. If a subject is still in the hospital and exits the study for any reason before the 30-day Visit, evaluation of primary endpoint components should be completed at the time of patient exit.

30-day visit: The following assessments will be performed at the 30 day visit (30 days +15 days):

- Anticoagulation regimen
- mMRC dyspnea score, Borg, and NYHA
- Oxygenation status
- PEmb-QoL and EQ-5D-5L
- Adverse event assessment

The 30-day visit assessments can be conducted in-person or remotely, if allowed by the IRB/EC.

The patient will be exited from the study at this visit if not already exited earlier for other reasons.

Note that the evaluation of endpoint considerations include All-cause mortality, ICH, Major bleeding, Clinical deterioration and/or escalation to a bailout therapy, and ICU admission and ICU length-of-stay. These are assessed at hospital discharge or 7 days after the index procedure, whichever is earlier. If a subject is still in the hospital and exits the study for any reason before the 30-day Visit, evaluation of primary endpoint components should be completed at the time of patient exit.

UNSCHEDULED FOLLOW UP VISITS

The study will only record subject visits during the follow up period (defined as discharge through completion of the 30-day visit, up to a maximum 45 days from Index Procedure) that are related to the patient's PE condition and treatment. The following assessments will be performed at the unscheduled visit:

- Anticoagulation regimen
- Adverse event assessment

WITHDRAWALS AND LOST TO FOLLOW UP

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

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

If the index catheter-based intervention procedure is aborted before treatment catheter insertion or is not performed, the subject is considered a screen fail.

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

COVID-19 Effect on Research

This study was designed to compare the clinical outcomes of patients treated with the FlowTriever System versus Catheter-Directed Thrombolysis (CDT) for use in acute pulmonary embolism (PE). As a result of the COVID-19 pandemic, clinical practice patterns may be affected, and subject visits may be postponed or eliminated. Additionally, subjects may not be willing to be seen by their provider potentially exposing both parties to the virus. In order to protect subject and provider safety, some data may be collected from subjects over the phone if allowed by the IRB/EC.

8. RISK ANALYSIS

Risks to Subjects

The PEERLESS Study involves the use and disclosure of deidentified health information. It collects only information relevant to the subject's PE condition and treatment.

The PEERLESS Study involves the collection of specific information for research and educational purposes only. It does not specify how the FlowTriever System or CDT will be used to treat PE (all products are commercially available), and other than allocation to a therapy strategy for subjects in the RCT Cohort, decisions regarding a subject's treatment are not influenced by the PEERLESS Study. Physicians participating in the PEERLESS Study are expected to review the indications, contraindications, warnings, precautions, and safety events described in the IFUs and/or Investigator Brochure, as applicable. As with any endovascular procedure, thrombolytic or anticoagulation administration, 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, or treatment-related informed consent per institutional policies and procedures.

Risk Mitigation

The PEERLESS Study was designed to evaluate subject outcomes for PE Treatment using the FlowTriever System and catheter-directed thrombolytics (CDT). The risks of providing this personal health information have been mitigated, as no personal information directly identifying the subject will be collected in the study database. At the time of participation, each participant will be assigned a unique study identification number. This number will be used in the database to identify the subject. All data handling will be in accordance with GDPR and HIPAA requirements and only de-identified information will be entered into the study database.

Study Justification

The Inari FlowTriever System offers an efficient treatment option for PE subjects without the need for thrombolytic drugs and the accompanying high bleeding risk including intracranial hemorrhage. The use of FlowTriever may provide quicker relief due to the mechanical approach to clot removal compared to a pharmacological approach, which can take several hours to show an effect. The study is designed to assess the treatment outcomes in acute subjects receiving FlowTriever Mechanical Thrombectomy versus subjects receiving Catheter-Directed Thrombolysis (CDT). Due to lack of evidence in the treatment of PE, this study will compare outcomes amongst

two of the most common advanced therapies. This study may guide therapies to minimize ICU bed usage providing potential benefit to cost and patient care.

9. SAFETY ASSESSMENT

DEFINING ADVERSE EVENTS

An Adverse Event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in *subjects*, users or other persons, whether or not related to the *investigational* medical device* and whether anticipated or unanticipated (ISO 14155:2020, 3.2).

*NOTE 1: All medical devices in the context of this clinical trial are considered investigational devices.

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

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

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

All AEs will be followed by the Investigator until resolution or until the 30 Day follow up visit is completed or until study exit. When the study subject's participation in PEERLESS has ended, after the 30-Day follow-up visit or in case of patient withdrawal, the patient will continue to be treated and followed-up as per the hospital's standard of care.

DEFINING ADVERSE DEVICE EFFECT (ADE)

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device.

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

NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.

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

DEFINING SERIOUS ADVERSE EVENT (SAE)

A Serious Adverse Event (SAE) is an adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, including chronic disease, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

5) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)

DEFINING SERIOUS ADVERSE DEVICE EFFECT (SADE)

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)

DEFINING UNANTICIPATED/ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE/ASADE)

A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

An ASADE is an anticipated serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. (ISO 14155:2020, 3.51)

DEFINING UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

DEVICE DEFICIENCY (DD)

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

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

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

EVENT SEVERITY

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

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

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

EVENT RELATIONSHIP

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

- **Device-related:** The event is directly related to the FlowTriever System or CDT system, as defined by its intended use. AEs will be considered unrelated to the device if the complication could have occurred if the device functioned entirely within its specifications.
- **Procedure-related:** Procedure-related events include all AEs that occur at any time of patient participation that was directly related to the procedure. The exception to this rule is an event that is device-related; such events should not also be classified as procedure-related.
- **Drug-related:** Event is attributable to thrombolytic or anticoagulant therapy. These events may occur from inadequate (thrombosis) or excessive therapy (bleeding). A drug-related AE cannot also be classified as device-related, but many will be classified as procedure-related, since the drug may be part and parcel of the index procedure.

ADVERSE EVENT REPORTING

Subjects will be carefully monitored during the study for possible adverse events. Any adverse event that occurs after the time of enrollment through end of study participation will be fully evaluated by the investigator. Appropriate treatment will be initiated for AEs and the study follow up will continue as completely as possible.

The investigator will document all observations and clinical findings of adverse events, including the nature, severity and relationship, on the appropriate CRFs.

For US sites, the investigator is required to report all SAEs as soon as possible but no later than 5 calendar days upon learning of the SAE. All UADEs must be reported to the sponsor within 24 hours after first learning of the event.

For European sites, the investigator is required to report all SAEs as soon as possible but no later than 3 calendar days upon learning of the SAE. All UADEs and device deficiencies must be reported to the sponsor within 24 hours after first learning of the event.

The investigator must follow their local IRB/EC policy for SAE/UADE reporting. UADEs have special reporting requirements. The sponsor will notify the sites, IRBs/ECs and regulatory bodies as per specific regulations.

The investigator will send the completed AE CRF and all available supporting source documentation to the sponsor.

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

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

Clinical Events Committee (CEC)

A Clinical Events Committee (CEC) will be utilized in this study for the purposes of adjudicating safety related 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 subjects enrolled in the study.

Events to be adjudicated by the CEC are as follows:

Safety related Primary Endpoint:

- All-cause mortality
- Intracranial hemorrhage (ICH)
- Major bleeding per ISTH definition[4]
- Clinical deterioration defined by hemodynamic or respiratory worsening, and/or escalation to a bailout therapy

Safety related Secondary Endpoints:

- All-cause mortality within 30 days from index procedure
- PE-related and all-cause readmission within 30 days from index procedure
- Device and drug-related serious adverse events within 30 days from index procedure
- Clinically Relevant Non-Major (CRNM) and Minor bleeding events before hospital discharge up to a maximum of 7 days after the index procedure

For each event presented to the CEC, the following parameters will be adjudicated:

- Determination if event meets an endpoint definition
- Determination if the event is a Serious Adverse Event (SAE)
- Determination of relatedness (unrelated, related, unknown):
    - Relation to the Index Procedure
    - Relation to the Index Device
    - Relation to subsequent thrombus removal Device/Therapy (Bailouts)
    - Relation to thrombolytic therapy
    - Relation to anticoagulation therapy
- Determination of severity (mild, moderate, or severe)

Event adjudication will be conducted according to the CEC Charter.

PRODUCT COMPLAINT REPORTING

Product complaint and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the study and should be done in addition to the AE reporting requirements per local regulations for market released product.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

In addition, the sponsor will comply with Medical Device Reporting (MDR) requirements. (21CFR803, EU MDR 2017/745.

10.STATISTICS & DATA ANALYSIS

SAMPLE SIZE

By assuming an 80% power with one-sided alpha of 2.5%, the win ratio methodology is applied to the primary endpoint that consists of five components. The required sample size is 432 subjects (216 subjects per arm); and planning for follow up attrition and further describing secondary endpoints/exploratory analysis, the study will enroll up to a total of 550 randomized subjects (RCT Cohort). The sample size assumptions are based on Inari sponsored studies and a review of literature.

Up to 150 additional subjects who meet all eligibility criteria and who have an absolute contraindication to thrombolytics, whose initial planned primary treatment strategy includes FlowTriever, will be enrolled as part of the Contraindication Cohort. The same clinical assessments and follow up schedule will be administered in this cohort as is described for the RCT Cohort. The Contraindication cohort data will not be used for any PEERLESS protocol-defined hypothesis testing nor used to calculate any primary or secondary endpoints.

STATISTICAL METHODOLOGY

The statistical design objective for this trial is to compare the clinical outcomes of the FlowTriever System versus Catheter-Directed Thrombolysis (CDT) for use in the treatment of acute pulmonary embolism (PE). Since the primary endpoint is a composite clinical endpoint, a modified generalized Wilcoxon test (F-S test) proposed by Finkelstein & Schoenfeld[73] will be applied to examine the performance differences between the two treatment arms.

In this trial, the primary endpoint is a hierarchy of five clinical outcome components. Each subject in the study will be compared to each of the other subjects in a pairwise manner, regardless of which treatment arm the compared subject is in, and assigned a score, u_{ij}, of 1, -1, or 0, depending on whether the comparison has a favorable, unfavorable, or unsettled outcome in the hierarchy of the clinical events; *i* is the index subject to be compared with all other subjects in a pairwise fashion and *j* represents j^{th} subject comparison. For example, if a subject *i* is alive while a subject *j* died, the score is 1; if a subject *i* died while subject *j* is alive, the score is -1. If both subjects are alive or dead, the second clinical outcome (Intracranial hemorrhage) is compared and assigned a score of 1, -1, or 0 in a similar comparison logic. Subsequently, within each pairwise comparison, the score is determined by comparing five clinical outcomes sequentially in the order of outcome priorities. In summary, for each pair of subjects (*i*, *j*), the score is defined as

$$u_{ij} = \begin{cases} 1, \text{if subject } i \text{ does better than subject } j \\ -1, \text{if subject } j \text{ does better than subject } i \\ 0, \text{if it cannot be determined} \end{cases}$$

Finkelstein & Schoenfeld[73] then assigned a score $U_i = \sum_{i \neq j} u_{ij}$ to each subject *i*. Their proposed test is a score test based on the sum of the ranks for the treated group (see the following eqation).

$$T = \sum_{i=1}^{N} U_i D_i$$

where D_i= 1 for subjects in FlowTriever arm and D_i= 0 for subjects in CDT arm, and N is the number of total subjects in the trial. The proposed FS statistic for the hypothesis of interest is $T/\sqrt{V}$, where $V = \frac{n_{FT}n_{CDT}}{N(N-1)}\sum_i U_i^2$ is the variance of T, n_{FT} and n_{CDT} are the number of subjects in FlowTriever and CDT arms, respectively, and $n_{FT} + n_{CDT} = N$. The hypothesis is tested by comparing the FS statistic to the standard normal distribution (Finkelstein & Schoenfeld, 1999)[73].

To determine the sample size required to achieve 80% power given one-sided alpha of 2.5%, we first will simulate subject level data per data replicate. For a data replicate and within a treatment arm, clinical outcomes with event proportions are sampled from binomial distribution; ICU is from a multinominal distribution with 3 categories, including no ICU admission, < 24 hours, and ≥24 hours. We will assume each clinical outcome is independent of each other. For example, we may sample 100 subjects per treatment arm, and within each treatment arm has different clinical outcome proportions or means. Once we generate 200 subjects in total (100 per treatment arm), we may derive the F-S test statistic and its p-value. We will then repeat the process for 2,500 data replicates and derive 2,500 p-values based on F-S test statistics; power is the proportion of p-values that are ≤ 0.05. Each given sample size number will thus lead to one power number to be calculated. As we alter the sample sizes in the simulation scenario, we can conduct a grid search to determine the minimal sample size required to achieve at least 80% power.

In addition, the win ratio defined by Pocock el al.,[74] will be reported to summarize the performance differences between two treatment arms. The win ratio is defined as $\frac{N_W}{N_L}$, where N_W is the number of winners for the FlowTriever System (i.e., counting the number of pairs in which the subject in FlowTriever System does better than that in CDT arms), and N_L is the number of losers for the FlowTriever System (i.e., counting the number of pairs in which the subject in FlowTriever System does worse than that in CDT arms); the 95% CI of the win ratio estimate can be derived via a bootstrap method.

The analysis population for primary and secondary endpoints is described in the statistical analysis plan (SAP). Meanwhile, for the contraindication cohort, the descriptive summary will be provided.

11.STUDY MANAGEMENT CONSIDERATIONS

PROTOCOL MODIFICATIONS

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

PROTOCOL DEVIATIONS

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

The Sponsor will address deviations and take appropriate corresponding action. Protocol deviations will be reported to the IRBs/ECs by the sponsor and/or clinical sites, per local requirements. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

INFORMATION FOR STUDY PERSONNEL

The Sponsor or designee is responsible for explaining the protocol to all study staff, including the Investigator, and for ensuring their compliance with the protocol throughout the study. Additional information will be made

available during the study when new staff become involved in the study, and as otherwise agreed upon with either the Investigator or the Sponsor or designee.

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

12.STUDY ADMINISTRATION

SITE SELECTION AND QUALIFICATION

A Site Qualification Visit (SQV) may be conducted by the Sponsor or designee in-person or via teleconference. 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.

SITE INITIATION

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

SITE MONITORING

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

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

SITE CLOSE-OUT

A Site Close-out Visit (COV) visit may be conducted by the Sponsor or designee in-person or via teleconference to ensure proper close-out and archiving of trial documentation. This may be combined with a final Interim Monitoring Visit. Any COVs performed will be documented and kept in the study files.

STUDY TERMINATION

Inari Medical and applicable regulatory authorities have the right to terminate the entire study or a specific study site at any time. Situations that could warrant study termination include, but are not limited to:

- Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard
- Insufficient subject enrollment rates
- Recurrent protocol deviations or other non-compliances
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis

- Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

DATA HANDLING AND RECORDKEEPING

Completing, Signing and Archiving Case Report Forms

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

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

Data Management and Archiving

The Sponsor and/or designee will be responsible for the processing and quality control of the data. All CRFs, copies of protocols and protocol amendments, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a minimum of 10 years post study completion or 10 years after the last FlowTriever system or CDT system has been placed on the market (whichever is longer).

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

Direct Access to Source Data/Documentation

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

The Investigator may keep a separate subject identification list showing enrollment numbers and names to allow unambiguous identification of each subject included in the study. The Sponsor will not collect subject identification lists.

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

13.ETHICS AND CONFIDENTIALITY

INFORMED CONSENT

It is the Investigator's responsibility to ensure written or electronic (if applicable) Informed Consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-1, 21 CFR Part 50).

Subjects will be screened to determine their initial eligibility and interest in the study. Written or electronic (if applicable), study-specific Informed Consent will be obtained from each subject via the current IRB/EC approved Informed Consent Form (ICF) prior to the subject's participation in any study-related procedures, and prior to de-identified medical record or personal health information (PHI) being shared with any study representative. The subject's willingness to participate in the study will be documented in a study-specific Informed Consent Form, which will be signed and dated by the subject or their Legally Authorized Representative. The subjects will also be informed about study purpose, alternative treatments, potential risks/benefits of study participation, and the study assessment schedule.

The Investigator will keep the original consent form and a copy may be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

If, at any time during the study, new information becomes available or a protocol amendment requires an amendment to the ICF, active subjects may be asked to re-consent by signing an updated ICF. Copies of all signed ICFs will be maintained by the Investigator and will be made available to the Sponsor for monitoring purposes.

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

This study must be approved by an appropriate IRB/EC at each study site. Securing IRB/EC approval is the responsibility of the Investigator, as defined by GCP, ISO 14155-1 and FDA regulations (21 CFR Part 56), prior to starting the study.

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

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

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

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

STUDY SUBJECT CONFIDENTIALITY

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal health information. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an individual identification code (i.e., subject identification number).

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

INDEPENDENT IMAGE REVIEW AND IMAGE TRANSFER

An independent reviewer may be utilized in the study, at the Sponsor's discretion. The independent reviewer will evaluate selected CT and Echocardiography images collected at baseline, 24 hours, and any unscheduled visits (if collected).

De-identified, electronic echocardiograms and CT images will be sent via secure electronic transfer to a secured imaging repository per US FDA/EU GDPR regulations. Where an electronic submission is not possible, de-identified images will be sent by other secure means per US FDA/EU GDPR regulations. Copies of images will be securely stored for a minimum of 10 years post study completion or 10 years after the last FlowTriever system or CDT system has been placed on the market (whichever is longer).

INVESTIGATOR RESPONSIBILITIES

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

- Conducting the study in accordance with this investigational plan, signed agreement, GCP, and applicable regulations protecting the rights and safety of study subjects
- Ensuring that informed consent is obtained for each study subject in accordance with GCP and applicable regulations (e.g., ISO 14155-1, 21 CFR Part 50)
- Ensuring that IRB/EC approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
- Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to a conflict of interest (financial disclosure is required)

14.ELECTRONIC DATA

Electronic data will only be accessible to authorized personnel with a unique user identifier and password for the EDC. Passwords will be set to expire periodically. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and subject data at their site. The Sponsor and designee will have read-only access and can post queries for potential data-related discrepancies.

15.PUBLICATION OF TRIAL RESULTS

A description of the clinical trial results will be available on http://www.ClinicalTrials.gov (Ref: NTC05111613), within 1 year after the completion of the clinical trial. This web site will not include any identifiable subject information but will include a summary of the results.

The sponsor will also seek publication of the trial primary and secondary objectives in international peer-reviewed journals.

16.FUTURE USE OF DATA FOR RESEARCH PURPOSES

The subject clinical data and echocardiography images collected in the PEERLESS Study could play an important role in answering clinical questions in the future and could therefore be used in clinical investigations that have not been defined yet (= further use).

For research projects with not yet defined research questions we will collect the consent for "further use of data" and only data from patients who agreed to the "further use of data" will be considered.

17.TERMS AND DEFINITIONS

Primary Endpoint Definitions	
Index Procedure	The index procedure begins when access for treatment is obtained. The index procedure is considered complete when the subject leaves the procedure room.
Intracranial Hemorrhage	Intracranial hemorrhage (ICH) is defined as ANY bleeding involving the brain parenchyma, ventricular system, or subarachnoid, subdural, or epidural regions, as identified by CT scan or MRI, regardless of symptoms.
Major Bleeding	ISTH Major Bleeding[4] in non-surgical subjects: • Fatal bleeding; and/or • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or • Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.
Clinical Deterioration	**Clinical deterioration** is defined as documented objective hemodynamic or respiratory worsening that is new (i.e. not present at the time of enrollment). Clinical deterioration is when one or more of the following is ***definitively documented***, with relation to both the severity ***and*** the duration of the event: • Hypotension with systolic blood pressure <90 mm Hg lasting at least 30 minutes, unresponsive to fluid resuscitation, and requiring the addition of or increased dose of vasopressors • Fall in systolic blood pressure by 40 mm Hg or more, lasting at least 30 minutes, and accompanied end-organ hypoperfusion (such as oliguria, mental status changes, ischemic extremities) • Cardiac arrest requiring cardiopulmonary resuscitation • Bradycardia lasting more than 10 minutes, accompanied by hypotension, and requiring pharmacologic intervention or insertion of a pacemaker

	• Ventricular tachycardia or fibrillation requiring pharmacologic intervention or defibrillation • Requirement for an increase in fraction of inspired oxygen requirements 0.20 or greater, lasting longer than 30 minutes (e.g. from 0.21 to 0.41) • Need for intubation in a previously non-intubated subject, or unplanned use of extracorporeal membrane oxygenation (ECMO) Note that transient fluctuations in hemodynamic and/or respiratory function may be common during thrombectomy and thrombolysis procedures, and events not meeting both severity and duration requirements are not considered meeting the definition of Clinical Deterioration. Such changes may resolve spontaneously upon continuation of an existing treatment plan, and as such are unremarkable. Vagal episodes are also, in themselves, not considered Clinical Deterioration. Shorter term changes in hemodynamic or respiratory function, when accompanied by an unplanned escalation of therapeutic measures under the primary clinician's judgement to avoid overt deterioration, may be considered Bailout Therapy. Any such escalations of therapy will be documented in detail and adjudicated by a Clinical Events Committee (CEC).

Bailout	**Bailout** therapy is an unplanned escalation of therapeutic measures, taken when the patient's condition has not improved or is not improving according to expectations. Potential Bailout Therapy events will be adjudicated by a Clinical Events Committee, including when any of the following occur:
	
	• Unplanned use of additional mechanical, pharmacomechanical, pharmacologic catheter-based therapies, or systemic thrombolytics, or changing from the assigned treatment strategy, after initial treatment strategy as assigned was initiated.
	  ○ If catheter-directed thrombolysis (CDT) was the assigned treatment strategy and emergent/clinically driven systemic thrombolytic administration (e.g. ≥ 10 mg tPA) was required after CDT was initiated, this would be considered a bailout.
	  ▪ If the length of thrombolytic administration is simply extended and is not emergent or clinically driven, this would not qualify as a bailout.
	  ○ If mechanical thrombectomy was the assigned treatment strategy, low-dose catheter-directed adjunctive thrombolytic therapy (less than 10 mg tPA) that is administered intra-procedurally or post-procedurally will be *strongly discouraged* but not considered a bailout
	• Surgical thrombectomy
	
	Before escalating to a Bailout Therapy, physicians are encouraged to consider the patient's condition and identify one or more reasons from the

	following list to justify the need for Bailout Therapy. These reason(s) will be documented in the study case report forms (CRFs). • Persistent elevated respiratory rate • Ongoing or increased requirement for supplemental oxygen • Persistent or new-onset tachycardia • Sustained or sudden bradycardia • Sudden or persistent hypotension, not associated with a vagal episode, or signs of end-organ hypoperfusion • Hemodynamic worsening or lack of hemodynamic improvement • Lack of improved lung perfusion, or inadequate clot resolution • New-onset, persistent, or worsening symptoms of PE Any unplanned escalation of therapy adjudicated by the CEC to not meet clinical definitions for Bailout Therapies will be considered a protocol deviation.
ICU Admission/ICU Length of Stay	ICU Admission will be defined as admission or transfer to an Intensive Care Unit (ICU), Critical Care Unit (CCU), or similar high-acuity floor, collectively referred to as "ICU." For the purpose of the endpoint assessment, ICU Admission is met under the following conditions: • Orders are entered for Subject to be admitted or transferred to the ICU after the end of the Index Procedure and before hospital discharge from the index hospitalization, up to a maximum of 7 days from the end of the Index Procedure, or • Subject had been in the ICU leading up to the Index Procedure, with plans to return to the ICU immediately after the end of the Index Procedure, with or without a transfer to a PACU, recovery room, or similar temporary step-down unit according to local standard. ICU Length of Stay (LOS) is the total number of hours a subject is medically required to be in the ICU, measured from the end of the Index Procedure or the time of ICU Admission, whichever is later, until the time of an *order to discharge* the subject from the ICU or transfer the subject to a standard or lower-acuity unit. If a subject remains physically located in the ICU due to hospital bed availability, transport delays, or other non-medical reasons instead of a need for high acuity of care, the time of the order for discharge or transfer, rather than the actual time a subject physically leaves the ICU, is used for assessing ICU LOS. For subjects getting discharged from or transferred off the ICU and returning again during the index hospitalization, up to a maximum of 7 days after the Index Procedure, the total hours of all ICU admissions or transfers during that period (i.e., after the Index Procedure and until hospital discharge up to a maximum of 7 days) are used for assessing ICU LOS.

	Subjects who had been in the ICU leading up to the Index Procedure, but *not* returning to the ICU after the end of the Index Procedure, are *not* considered to have had an ICU Admission per the endpoint definition. For the win ratio primary endpoint, ICU admission and ICU LOS are characterized hierarchically as follows: 1. No ICU Admission 2. ICU Admission, lasting between 0 – 24 hours 3. ICU Admission, lasting longer than 24 hours

Additional Safety Definitions	
Adverse Device Effect (ADE)	An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device. NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: This includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Adverse event (AE)	An Adverse Event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in *subjects*, users or other persons, whether or not related to the *investigational* medical device* and whether anticipated or unanticipated (ISO 14155:2020, 3.2). *NOTE 1: All devices used in this study are commercially available and, therefore, not considered investigational. NOTE 2: This adverse event definition includes events related to the procedures involved.
CRNM	Clinically Relevant Non-Major (bleeding): Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding[4] but does meet at least one of the following criteria: i. requiring medical intervention by a healthcare professional ii. leading to hospitalization or increased level of care iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Device Deficiency (DD)	A Device Deficiency (DD) is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Device-related event	The event is directly related to the FlowTriever System or CDT system, as defined by its intended use. AEs will be considered unrelated to the device if the complication could have occurred if the device functioned entirely within its specifications.
Drug-related event	Event is attributable to thrombolytic or anticoagulant therapy. These events may occur from inadequate (thrombosis) or excessive therapy (bleeding). A drug-related AE cannot also be classified as device related, but many will be classified as procedure-related, since the drug may be part and parcel of the index procedure.
Minor bleeding	Any bleeding not classified as Major Bleeding or Clinically Relevant Non-Major, by ISTH definitions
Procedure-related event	Procedure-related events include all AEs that occur at any time of subject participation that was directly related to the procedure. The exception to this rule is an event that is device-related; such events should not also be classified as procedure-related.
Serious Adverse Device Effect (SADE)	A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Serious Adverse Event (SAE)	A Serious Adverse Event (SAE) is an adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

	5) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Unanticipated/Anticipated Serious Adverse Device Effect (USADE/ASADE)	A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. An ASADE is an anticipated serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. (ISO 14155:2020, 3.51)
Unanticipated Adverse Device Effect (UADE)	An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Other Definitions	
Asymptomatic PE	Pulmonary embolism detected on an imagining study in a subject without clinical symptoms.
CTED/Post PE Syndrome	Chronic thromboembolic Disease: Per 2019 ESC Guidelines,[1] some subjects may present with normal pulmonary hemodynamics at rest despite symptomatic disease. If other causes of exercise limitation are excluded, these subjects are considered as having chronic thromboembolic disease (CTED). From Respiratory medicine journal on PE, CTED is characterized by similar symptoms and imaging findings to CTEPH but without pulmonary hypertension at rest.
CTEPH	Chronic thromboembolic pulmonary hypertension: Per 2019 ESC Guidelines,[1] CTEPH is a disease caused by the persistent obstruction of pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodeling of the pulmonary microvascular bed. The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation, to distinguish this condition from acute PE. The diagnosis requires a mean PAP of ≥25 mmHg along with a pulmonary arterial wedge pressure of ≤ 15 mmHg, documented at right heart catheterization in a subject with mismatched perfusion defects on V/Q lung scan.
High-Risk PE	Per ESC guidelines 2019[1]: High-Risk PE determined by hemodynamic instability, PESI III-V or sPESI ≥1, RV Dysfunction, and Elevated cardiac troponins. Note definition of hemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation). 1. Cardiac Arrest: Need for cardiopulmonary resuscitation, 2. Obstructive Shock: Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status AND end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum

	lactate), OR 3. Persistent Hypotension: Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis
Intermediate-High-Risk PE	Per ESC guidelines 2019[1]: Intermediate-High-Risk PE determined by no hemodynamic instability, PESI III-V or sPESI ≥1, RV Dysfunction, and Elevated cardiac troponins
Intermediate-Low-Risk PE	Per ESC guidelines 2019[1]: Intermediate-Low-Risk PE determined by no hemodynamic instability, PESI III-V or sPESI ≥1, and 1 or none of the following: RV Dysfunction; Elevated cardiac troponins.
Patient/Subject	Participants in the study.
Product Complaint:	Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.
Recurrent PE	Symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure with documentation of a change on CTPA or other suitable imaging modality.
Symptomatic PE	Clinical pulmonary embolism symptoms and/or signs such as chest pain, dyspnea, hemoptysis, palpitations, or tachycardia.

18.REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2019;41(4):543-603.
2. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019;40(11):902-10.
3. Klok FA, Hösel V, Clemens A, Yollo WD, Tilke C, Schulman S, et al. Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment. Eur Respir J. 2016;48(5):1369-76.
4. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
5. Yusuf HR, Tsai J, Atrash HK, Boulet S, Grosse SD. Venous Thromboembolism in Adult Hospitalizations - United States, 2007-2009. Centers for Disease Control and Prevention. Venous Thromboembolism (Blood Clots). Data & Statistics. MMWR Morb Mortal Wkly Rep2012. p. 401-4.
6. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4 Suppl):S495-501.
7. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4):756-64.
8. Smith SB, Geske JB, Kathuria P, Cuttica M, Schimmel DR, Courtney DM, et al. Analysis of National Trends in Admissions for Pulmonary Embolism. Chest. 2016;150(1):35-45.
9. Maynard G, Stein J. Preventing hospital-acquired venous thromboembolism: a guide for effective quality improvement. AHRQ. 2008;Publication No. 08-0075.
10. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, et al. Pregnancy-related mortality surveillance - US, 1991-1999. MMWR Surveill Summ. 2003;52(2):1-8.
11. Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med. 2008;168(19):2131-6.
12. Sanders S, Doust J, Glasziou P. A systematic review of studies comparing diagnostic clinical prediction rules with clinical judgment. PLoS One. 2015;10(6):e0128233.
13. Penaloza A, Verschuren F, Meyer G, Quentin-Georget S, Soulie C, Thys F, et al. Comparison of the unstructured clinician gestalt, the Wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. Ann Emerg Med. 2013;62(2):117-24.e2.
14. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354(22):2317-27.
15. Becattini C, Agnelli G, Vedovati MC, Pruszczyk P, Casazza F, Grifoni S, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. Eur Heart J. 2011;32(13):1657-63.
16. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.
17. Konstantinides S, Goldhaber SZ. Pulmonary embolism: risk assessment and management. Eur Heart J. 2012;33(24):3014-22.
18. Aujesky D, Roy PM, Le Manach CP, Verschuren F, Meyer G, Obrosky DS, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur Heart J. 2006;27(4):476-81.
19. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9.

20. Lankeit M, Jiménez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P, et al. Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. Circulation. 2011;124(24):2716-24.
21. Righini M, Roy PM, Meyer G, Verschuren F, Aujesky D, Le Gal G. The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism. J Thromb Haemost. 2011;9(10):2115-7.
22. Penaloza A, Soulié C, Moumneh T, Delmez Q, Ghuysen A, El Kouri D, et al. Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): a multicentre, prospective, observational study. Lancet Haematol. 2017;4(12):e615-e21.
23. Freund Y, Cachanado M, Aubry A, Orsini C, Raynal PA, Féral-Pierssens AL, et al. Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients: The PROPER Randomized Clinical Trial. JAMA. 2018;319(6):559-66.
24. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116(4):427-33.
25. Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care. 2011;15(2):R103.
26. Bajaj A, Rathor P, Sehgal V, Shetty A, Kabak B, Hosur S. Risk stratification in acute pulmonary embolism with heart-type fatty acid-binding protein: A meta-analysis. J Crit Care. 2015;30(5):1151.e1-7.
27. Vanni S, Nazerian P, Bova C, Bondi E, Morello F, Pepe G, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate-high risk of adverse clinical outcome: the prognostic role of plasma lactate. Intern Emerg Med. 2017;12(5):657-65.
28. Giri J, Sista AK, Weinberg I, Kearon C, Kumbhani DJ, Desai ND, et al. Interventional Therapies for Acute Pulmonary Embolism: Current Status and Principles for the Development of Novel Evidence: A Scientific Statement From the American Heart Association. Circulation. 2019;140(20):e774-e801.
29. Kalra R, Bajaj NS, Arora P, Arora G, Crosland WA, McGiffin DC, et al. Surgical Embolectomy for Acute Pulmonary Embolism: Systematic Review and Comprehensive Meta-Analyses. Ann Thorac Surg. 2017;103(3):982-90.
30. Neely RC, Byrne JG, Gosev I, Cohn LH, Javed Q, Rawn JD, et al. Surgical Embolectomy for Acute Massive and Submassive Pulmonary Embolism in a Series of 115 Patients. Ann Thorac Surg. 2015;100(4):1245-51; discussion 51-2.
31. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e96S.
32. Sasahara AA, Criss AJ, Morse RL, Belko JS. Management of pulmonary embolism. N Engl J Med. 1968;278(6):339-40.
33. Hyers TM, Stengle JM, Sherry S. Treatment of pulmonary embolism with urokinase. Results of clinical trial (phase 1). Circulation. 1970;42(6):979-80.
34. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA. 1970;214(12):2163-72.
35. Walsh PN, Stengle JM, Sherry S. The urokinase-pulmonary embolism trial. Circulation. 1969;39(2):153-6.
36. Sasahra AA, Bell WR, Simon TL, Stengle JM, Sherry S. The phase II urokinase-streptokinase pulmonary embolism trial: a national cooperative study. Thromb Diath Haemorrh. 1975;33(3):464-76.
37. Bell WR, Simon TL, Stengle JM, Sherry S. The urokinase-streptokinase pulmonary embolism trial (phase II) results. Circulation. 1974;50(6):1070-1.
38. Simon TL, Stengle JM, Sasahara AA. Urokinase in pulmonary embolism. Lancet. 1973;2(7827):501.
39. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402-11.
40. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2015;36(10):605-14.
41. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014;311(23):2414-21.

42. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol. 2009;20(11):1431-40.
43. Avgerinos ED, Liang NL, El-Shazly OM, Toma C, Singh MJ, Makaroun MS, et al. Improved early right ventricular function recovery but increased complications with catheter-directed interventions compared with anticoagulation alone for submassive pulmonary embolism. J Vasc Surg Venous Lymphat Disord. 2016;4(3):268-75.
44. Arora S, Panaich SS, Ainani N, Kumar V, Patel NJ, Tripathi B, et al. Comparison of In-Hospital Outcomes and Readmission Rates in Acute Pulmonary Embolism Between Systemic and Catheter-Directed Thrombolysis (from the National Readmission Database). Am J Cardiol. 2017;120(9):1653-61.
45. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129(4):479-86.
46. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv. 2015;8(10):1382-92.
47. Tapson VF, Sterling K, Jones N, Elder M, Tripathy U, Brower J, et al. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial. JACC Cardiovasc Interv. 2018;11(14):1401-10.
48. Tafur AJ, Shamoun FE, Patel SI, Tafur D, Donna F, Murad MH. Catheter-Directed Treatment of Pulmonary Embolism: A Systematic Review and Meta-Analysis of Modern Literature. Clin Appl Thromb Hemost. 2017;23(7):821-9.
49. Avgerinos ED, Jaber W, Lacomis J, Markel K, McDaniel M, Rivera-Lebron BN, et al. Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. JACC Cardiovasc Interv. 2021;14(12):1364-73.
50. Avgerinos ED, Saadeddin Z, Abou Ali AN, Fish L, Toma C, Chaer M, et al. A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism. J Vasc Surg Venous Lymphat Disord. 2018;6(4):530-40.
51. Nosher JL, Patel A, Jagpal S, Gribbin C, Gendel V. Endovascular treatment of pulmonary embolism: Selective review of available techniques. World J Radiol. 2017;9(12):426-37.
52. Dudzinski DM, Giri J, Rosenfield K. Interventional Treatment of Pulmonary Embolism. Circ Cardiovasc Interv. 2017;10(2).
53. Bloomer TL, El-Hayek GE, McDaniel MC, Sandvall BC, Liberman HA, Devireddy CM, et al. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: Results of a multicenter registry and meta-analysis. Catheter Cardiovasc Interv. 2017;89(4):754-60.
54. Boon G, Bogaard HJ, Klok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. Res Pract Thromb Haemost. 2020;4(6):958-68.
55. Sista AK, Klok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. Thromb Res. 2018;164:157-62.
56. Klok FA, Delcroix M, Bogaard HJ. Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism. J Thromb Haemost. 2018;16(6):1040-51.
57. Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv. 2019;12(9):859-69.
58. Horowitz J. Safety and effectiveness of FlowTriever thrombectomy in a real-world pulmonary embolism population: results from the FLASH registry. Journal of Vascular and Interventional Radiology. 2021;32(5):S23.
59. Toma C. Acute Hemodynamic Improvement With Percutaneous Mechanical Thrombectomy in a Real-World Pulmonary Embolism Population: Interim Results of the FLASH Registry. J Am Coll Cardiol. 2020;76(17S):B5.
60. Toma C. Abstract 16623: Interim Acute and 30-day Results of the Flash Registry. Circulation. 2020;142(Suppl_3):A16623-A.

61. Wible BC, Buckley JR, Cho KH, Bunte MC, Saucier NA, Borsa JJ. Safety and Efficacy of Acute Pulmonary Embolism Treated via Large-Bore Aspiration Mechanical Thrombectomy Using the Inari FlowTriever Device. J Vasc Interv Radiol. 2019;30(9):1370-5.
62. Toma C, Khandhar S, Zalewski AM, D'Auria SJ, Tu TM, Jaber WA. Percutaneous thrombectomy in patients with massive and very high-risk submassive acute pulmonary embolism. Catheter Cardiovasc Interv. 2020;96(7):1465-70.
63. Markovitz M, Lambert N, Dawson L, Hoots G. Safety of the Inari FlowTriever device for mechanical thrombectomy in patients with acute submassive and massive pulmonary embolism and contraindication to thrombolysis. American Journal of Interventional Radiology. 2020;4(18):1-6.
64. Buckley JR, Wible BC. In-Hospital Mortality and Related Outcomes for Elevated Risk Acute Pulmonary Embolism Treated With Mechanical Thrombectomy Versus Routine Care. J Intensive Care Med. 2021:1-6.
65. Balanescu DV, Kado HS, Mertens A, Chand R, Savin M, McNally V, et al. Mechanical Thrombectomy in Pulmonary Embolism Associated with COVID-19: A "Clotography" Gallery. Vasc Endovascular Surg. 2021:1-4.
66. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386-9.
67. Lin PH, Annambhotla S, Bechara CF, Athamneh H, Weakley SM, Kobayashi K, et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. Vascular. 2009;17 Suppl 3:S137-47.
68. Engelhardt TC, Taylor AJ, Simprini LA, Kucher N. Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism. Thromb Res. 2011;128(2):149-54.
69. Kennedy RJ, Kenney HH, Dunfee BL. Thrombus resolution and hemodynamic recovery using ultrasound-accelerated thrombolysis in acute pulmonary embolism. J Vasc Interv Radiol. 2013;24(6):841-8.
70. Quintana D, Salsamendi J, Fourzali R, Narayanan G. Ultrasound-assisted thrombolysis in submassive and massive pulmonary embolism: assessment of lung obstruction before and after catheter-directed therapy. Cardiovasc Intervent Radiol. 2014;37(2):420-6.
71. An International Pulmonary Embolism Registry Using EKOS (KNOCOUT PE). Available from: https://clinicaltrials.gov/ct2/show/NCT03426124.
72. Ultrasound-facilitated, Catheter-directed, Thrombolysis in Intermediate-high Risk Pulmonary Embolism (HI-PEITHO). Available from: https://clinicaltrials.gov/ct2/show/NCT04790370.
73. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999;18(11):1341-54.
74. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012;33(2):176-82.

19.APPENDIX 1

TABLE A1: KNOWN RISKS FOR FLOWTRIEVER SYSTEM *

Event Category	Event
Cardiac	Myocardial infarction
	Angina
	Arrhythmias, bradycardia, tachycardia
	Right bundle branch block
	Cardiac tamponade
	Cardiac perforation
	Pericardial effusion
	Valve disruption/injury
	Ventricular rupture
	Hypertension
	Hypotension
	Cardiogenic shock
Wound	Access site hematoma
Peripheral vascular	Vessel dissection/perforation
	Aneurysm
	Pseudoaneurysm
	Vessel stenosis
	Arteriovenous fistula
	Vascular spasm
	Vasovagal reaction
	Embolism, Distal embolism, foreign body embolism
	Air embolism
Cerebrovascular	Stroke/Transient ischemic attack
Pulmonary	Perforation of pulmonary arteries
	Pneumothorax
	Pulmonary edema
	Pulmonary infarct
	Hemoptysis
	Respiratory failure
Miscellaneous	Fever
	Infection
	Fistulation

Event Category	Event
	Hemoglobinuria
	Hemolysis
	Hypoxemia
	Drug reaction to contrast, thrombolytic or anticoagulation
	Adverse reaction to device materials
	Inflammatory response
	Nausea/vomiting
	General discomfort, tenderness, or pain
	Neurological deficit, peripheral nerve damage
	Organ impairment, renal failure
	Retroperitoneal hemorrhage
	Death

* From IFUs for FlowTriever Catheter (LB-0047 RevJ), Triever 16 (LB-0060 RevL), Triever 20 (LB-0139 RevM), Triever 20 Curve (LB-0144 RevJ), and Triever 24 (LB-0151 RevE)

TABLE A2: KNOWN RISKS FOR CATHETER-DIRECTED THROMBOLYSIS**

Event Category	Event
Cardiac	Arrhythmia
	Right bundle branch block and complete heart block
	Hypotension
	Tricuspid and pulmonic valve damage
	Intimal disruption
Wound	Hematoma
Peripheral vascular	Vessel perforation
	Arterial dissection
	Arteriovenous fistula
	Thromboembolic episodes
	Thrombophlebitis
	Distal embolization
	Vessel spasm
Venous	Vascular thrombosis
	Cholesterol embolization
	Thromboembolism
Cerebrovascular	Intracranial hemorrhage
Pulmonary	Perforation of the pulmonary artery
	Pulmonary re-embolization
	Pulmonary edema
	Pleural effusion
	Pneumothorax
	Pulmonary infarct due to tip migration and spontaneous wedging, air embolism, and/or thromboembolism
Miscellaneous	Hemorrhage
	Contrast extravasation
	Pain and tenderness
	Sepsis/Infection
	Drug reactions
	Allergic reaction to contrast medium
	Orolingual angioedema
	Neurological deficits including stroke and death
	Amputation
	Death

** From EKOS Endovascular System product brochure (PI-726201-AA), Label for Activase (Reference ID: 3702389), Uni-Fuse Product information (https://www.angiodynamics.com/about-us/risk-information)

20.SIGNATURE APPROVAL PAGE

PEERLESS Study

Protocol Number: 21-002

Version: 4.0

August 23, 2023

Signed: _____

Ashleigh Willson

Senior Director, Clinical Research

Inari Medical, Inc.