CLINICAL INVESTIGATION PLAN

Selective Pulmonary-artery Intervention to Reduce Acute Right-heart tEnsion-I

The SPIRARE I Study

CIP No: CSP-01
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Revision A
Date: 01 March 2024

Study Sponsor	Neptune Medical Inc 1828 El Camino Real, Suite 508, Burlingame, CA 94010
Legal Representative in EU	MedNet EC-REP GmbH Borkstrasse 10, 48163 Münster, Germany

REVISION HISTORY

Revision	Description of Change	Date (dd/mmm/yyyy)
A	Initial release.	01 Mar 2024 (authored) 19 Mar 2024 (released)

Clinical Investigational Plan Approval Page

Study Title:	**Selective Pulmonary-artery Intervention to Reduce Acute Right-heart tEnsion. The SPIRARE I Study**.
Device:	Vertex Pulmonary Embolectomy System
CIP Number:	CSP-01
Rev	A
Date:	01 March 2024

Herein, Neptune Medical Inc agrees to conduct this clinical investigation in accordance with the design and specific provisions as outlined in this Clinical Investigation Plan (CIP).

Any changes or deviation of its content will only be acceptable in case of emergency to protect the rights, safety and welfare of patients.

The information contained in this CIP and all information provided to this CIP is confidential and proprietary of Neptune Medical Inc and may not be disclosed to third parties.

Neptune Medical Inc

DocuSigned by:
Aadi Chachad
F78E36D279FB4FE...

3/19/2024

Aaditya Chachad, MD, MPH
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Date

Investigator Agreement / Signature Page

CIP No: CSP-01
Rev A
Date: 01Mar2024

I, the Principal Investigator, have read this Clinical investigation plan, appendices and amendment(s) if applicable, and agree to adhere to the requirements. I will provide copies of this Clinical investigation plan and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the IMD and the conduct of the study.

I will conduct the study in accordance with the Clinical Investigation Plan, the Investigator Agreement, Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (ISO 14155, Clinical investigation of medical devices for human subjects), General Data Protection Regulation (GDPR), and the applicable law and regulations.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the Study will be given; and that any discrepancies and serious breaches of GCP from the Study as planned in this clinical investigation plan will be explained.

PRINCIPAL INVESTIGATOR

_____	_____	_____
Principal Investigator name (Print)	Signature	Date

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Study funding	Neptune Medical Inc 1828 El Camino Real, Suite 508 Burlingame, CA 94010
Study sites	Sites list with all contact information is maintained under the separate list and will be made available upon request.
Vendors	CRO: KCRI Wadowicka 7 30-347 Kraków Poland
	EDC: Merative Clinical Development 100 Phoenix Drive Ann Arbor Michigan 48108 USA
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CLINICAL INVESTIGATION PLAN SYNOPSIS

Device	The Vertex Pulmonary Embolectomy System is intended for the non-surgical removal of emboli and thrombi from blood vessels as a means for treating pulmonary embolism (PE). The Vertex Pulmonary Embolectomy System is a single use medical device comprised of the Vertex™ Catheter, Meridian™ Catheter, and Meridian™ Extraction Set. The Vertex and Meridian Catheters are used with a commercially available vacuum pump connected via the Meridian Extraction Set to aspirate thrombi. Removal of occlusive thrombi via aspiration is meant to restore blood flow, leading to reduction in right heart strain.
Study Objective	Evaluate the safety and effectiveness of the Vertex Pulmonary Embolectomy System for aspiration mechanical thrombectomy in the treatment of acute pulmonary embolism (PE).
Study Design	A prospective, single-arm, multicenter controlled trial of the Vertex Pulmonary Embolectomy System.
Number of Subjects	Up to **ten (10)** Subjects
Number of Sites	Up to **two (2) sites** in **Poland and Austria**
Patient Population	Patients presenting with clinical signs and symptoms of acute PE and who meet the study criteria will be treated with the Vertex Pulmonary Embolectomy System.
Study Duration	The trial is anticipated to last **10 months** and each patient will be in the trial for approximately 30 days. • Enrollment: **6 months** • Follow-up Period: **30 days** • Analysis: 1 month Total Study Duration: **10 months**

Primary Endpoints	<u>Safety:</u>
	Major Adverse Events, a composite of:
	• Device-related death within 48 hours
	• Major bleeding within 48 hours
	• Device-related AEs within 48 hours, including:
	  ○ Clinical deterioration
	  ○ Pulmonary vascular injury
	  ○ Cardiac injury
	<u>Efficacy:</u>
	• Reduction in RV/LV ratio from baseline to 48 hours or discharge by (*core lab assessed*) CT angiography

Secondary Endpoints	Safety: • Device-related death within 48 hours • Major bleeding within 48 hours • Device-related clinical deterioration within 48 hours • Device-related pulmonary vascular injury within 48 hours • Cardiac injury within 48 hours • Any-cause mortality within 30 days • Device-related SAEs within 30 days • Symptomatic recurrence of PE within 30 days Efficacy: • Change in modified Miller index score between baseline and 48 hours post-procedure as assessed by CTA (*core lab assessed*) • Procedural change in cardiac index • Length of stay in the ICU associated with the index procedure • Length of total hospital stay and post-index-procedure hospital stay • Procedural reduction in pulmonary artery mean and systolic pressure • Procedural reduction in total pulmonary vascular resistance • Change from baseline in Dyspnea severity by mMRC score [Time Frame: at the 48-hour and 1-month visits]
Eligibility Criteria	**Inclusion Criteria:** 1. Age ≥ 18 years < 80 years 2. Acute onset of symptoms ≤ 14 days consistent with the presence of pulmonary embolism. 3. CTA evidence (*site determined*) of proximal PE (filling defect in at least one main or interlobar pulmonary artery) 4. RV/LV ratio of > 0.9 on CTA as assessed by investigator (*site determined*). 5. Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with fluids) 6. Subject is willing and able to provide written informed consent prior to receiving any non-standard of care clinical investigation plan specific procedures 7. Subject is willing and able to comply with all clinical investigation plan required follow-up visits **Exclusion Criteria:** 1. Thrombolytic use within 30 days of baseline CTA 2. Pulmonary hypertension with peak pulmonary artery pressure > 70 mmHg by right heart catheterization (*site determined*) 3. Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg 4. Unstable heart rate ≥ 130 beats per minute prior to procedure 5. FiO2 requirement > 40% or > 6 LPM to keep oxygen saturation > 90% 6. Hematocrit < 28% 7. Platelets < 100,000/µL 8. Serum baseline creatinine > 1.8 mg/dL 9. International normalized ratio (INR) > 3 10. Major trauma injury severity score (ISS) > 15 within the past 14 days 11. Presence of intracardiac lead in the right ventricle or right atrium placed <180 days prior to the index procedure

	12. Cardiovascular or pulmonary surgery within last 30 days 13. Actively progressing cancer requiring chemotherapy 14. Known bleeding diathesis or coagulation disorder 15. Left bundle branch block 16. History of severe or chronic pulmonary arterial hypertension 17. History of chronic left heart disease with left ventricular ejection fraction ≤ 30% 18. History of decompensated heart failure 19. Patients on extracorporeal membrane oxygenation (ECMO) 20. History of underlying lung disease that is oxygen dependent 21. History of chest irradiation 22. History of heparin-induced thrombocytopenia (HIT) 23. Contraindication to systemic or therapeutic doses of heparin or anticoagulants 24. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated 25. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for mechanical thrombectomy intervention 26. Life expectancy of < 365 days, as determined by Investigator 27. Female who is pregnant or nursing 28. Current participation in another investigational drug or device treatment study 29. Inability to lay flat for procedure 30. Known presence of right-to-left cardiac shunt 31. History of Hemorrhagic or Ischemic Stroke, including Transient Ischemic Attack, within last 90 days 32. Current or history of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis
Study Procedure	The Vertex Pulmonary Embolectomy System is designed to achieve direct and proximate catheter access to an embolic mass within the pulmonary arteries. The Vertex Catheter is introduced into the pulmonary arteries in a flexible relaxed state using standard techniques over a guidewire through a compatible introducer sheath. When desired, the Vertex Catheter can be fixed in place by attaching an insufflator to the Vertex fixation line and pressurizing to a maximum of 6 atm. If used, the Meridian Catheter is introduced through the Vertex Catheter and may be advanced over a guidewire. The Vertex and Meridian Catheters are used with a commercially available vacuum pump connected via the Meridian Extraction Set to aspirate thrombi. Contrast may be injected through the Vertex or Meridian Catheter to aid in fluoroscopic visualization during the procedure. The Vertex Catheter may be relaxed and repositioned by de-pressurizing the insufflator. After aspiration is complete, the Vertex Catheter is relaxed, and all devices are removed from the patient. PE is the third leading cause of cardiovascular death in the western world with a 5-10% in hospital mortality.[ii] The incidence of Acute PE is 100–200 per 100,000 inhabitants each year[ii].

Study Rationale	Newer treatment modalities, such as catheter directed therapy (CDT), have emerged as alternatives to systemic thrombolytics and anticoagulation. These involve the use of mechanical thrombectomy/fragmentation, mechanical thrombectomy plus thrombolytic therapy, and catheter delivered thrombolytic therapy that are minimally invasive approaches to treat PE. Catheter directed thrombectomy may provide clinically meaningful improvement to intermediate risk patients with acute PE that are at risk of decompensation if not treated quickly. Use of the Vertex Pulmonary Embolectomy System for aspiration thrombectomy may allow for thrombus removal without the use of thrombolytic drugs with an acceptable device-related serious adverse event rate. Use of tissue plasminogen activator (tPA) during procedure will not be permitted unless deemed medically necessary by site investigator

Schedule of Assessments:

Assessment/Method	Screening/ Baseline	Procedure Day 0	Post-Procedure	48 (± 8) Hours* Follow-up Day 2	30 (± 3) Days Follow-up Day 30 ~ (Clinic or Phone visit)
Informed Consent	X				
Demographics	X				
Medical/Surgical History	X				
Physical Examination/Vitals	X	X+	X	X	
Blood Labs (Hematocrit, Platelets, Sr creatinine, INR, BNP, Troponin, Serum lactate)	X		X		
Room Air SpO2	X			X	
mMRC dyspnea score	X			X	X
CT Angiography	X			X	
Echocardiogram	X			X	
Right heart Catheterisation (Invasive Hemodynamic Assessment)		X	X		
Pulmonary Aspiration Thrombectomy		X			
Pregnancy Test	X=				
Major trauma injury severity score (ISS)	X]				
Concomitant Medications#	X		X	X	X
Assessment of AEs/DDs	X^	X	X	X	X

*or discharge; whichever occurs first
= Only for females of childbearing age who are not surgically sterilized
] As applicable for subjects suspected of enduring trauma
+ Vitals only
#Relevant concomitant medications to be documented for the study are anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study
~ 30-day visit can be completed onsite or via televisit
^ Any adverse event/device deficiency occurring since subject signed ICF will be recorded in the subject's CRF.
Note: Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an adverse event further in the study. However, if that subject's condition deteriorates at any time during the study, it will be recorded as an AE.

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ABBREVIATIONS

Abbreviation	Abbreviated Term	Definition
CDA	Confidential Disclosure Agreement	A contract through which the parties agree not to disclose information covered by the agreement.
CDT	Catheter-Directed Thrombolysis	Percutaneous procedure used to dissolve blood clots (thrombus) by administering a lytic directly into the clot through a catheter.
CSA	Clinical Study Agreement	A contract through which the parties agree upon terms and conditions of a basic relationship between investigational site and a sponsor.
CTA	Computed Tomography Angiography	A specialized X-ray that examines blood flow in blood vessels when they are filled with a contrast material.
FDF	Financial Disclosure Form	Term referring to the requirement of an applicant (i.e., Sponsor) for a marketing application to certify the absence of certain financial interest of Clinical Investigators or to disclose those financial interests.
ITT	Intent to Treat	All patients who provide written informed consent, meet the inclusion/exclusion criteria, and in whom the Vertex Catheter is introduced past the pulmonic valve; enrollment occurs when Vertex Catheter is introduced past the pulmonic valve. Any patient enrolled into the trial, but in whom the Vertex Pulmonary Embolectomy System is not able to access a pulmonary embolus is considered an Intent to Treat patient
NPI	National Principal Investigator	Study advisors who provide study leadership and guidance; they oversee all clinical study activities including clinical investigation plan development and any changes that may be desired or required during the conduct of the study.
Vertex PES	Vertex Pulmonary Embolectomy System	All components of the Vertex Pulmonary Embolectomy System which comprise of the Vertex Catheter, Meridian Catheter, and the Meridian Extraction Set.

TERMS AND DEFINITIONS

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

Bleeding	Major Bleeding	The Bleeding Academic Research Consortium (BARC) Classification System Definitions will be used for this study, level 3b, 3c, 5a and 5b. 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation †Overt bleeding was determined by the site investigator to be bleeding visible to the eye or detectable on an imaging study.
Bleeding	Clinically relevant non major (CRNM)	Requires or prolongs hospitalization or results in laboratory testing, imaging, compression, a procedure, interruption of the study medication, or a change in concomitant therapies.
Bleeding	Minor Bleeding	Overt† bleed that does not meet criteria for CRNM or major
Bleeding	Fatal Bleeding	Fatal bleeding was defined as a death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or nonintracranial bleeding.
Clinical deterioration	Clinical deterioration	Hemodynamic or respiratory worsening and will include treatment-related events, such as; • Unplanned endotracheal intubation, • Unexpected requirement for mechanical ventilation, • Arterial hypotension (>1 hour or requiring vasopressors) or shock, • Cardiopulmonary resuscitation,

		• Persistent worsening in oxygenation, and • Emergency surgical embolectomy.
Device	Ancillary Device	Any device other than Vertex Pulmonary Embolectomy System, such as an infusion catheter or guidewire.
Device	Study / Investigational	Neptune Medical Vertex Pulmonary Embolectomy System
Event Severity	Mild	No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
Event Severity	Moderate	Some limitation of usual activities or specific therapy is required.
Event Severity	Severe	Inability to carry out usual activities, hospitalization, emergency room treatment, life-threatening events, or death.
Injury	Cardiac Injury	Cardiac injury is defined as any damage to the heart requiring intervention to avoid permanent injury. Examples of possible cardiac injury : Acute heart failure • Acute myocardial infarction • Arrhythmia requiring intervention • Cardiac hematoma • Tricuspid or Pulmonic valve damage
Injury	Pulmonary Vascular Injury	Pulmonary vascular injury is defined as perforation or injury of a major pulmonary arterial branch requiring intervention to avoid permanent injury. Examples of possible pulmonary vascular injury: Arterial Venous Fistula • Dissection • Hemorrhage • Intimal flap • Perforation • Rupture • Thromboembolic occlusion resulting in permanent damage i.e. infarction
Study Population	Operative Screen Failure	Any eligible patient in whom the Vertex Catheter is not attempted or placed for any reason. Up until this point, the procedure may be converted to another therapeutic treatment or discontinued without the patient receiving any investigational treatment.
Study Population	Intent to Treat (ITT)	All patients who provide written informed consent, meet the inclusion/exclusion criteria, and in whom the Vertex Catheter is introduced past the pulmonic valve; enrollment occurs when Vertex catheter is introduced past the pulmonic valve. Any patient enrolled into the trial, but in whom the Vertex Pulmonary Embolectomy System is not able to access a pulmonary embolus is considered an Intent to Treat patient
Study Population	Screen Failure	Any screened patient who signs the ICF but does not meet the inclusion and exclusion criteria.

1. BACKGROUND AND SIGNIFICANCE OF THE PROBLEM

1.1 Pulmonary Vascular Disease

Pulmonary vascular disease is broadly defined as any condition that affects the blood vessels along the route between the heart and lungs. Oxygen-depleted blood travels from the right side of the heart to the lungs for gas exchange, and back to the left side of the heart which propels oxygen-rich blood to various organs and tissues (*Figure 1*). Any part of the heart-lung blood circuit can become damaged or blocked and compromise the ability of the heart and lungs to function correctly.

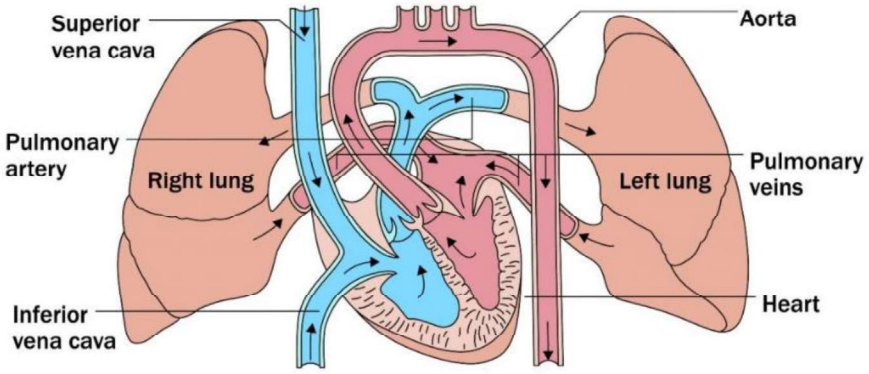


Figure 1: Pulmonary Vascular Circuit (https://umich.edu)

Occlusions and stenoses within the pulmonary vascular circuit can critically elevate right heart pressures and reduce the flow and volume of oxygenated blood to the left side of the heart depriving the tissues of a sufficient amount of oxygenated blood.

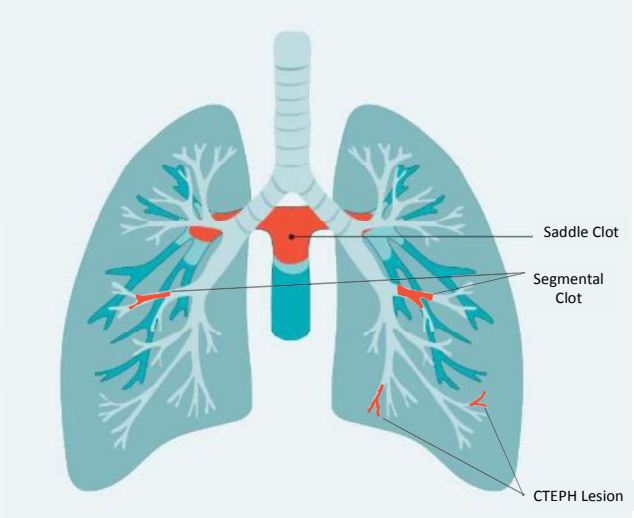


Figure 2: Forms of pulmonary artery occlusive disease

1.2 Pulmonary Embolism

In the United States, pulmonary embolism (PE) affects about 500,000 to 600,000 people per year, with 200,000 to 300,000 deaths per year.[I] PE is the third most frequent cardiovascular disease after acute myocardial infarction (AMI) and stroke, with an annual incidence of 1–2 per 1,000 people (100–200 per 100,000 inhabitants).[II] Pulmonary embolism (PE) is an unpredictable disease that can have immediate and devastating consequences. After years of

decline, the incidence of PE is increasing and disproportionately affecting certain at-risk populations.[III] Pulmonary embolism (PE) and other occlusive diseases in the lung (e.g., CTEPH) exist on the spectrum of sequalae that result from Venous Thrombo Embolism (VTE). The sudden clinical presentation of acute PE is often the most devastating presentation of VTE, and ranges from incidentally discovered asymptomatic clots to massive thrombi that can cause immediate death.[IV] Based on a review of national inpatient data, the number of admissions for PE increased from nearly 60,000 in 1993 (23 per 100,000) to more than 200,000 in 2012 (65 per 100,000).[V] Data from a comprehensive review of Centers for Medicare & Medicaid Services (CMS) in-patient data indicates that the current national incidence of acute (intermediate/high-risk) PE is 280,000 cases per annum. Low-risk PE is similarly estimated at 280,000 cases per annum (Figure 3).[VI]

Hemodynamically unstable patients are considered to have high-risk PE, whereas hemodynamically stable patients are considered to have non-high-risk PE. After classification into one of these two risk groups, patients undergo further diagnostic evaluation for PE according to an appropriate risk-adapted algorithm.

The United States and Europe have further stratified the risks associated with PE into 3 (US) and 4 (Europe) strata (*Figure 3*).

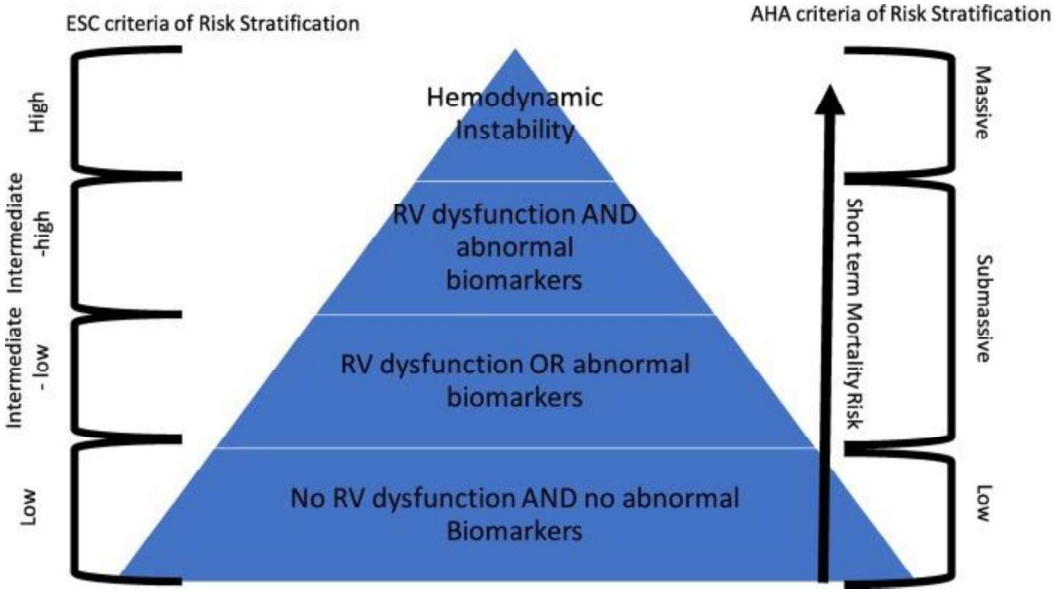


Figure 3: Risk Stratification for PE[VII]

There are no clear cut-offs in the risk stratification for PE, and the heterogeneity of this patient population greatly complicates risk assessment. RH dysfunction varies by patient and elevated biomarkers are indicative but not conclusive of PE risk. The main determinants of PE severity are presence of right heart strain either on echocardiography or computed tomography, myocardial damage based on troponin (or other biomarkers) elevation, and overall clot burden. Although the overall clot burden appears to have only a variable relationship to outcomes (and is a current subject of debate), clot burden is associated with elevated D-dimer levels,[VII] and D-dimer concentration is an independent predictive factor associated with all-cause and pulmonary embolism-related death.[IX]

> **High Risk:** Patients with PE who present with hypotension, syncope, bradycardia, or the inability to maintain adequate oxygenation are at risk for sudden death, even with appropriate treatment. Patients with large PE and residual clot present in the heart ("clot-in-transit") or iliofemoral veins

should also be considered at high risk for decompensation (RV failure). High-risk patients often require emergent intervention and admission to the intensive care unit.

Intermediate Risk: This category can include patients who present with end organ damage (indicative of sustained RH impairment) but are hemodynamically stable. Right heart strain on echocardiography, in the setting of a large PE, is also associated with an increased risk of clinical deterioration and/or short-term death. Other factors, such as an elevated troponin indicating cardiac ischemia, altered mental status, and the presence of co-morbid illness have also been correlated with early clinical deterioration and higher incidence of short-term death.

Low Risk: Patients found to have PE without evidence of end organ damage or hemodynamic instability may be able to be safely discharged early after initiation of anticoagulation. Patients who present with no risk factors (RH strain and/or elevated biomarkers) are likely at low risk for early clinical deterioration and are often ideal candidates for early discharge after initiation of anticoagulation.

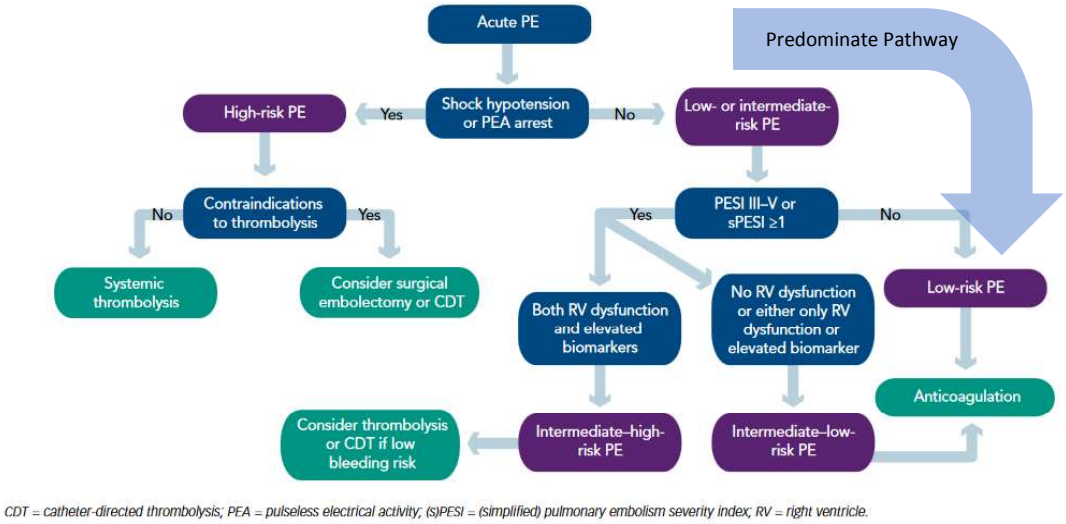
Table 1: Relative incidence and mortality by PE risk stratification[X]

Risk stratification	Indications	90-day mortality (%)[XIII]	Incidence (%)[XII]	Incidence (,000)	Mortality (,000)
High Risk	acute PE with sustained hypo tension (< 90mmHg systolic); > 15 min. inotropic support	25-65%	5-10%	12.5-25	3-16
Intermediate Risk	Systolic pressure > 90 mmHg and either: RV dysfunction (CT, BNP, ECG), or myocardial necrosis (troponin)	3-6%	20-25%	50-62.5	2-4
Low Risk	Absence of hypotension, RV dysfunction, and myocardial necrosis.	<1%	70	175	<2

1.3 Current Treatment Strategies

The majority of patients who present with non-emergent (i.e., not in respiratory collapse) are treated medically with either anticoagulants (e.g., vitamin k antagonists) or thrombolytic drugs (e.g., Alteplase). The latter can be delivered locally (i.e., with a catheter placed near the clot) or systemically.

The current clinical approach to triaging and treating PE is depicted in figure 4.



CDT = catheter-directed thrombolysis; PEA = pulseless electrical activity; (s)PESI = (simplified) pulmonary embolism severity index; RV = right ventricle.

Figure 4: Patient Management Following Acute PE

According to current guidelines,[XI]**Error! Bookmark not defined.** anticoagulation should be initiated as soon as the diagnosis of PE is suspected. Direct oral anticoagulants are first-line therapy for low-risk patients and intermediate- and high-risk patients once they have achieved hemodynamic stability. Systemic thrombolytic (ST) therapy is recommended in high-risk sub-massive PE in the absence of contraindications (e.g., bleeding). ST therapy has been shown to improve hemodynamics, reverse RV dilatation, and prevent hemodynamic decompensation, though no significant short-term mortality reduction has been observed compared to surgery. [XIII]

Moreover, systemic thrombolytic therapy is associated with significant bleeding, including a 6% risk of major bleeding and up to 3% of intracranial hemorrhage (ICH). Use of thrombolytics in normotensive patients has not been demonstrated to reduce mortality. [XIV]

1.3.1 Pharmacologic Treatment

Both US and European guidelines call for pharmacological treatment as the first line of therapy for non-life-threatening, lower risk PE (figure 5).[XV,XVI] Typically, treatment of PE consists of an initial treatment phase, followed by an acute phase lasting 3-6 months and a chronic or extended phase of anticoagulation aimed for long-term prevention of recurrence.

	Low Risk	Intermediate Risk (Submassive)	High Risk (Massive)
Presentation	• Normotensive • Low risk per PESI and sPESI • Normal biomarkers	• PESI class III-IV • sPESI ≥1 • Echo or CT evidence of RV strain • Positive troponin • Elevated B-type natriuretic peptide or N-terminal B-type natriuretic peptide	• Hypotension (systolic blood pressure <90 mmHg for ≥15 min, drop in systolic blood pressure of ≥40 mmHg or vasopressor) • Thrombus in transit • Syncope • Cardiac arrest
Treatment	• Anticoagulation: Direct oral anticoagulants are preferred • Candidates for early discharge	• Anticoagulation: Consider unfractionated heparin over others if any of the therapies below are possible • Systemic thrombolytic (100 mg over 2 h) • High risk of bleeding: Half-dose thrombolytic (50 mg over 2 h) • Catheter-directed therapy • Surgical embolectomy • High-risk PE and cardiogenic shock: Mechanical support to allow stability for thrombolysis, catheter-directed therapy, or surgical embolectomy	

Figure 5: Guideline Criteria for Treatment of PE (ACC)

1.3.2 Catheter Directed Therapy

Catheter directed therapy (CDT) of PE involves the use of mechanical thrombectomy/fragmentation, mechanical thrombectomy plus thrombolytic therapy, and catheter delivered thrombolytic therapy. The goal of catheter directed

therapy is to rapidly decrease afterload on the right ventricle while reducing clot burden. Displacement of centrally occlusive thrombus to a more peripheral distribution in pulmonary arterial branches may decrease afterload in the right ventricle, increase clot surface area for faster dissolution, but may not address overall clot burden.

Unresolved thrombi can result in persistent perfusion defects and can produce residual symptoms of reduced functional status, persistent thrombi, limitations of cardiopulmonary function.

A recent meta-analysis showed catheter directed thrombolysis was associated with lower mortality but increased risk of bleeding when compared with anticoagulation alone. It was found to be decreased however when compared with systemic thrombolytics. [XVIII]

1.3.3 Surgical Intervention for PE

Several surgical treatment options are available for the management of PE. Historically, surgical pulmonary embolectomy has been indicated in patients who are hemodynamically unstable secondary to acute massive PE. Candidates for surgical embolectomy have failed or are not candidates for thrombolytic therapy. Surgical pulmonary embolectomy is also recommended for patients with persistent hemodynamic instability, or in patients with significant RV dysfunction that persists despite the use of fibrinolytic therapy.[XVII]

In another study, patients with high-risk PE were assigned to either thrombolytic therapy or pulmonary surgical embolectomy. Early and late mortality, systolic pulmonary artery pressure (sPAP), right ventricular diameter (RVD), and bleeding complications were evaluated. Seventy-eight patients were treated with thrombolytic therapy and 30 patients underwent surgery. The difference between pre-intervention and third-day post-intervention in terms of RVD and sPAP was significantly greater in patients under surgical embolectomy ($P < 0.001$). There was a significant decline in RVD and sPAP in both groups during follow-up ($P < 0.001$). Mortality rate in the surgical embolectomy group was lower than the thrombolytic group, although not significantly.[XIX] However, early surgical treatment was associated with fewer complications in comparison to thrombolytic therapy in this high-risk patient population.

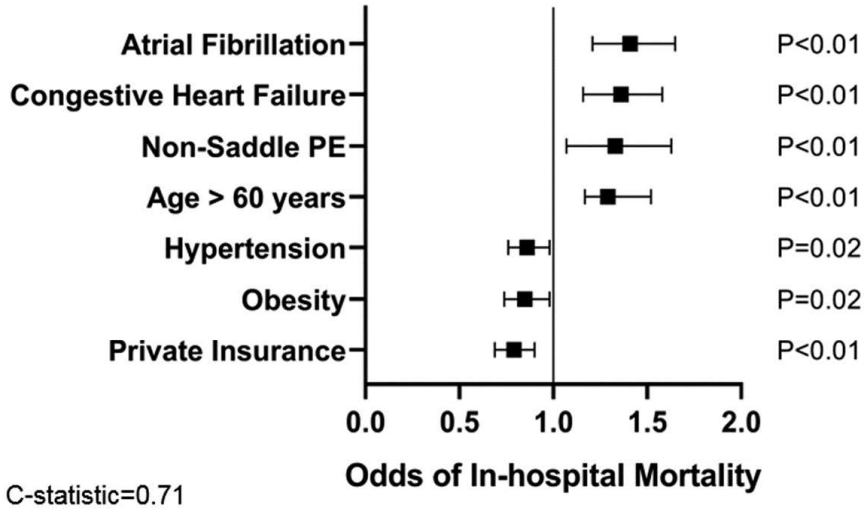


Figure 6: Predictors of in-hospital mortality among patients undergoing surgical embolectomy for acute pulmonary embolism (PE) in the National Inpatient Sample. Data are shown as the odds ratio (square) and 95% confidence interval (horizontal whiskers). [XVII]

In experienced centers, surgical embolectomy is considered to be a safe procedure with low mortality, providing improved postoperative right ventricular function and pulmonary pressure as well as improved long-term outcome. In a study of 37 consecutive cases, Edelman et al. demonstrated that elimination of a large portion of the clot burden could be lifesaving. They concluded that pulmonary embolectomy should be considered as an initial treatment strategy in patients with massive or sub-massive pulmonary embolus with a large burden of proximal clot. [XX]

However, surgical intervention for PE remains a highly invasive procedure that relies on cardiopulmonary bypass and is limited to specialists and centers with specific training and experience.

1.3.4 The Emerging Opportunity for Embolectomy Devices to Treat PE

There has been a renewed interest in catheter-based embolectomy as the primary means of treating PE.[XIX] The goal of treatment for high-risk PE is to rapidly reverse hemodynamic instability given the high mortality associated with this diagnosis. For intermediate risk PE, goals are to expedite symptom resolution and avert hemodynamic decompensation. The reasons for the therapeutic shift towards devices include:

1. Although medical reperfusion strategies have lowered morality rates in PE, survival has been slow to improve (*Figure 7*).

After 20 years, **mortality is still high** in PE patients

		1999 ICOPER[1]	2018 MGH PERT data[2]	2020 PERT Consortium data[3]
30-day	**Mortality** (High-Risk / Massive)	~51.0%	34.8%	25.9%
	Mortality (Intermediate-risk / Sub-massive	~11.0%	8.2%	6.1%
	Major Bleeding	10.5%*	11.5%	5%

* 90-day major bleeding rate

Figure 7: From Andrew Sharp, MD University Hospital of Wales, Cardiff.

The residual risks of bleeding and death associated with intermediate risk PE and medical reperfusion strategies combined with the advent of new endovascular tools to treat PE is changing the approach to patient management in the presence of acute PE.

2. Rapid reversal of hemodynamic instability contributes to better outcomes. Patients with sub-massive PE are typically managed conservatively with anticoagulation; however, the presence of RV dysfunction has been demonstrated to predict poor outcomes, including increased mortality. [XXI]

3. Large-bore systems (e.g., Inari Medical) have been sufficiently improved to provide better flexibility and access to the pulmonary artery anatomy.
    a. From April 2016 to October 2017, as part of a pivotal clinical study, Inari Medical (NASDQ NARI) enrolled 106 patients at 18 sites who were treated with their FlowTriever System, a large bore catheter system intended for the aspiration of large pulmonary artery clots. The authors reported a low complication rate (3.8%) and an average RV/LV ratio reduction of 25%.
    b. These data were followed by a second pivotal trial conducted by Penumbra (NASDQ PEN) similar in design to Inari Medical's trial. Penumbra's Lightning-12 systems demonstrated a similar safety profile to Inari's FlowTriever device, and a better improvement in RV/LV ratio of 43%.
4. Device intervention is associated with fewer in-hospital and ICU stays. [XXII]

1.4 Clinical Data Driving the Use of Embolectomy Devices to Treat PE

The use of aspiration catheters to retrieve life-threatening pulmonary emboli was first described by Greenfield and colleges in 1969.[XXIII] Following Greenfield's experience with a large-bore but relatively stiff catheter-based device to perform aspiration embolectomy, other groups attempted similar procedures.

Aspiration thrombectomy for PE remained largely a research interest and was not routinely used to treat massive or sub-massive PE due to a high complication rate. These patients, when possible, were referred to surgery.

Both Inari Medical and Penumbra recently published data from their pivotal studies demonstrating the effectiveness of aspiration embolectomy in high-risk PE patients. These studies, in combination with ongoing studies and registries, have established a role for aspiration thrombectomy in the high-risk segment for PE. The two pivotal studies demonstrated early success by reducing the RV/LV ratio which is a surrogate marker for RH strain. Other relevant studies are summarized in *Table 2*.

Table 2: Recent studies in catheter-based pulmonary embolectomy

Study		Design			P I C O * (Patients included, Intervention, Control, and Outcome)						Results
Year	**Study (Author)**	**Type**	**Sites+**	**Size (N)**	**Patients included**	**Age (yrs)**	**Female (%)**	**Intervention**	**Control**	**Outcome (Primary)**	**Based on Primary Outcome**
2023	FLASH Registry[XXIV] (Catalin) (INARI)	Obser.	50	800	Acute intermediate- and high-risk PE in a large real-world population.	61.2 ± 14.6	46	Percutaneous aspiration thrombectomy - *FlowTriever System* (Inari)	None	Composite of major adverse events (MAE)	MAE 1.8% mortality 0.3% at 48-hour follow-up and 0.8% at 30-day follow-up, with no device-related deaths.
2021	EXTRACT-PE[XXV] (Sista) (PEN)	Obser.	22	119	Acute intermediate-risk PE~ (symptomatic, normotensive, PE by CTA, RV/LV ratio >0.9)	59.8 ± 15	44.5	Percutaneous aspiration thrombectomy - *Indigo Aspiration System* (Penumbra)	None	Change in RV/LV ratio from baseline to 48hrs	0.43 (reduction of the RV/LV ratio at 48-hr); $p < 0.0001$. Major AEs[+]: 1.7% Major Bleeding: 1.7%
2019	FLARE[XXVI] (Tu) (INARI)	Obser.	18	116	Acute intermediate-risk PE (symptomatic, normotensive, PE by CTA, RV/LV ratio >0.9)	55.6 ± 13.7	46.2	Percutaneous aspiration thrombectomy - *FlowTriever System* (Inari)	None	Change in RV/LV ratio from baseline to 48hrs	0.38 (reduction of the RV/LV ratio at 48-hr); $p < 0.0001$. Major AEs: 3.8% Major Bleeding: 1.0%
2009	Meta-analysis[XXVII] (Kuo)	35 studies (6 Prosp, 29 Retro.)	Mult.	594	Acute high-risk PE	53	NR**	catheter-directed thrombolysis, and catheter embolectomy	None	Technical success: 86.5% Major procedural complication rate: 2.4% (see Analysis on subgroup reporting)	
2009	Rheolytic Thromb-ectomy[XXVIII] (Chechi)	Obser., retrospective	1	51	Acute- and intermediate-risk PE	66.7 ± 13.8	51	AngioJet rheolytic thrombectomy	None	Mult, incl all-cause in-hosp mortality	Death in hospital: 15.7% Major bleeding: 17.8% Renal failure: 24%

1.4.1 Limitations of Currently Approved Therapy

Most guidelines agree that the mainstay of treatment for massive and submassive PE is anticoagulation and that thrombolysis should be offered to unstable patients. However, for many patients the use of thrombolytic or anticoagulation may not be appropriate due to the associated risks of bleeding and the unpredictability of right heart decompensation.

The goal of a successful interventional procedure is to immediately reduce right heart afterload and prevent hemodynamic collapse safely and effectively. There is a strong clinical need to develop a reliable, rapid, percutaneous method of clot removal for the treatment of clinically significant acute PE. In patients with the presence of right heart strain, the need to rapidly unload the right heart may be particularly acute given that these patients may decompensate rapidly. Catheter-based embolectomy systems cannot exacerbate RV function by impinging on hemodynamic performance.

1.4.2 Potential Benefits of the Vertex Pulmonary Embolectomy System Therapy

The Vertex Pulmonary Embolectomy System is intended to be used in patients with acute PE with diagnostic evidence of right ventricular dysfunction who are symptomatic but hemodynamically stable. The potential benefits of thrombectomy using the Vertex Pulmonary Embolectomy System include:

- Minimally invasive, lytic-free, single-session treatment

- Atraumatic access to the pulmonary arteries
- Enhanced intraprocedural control and navigation
- Efficient procedure completion

Minimally invasive, single-session, lytic-free treatment: Relative to surgical embolectomy, endovascular thrombectomy is a much less invasive procedure involving significantly less morbidity associated with access. The system allows for atraumatic access to the pulmonary arteries in order to aspirate thrombi. Compared to systemic or catheter-directed thrombolysis, thrombectomy using the Vertex Pulmonary Embolectomy System without lytics may reduce the systemic bleeding and intracranial hemorrhage risks associated with lytic-based treatments. Relative to catheter-directed thrombolysis, which requires two separate procedures to place and subsequently remove an infusion catheter with extensive patient monitoring in between, thrombectomy using the Vertex Pulmonary Embolectomy System carries the benefit of simplifying the treatment to one procedure for the patient while potentially reducing the resource burden associated with intensively monitoring the patient for an extended period.

Enhanced intraprocedural control and navigation: The Vertex Pulmonary Embolectomy System is designed to provide the procedural operator with a superior level of control while accessing the pulmonary arteries and thrombi. By creating a stable pathway into the pulmonary arteries that can be directed towards the vessels of interest, the Vertex Pulmonary Embolectomy System may reduce the likelihood of catheter prolapse into the right ventricle, as well as reducing inadvertent selection of non-target vessels. Additionally, this stabilization may provide a more precise and reliable means of accessing vessels that would be challenging to access with other catheter systems. SPIRARE I will gather various procedural data points related to vessel access, procedure time, ancillary device usage, and fluoroscopy and contrast utilization as surrogate markers to characterize this anticipated benefit.

Efficient procedure completion: A secondary benefit to enhanced intraprocedural control and navigation is the thorough reduction of clot burden and relieving right heart afterload, over an anticipated short procedure duration. To characterize the completeness of reducing both clot reduction and right heart afterload, SPIRARE I will gather secondary endpoint data on the Modified Miller Index reduction and various hemodynamic parameters as well as primary endpoint data on the RV/LV ratio reduction.

Use of the Vertex Catheter is anticipated to improve the efficiency of large-bore catheter aspiration for PE. Access to both the left and right pulmonary arteries is more feasible without having to exchange guidewires and losing access because the Vertex Catheter will maintain its fixed position. The ability to retain position within the pulmonary arteries may also reduce the total radiation exposure and contrast load for an equivalent procedure. SPIRARE I will collect data on radiation exposure and contrast utilization as comparative data.

Given that pulmonary embolism is a life-threatening disease with rapid progression to heart failure if not treated quickly, the ability to perform aspiration and quickly remove clots could be lifesaving. This treatment has the potential to benefit patients by reducing the hospital stay and need for intensive care. Beyond the potential benefits of the individual patient treated with the Vertex Pulmonary Embolectomy System, evaluating the safety, feasibility, and efficacy profile of pulmonary embolism treatment with the Vertex Pulmonary Embolectomy System can also contribute to the knowledge base of treatment options for PE patients using endovascular catheter-based approaches. Studies such as this can add important information to the collective knowledge on patient selection for the various catheter-directed aspiration thrombectomy techniques. Based on scientific literature, expert panels are publishing algorithms for the treatment of acute pulmonary embolism patients; this study evaluating Vertex Pulmonary Embolectomy System treatment could provide a significant refinement to those algorithms. Patients with acute PE who continue to be at risk of bleeding events despite the standard of care and optimal medical management may potentially benefit from this treatment. The potential benefits of pulmonary embolectomy treatment in this patient population are immediate relief from disabling symptoms of PE, recovery in heart rate, blood pressure, hemodynamics, and reduced right heart strain assessed by a change in RV/LV ratio.

1.4.3 Pre-Clinical Data

Neptune Medical has conducted sixteen (16) non-GLP studies animal studies in healthy animals from 24 June 2020 to 01 December 2023 to simulate pulmonary artery interventions using the VERTEX Pulmonary Embolectomy system. Of the 16 animal labs, 15 labs were conducted with porcine models, and one lab was conducted with an ovine model. The primary objective of these labs was to evaluate the VERTEX Pulmonary Embolectomy System performance in a healthy swine model and to gather physician input on product performance. The results from these

labs and feedback from physicians have built a body of pre-clinical data of the VERTEX Pulmonary Embolectomy System for pulmonary artery interventions.

An early animal study (ovine model) conducted on 24 June 2020, evaluated an early prototype of the Vertex catheter. The main goal of the study was to test proof of concept of the Vertex catheter (26F and 16F) by navigating them through vasculature and documenting results. One of each size device was used, and devices were used within one animal for no longer than an hour. Areas of improvement identified in this study were the need for longer length catheters, difficulty inserting/removing the device from vasculature, adjusting the fit between the guidewire (GW) and Vertex tip, coating the outer diameter of the outer coil wound tube (OCWT), and ensuring the device can adequately withstand compressive loads.

The second acute animal study (porcine model) was performed from 23-24 July 2020 to assess trackability and stability of Vertex. The main goals for this study were to characterize Vertex trackability, characterize Vertex fixation compared to a conventional catheter, and assess Vertex shape retention when fixed. Vertex showed a difference in motion between the fixed and flexible states, specifically in its ability to retain its shape as accessory devices were being inserted through Vertex. On the first day, two different sized Vertex Catheters were used in one animal for 2.5 hours. On the second day, two different sized Vertex Catheters were used in another animal for no longer than an hour. The introducer sheaths utilized were not large enough to accommodate the Vertex catheters, causing the catheters to collapse under compressive forces, preventing further testing. Additionally, excessive friction on the inner surface of Vertex prevented anything from being advanced through the catheter. The need for improvements to the inner coil wound tube (ICWT) coating and catheter crush resistance were identified. Following this study, the 22F Vertex size was no longer pursued as it was determined not necessary in clinical use.

The third animal study on 19 July 2021 and fourth study on 02 November 2021 tested and analyzed Vertex and Meridian design changes respectively. One animal was used in each lab. Both labs used two Vertex Catheters and two Meridian Catheters, and these remained in the animal for an estimated 2.5 hours. Physician feedback was positive on the control, depth of fixation, and ease of navigability provided by Vertex. Potential improvements mentioned were different-colored lines (one for flush and one for fixation), changing aspiration tubing angle, developing a visual element to the clot capture system, and improving overall durability of the Meridian Catheter. Vertex Catheter design updates included longer length catheters, blunt-tipped obturators, and in-house coated devices, all of which performed with no issues. For the Meridian Catheter, physician feedback for future improvements included a more user-friendly hemostatic seal design and an obturator to be provided.

A fifth study took place on 14 March 2022 with one animal and assessed the placement, navigability, and utility of the Vertex PES to access pulmonary arteries and remove pulmonary emboli. Two Vertex Catheters, four Meridian Catheters, and one Extraction Set were used in the animal for 3.5 hours. The system was evaluated based on its ability to remove blood clots safely, effectively, and without excessive blood loss. An animal clot model was evaluated as a blood clot simulant. Overall, Vertex performed as intended and conformed its shape to the anatomy. Positive feedback on Meridian focused on trackability and torqueability; improvement suggestions focused on the Meridian distal end being too floppy, which may have been exacerbated by the abruptness of the tip transition.

A sixth lab conducted on 09 May 2022 and seventh on 29 August 2022 assessed improvements made to the Vertex and Meridian devices and to test new iterations of the clot capture system and ergonomic improvements. One animal was used in each lab. In the May 2022 lab, five Vertex Catheters, three Meridian Catheters and an Extraction Set were used over a 4.5-hour animal lab. In the following lab, four Vertex Catheters, nine Meridian Catheters and two Extraction Sets were used over an 8-hour animal lab. Goals for Vertex were to assess the benefit of fixation, evaluate device performance during an embolectomy procedure, and monitor hemodynamic changes. Vertex performed as intended. Positive feedback was received on how Vertex conformed to anatomy. A Vertex catheter remained in the subject for the lab (around 2.5 hours) without significant hemodynamic impact, showing minimal intraprocedural stress on the heart. The overall user feedback received was positive, particularly on the stability of Vertex and the trackability of Meridian through Vertex. The clot capture system performed as intended. Feedback and observations suggesting areas for future improvement included the preparation process of the Meridian Extraction Set distal connector, improving the ability of the clot capture filter to trap clot, and the use of the hemostatic valve levers to minimize blood loss when using Vertex and Meridian devices together.

An eighth lab conducted on 02 December 2022 with one animal aided design selection for the Meridian Catheter distal tip and confirmed the design selection of the Extraction Set. Three Vertex Catheters, six Meridian Catheters

and one Extraction Set were used in this 6-hour lab. A ninth animal lab conducted on 09 December 2022 with one animal had physicians compare multiple Meridian Catheter designs in a head-to-head navigability assessment to drive design selection. Three Vertex Catheters, six Meridian Catheters, and one Extraction Set were used in this 6.5-hour lab. The results of the lab proved that a short tip outperformed a long tip design and that there were no significant differences in performance when comparing between two stiffness zones and three stiffness zones. Positive feedback was given regarding the softness of the Meridian obturator and the trackability and fixation of Vertex.

A tenth lab conducted over the course of two days on 09 May 2023 and 10 May 2023 assessed the hemodynamic disturbance caused by different PE devices (Neptune's and commercially available devices) within three healthy porcine models. Four setups were tested through three trials each: 18F Vertex with 12F Meridian, 26F Vertex with 20F Meridian, Inari T24 with Inari T20 Curve, and two 8F Guide Catheters inserted simultaneously. The latter setup was used to simulate an EKOS endovascular procedure set-up, a common PE procedure setup. Devices were tested in two of the animals on the first day, and the lab lasted roughly 7.5 hours. On the second day the same devices were tested in a third animal, and the lab lasted roughly 5.5 hours. The following hemodynamic data points were collected: LV pressure, PA pressure, flow rate of blood through the carotid artery and heart rate. Data was compiled and analyzed. The Inari setup and double Guide Catheter setup performed the worst compared to baseline hemodynamic data, with heart rate increases of around 20% above baseline and flow decreases of 8-14% for both setups. In comparison, the two Neptune setups showed a heart rate change of 1-5% from baseline and a flow increase of 1.5-7.9%.

Six labs conducted from 17 March 2023 - 01 December 2023 served as training for the Scientific Advisory Board and new users. One animal was used in each lab, and each lab lasted 4-8 hours depending on the number of physicians being trained. At minimum, each user was trained using a 26 Fr Vertex Catheter, a 20 Fr Meridian Catheter and an Extraction Set. Additional catheters were used as needed. These labs also helped the R&D team to conduct additional testing for various needs. This included visualizing vasculature and the straightening caused by Vertex, as well as characterizing the effects of inadvertently withdrawing the Vertex catheter while fixed. All physicians gave positive feedback on the performance of the catheters, particularly on the ability of the Vertex to navigate into the Pulmonary Arteries over a flexible workhorse guidewire. Similar to previous animal labs, hemodynamics remained stable throughout the procedure including when withdrawing the fixed 18F and 26F Vertex Catheters. Overall, these studies confirmed past results that the VERTEX Pulmonary Embolectomy System is reliable and able to achieve pulmonary embolectomy in a swine model with a low adverse event rate and positive operator feedback.

1.4.4 In-Vitro Studies

Neptune Medical has conducted two in vitro labs using the VERTEX Pulmonary Embolectomy System from June 2021 to June 2022. The in vitro labs were performed using a silicone model to simulate the venous, right heart, and pulmonary artery anatomy of a human patient. The primary objectives of these studies were to gain physician feedback on the system use, stability, and device design, understand procedural preferences in Vertex placement, and to quantify advancement and retraction forces of the Vertex Catheter and obturator. Feedback was also gained on guidewire compatibility, procedural ease of use, and ergonomics.

In the first lab conducted on 14 June 2021, Vertex was tracked through the silicone model to simulate pulmonary artery access, and the physicians gave positive feedback on device performance. Notable suggestions for design improvement were developing a means to provide visual feedback that the clot has been captured when aspirating, developing a soft and small tip for Vertex, and creating a system that gives ergonomic and precise control of the Meridian Catheter and guidewire.

In the second lab conducted on 28 June 2022, a mock catheter lab was set up to allow physicians to engage with Vertex Pulmonary Embolectomy System in an in vitro simulated use environment. The physicians used the Vertex Pulmonary Embolectomy System to remove clot from the model. Physician feedback centered around ergonomics of the extraction handle and distal connector, as well as guidewire compatibility. Overall physician feedback was positive on the design direction of the VERTEX Pulmonary Embolectomy system.

2. STUDY DESIGN

The study is a prospective, single-arm, multicenter study to evaluate the safety and effectiveness of the Vertex Pulmonary Embolectomy System in patients eligible for endovascular treatment of acute pulmonary embolism (PE) through the removal of clinically significant clot burden by means of aspiration.

The Vertex Pulmonary Embolectomy System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

Acute PE is defined as having clinical signs and symptoms for 14 days or less with an RV/LV ratio of >0.9 on CT angiography and systolic BP ≥90 mmHg.

2.1 Number of Sites and Subjects

A maximum of 2 sites will participate in the Study. The total population for the Study is expected to be a maximum of 10 Subjects.

2.2 Numbering of Study Subjects

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

2.3 Study Duration

The Subjects who meet the inclusion/exclusion criteria will be enrolled in the study on an ITT basis. The enrollment period is expected to last over a period of approximately 6 months. Each study Subject will actively participate for up to 30 days (±3 days) following treatment. Study participation includes screening, treatment, 48-hour follow-up or discharge, and 30-day follow-up. The screening through discharge visits will take place at the treating hospital. Subjects will be requested to complete a visit with research staff for 30-day follow-up.

2.4 Study Population

This study will treat eligible patients with symptoms of acute PE for ≤ 14 days with CTA evidence of filling defect in one main or interlobar pulmonary artery with RV dysfunction as defined by RV/LV Ratio > 0.9 on CTA scan, as determined by investigator.

2.5 Subject Enrollment Criteria

Only patients who meet all inclusion criteria and none of the exclusion criteria are considered eligible for enrollment. Written informed consent will be obtained prior to non-standard of care study-specific procedures. The decision to use the Vertex Pulmonary Embolectomy System will occur after informed consent has been obtained and prior to the procedure.

2.6 Enrollment

Patients that fit the inclusion/exclusion criteria and provide written informed consent to participate in the study will be enrolled on intent to treat basis (ITT). An enrolled patient is defined as all patients who met the inclusion/exclusion criteria and who provide written informed consent, meet the inclusion/exclusion criteria, and in whom the Vertex Catheter is introduced past the pulmonic valve. The study will continue to enroll subjects until there are 10 (ten) enrolled and treated subjects.

2.7 Informed Consent

The nature of the planned treatment and objectives of the SPIRARE I Clinical Study will be thoroughly explained to the patient. Details of the Study should include, but are not limited to, the following items:

- Purpose of the study
- Potential risks/benefits for participation
- Need to return to clinic for follow-up visit
- Contact information to ask questions or voice concerns

Patients will be informed by the Investigator that their participation is voluntary and that they may withdraw consent at any time, for any reason without penalty or prejudice to his/her future medical care. Patients will be informed about alternative treatments which are available and if they refuse to participate that such refusal will not prejudice future treatment.

The patient will be given sufficient time to read the informed consent form and to ask additional questions. The consent form must be appropriately recorded by means of the patient's and the Investigator's dated signature. The patient shall date the ICF personally. Two copies of the ICF will be signed by the Investigator and the patient. The copy is retained by the Investigator and filed in the ISF as part of the study records and one original is provided to the patients; a copy of the ICF will be filed in the patient's medical records. The process of consenting the patient to the study will be recorded in the patient charts.

Patients who are unable to comprehend the information provided will be excluded from study participation.

2.8 Subject Screening

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

Medical Screen failures will be defined as follows

- **Screen Failure:** Any screened patient who signs the ICF but does not meet all the inclusion or meets any of the exclusion criteria and also such who signed ICF but for whom the Vertex catheter was not introduced and past the pulmonic valve. All patients screened will be documented on the Screening/Enrollment Log. The reason for screen failure will be captured on the log and in the screening/enrollment section of the database. For operative screen failures please refer to section 5.1. for further details.

For Procedural screen failure definitions please refer to ***section 5.1***

2.9 Inclusion Criteria

Subjects must meet all following general inclusion criteria:

1. Age ≥ 18 years < 80 years
2. Acute onset of symptoms < 14 days consistent with the presence of pulmonary embolism.
3. CTA evidence (site determined) of proximal PE (filling defect in at least one main or interlobar pulmonary artery)
4. RV/LV ratio of > 0.9 on CTA as assessed by investigator (site determined).
5. Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with fluids)
6. Subject is willing and able to provide written informed consent prior to receiving any non-standard of care clinical investigation plan specific procedures
7. Subject is willing and able to comply with all clinical investigation plan required follow-up visits

2.10 Exclusion Criteria

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

1. Thrombolytic use within 30 days of baseline CTA
2. Pulmonary hypertension with peak pulmonary artery pressure > 70 mmHg by right heart catheterization (site determined)
3. Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg
4. Unstable heart rate > 130 beats per minute prior to procedure
5. FiO2 requirement > 40% or > 6 LPM to keep oxygen saturation > 90%
6. Hematocrit < 28%
7. Platelets < 100,000/µL
8. Serum baseline creatinine > 1.8 mg/dL
9. International normalized ratio (INR) > 3
10. Major trauma injury severity score (ISS) > 15 within the past 14 days
11. Presence of intracardiac lead in the right ventricle or right atrium placed <180 days prior to the index procedure
12. Cardiovascular or pulmonary surgery within last 30 days
13. Actively progressing cancer requiring chemotherapy

14. Known bleeding diathesis or coagulation disorder
15. Left bundle branch block
16. History of severe or chronic pulmonary arterial hypertension
17. History of chronic left heart disease with left ventricular ejection fraction ≤ 30%
18. History of decompensated heart failure
19. Patients on extracorporeal membrane oxygenation (ECMO)
20. History of underlying lung disease that is oxygen dependent
21. History of chest irradiation
22. History of heparin-induced thrombocytopenia (HIT)
23. Contraindication to systemic or therapeutic doses of heparin or anticoagulants
24. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated
25. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for mechanical thrombectomy intervention
26. Life expectancy of < 365 days, as determined by Investigator
27. Female who is pregnant or nursing
28. Current participation in another investigational drug or device treatment study
29. Inability to lay flat for procedure
30. Known presence of right-to-left cardiac shunt
31. History of Hemorrhagic or Ischemic Stroke, including Transient Ischemic Attack, within last 90 days
32. Current or history of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) diagnosis

3. DEVICE DESCRIPTION

3.1 Vertex Pulmonary Embolectomy System

The investigational device for this study is the Vertex Pulmonary Embolectomy System

The Vertex Pulmonary Embolectomy System is comprised of several components:

- Vertex Catheter
- Meridian Catheter
- Meridian Extraction Set

The Vertex Catheter is a single use catheter with variable stiffness consisting of a highly flexible multilayer shaft, a **hemostatic valve,** and a twist-style locking **obturator** as shown in **Figure 8**. The inner surface of the shaft has a hydrophilic coating and the outer surface has a hydrophobic coating. The handle of the Vertex Catheter includes a **flush line**, a **fixation line** for fixation control, and the hemostatic valve. The Vertex shaft and obturator bodies are radiopaque. The distal tip of the catheter has a non-radiopaque region that is no more than 5 mm in length. The Vertex Catheter is intended to be introduced over a guidewire through compatible introducer sheaths. The Meridian Catheter is a single use catheter with a twist-style locking **obturator** and a **hemostatic valve**. The handle of the Meridian Catheter includes a **flush line** and the hemostatic valve. The Meridian shaft and obturator bodies are radiopaque. The Meridian Catheter is intended to be introduced through the Vertex Catheter and may be advanced over a guidewire. As needed, the Vertex and Meridian Catheters may be used with a commercially available vacuum pump connected via the Meridian Extraction Set to aspirate thrombi. The Meridian Extraction Set consists of a **distal connector**, a **proximal connector**, an **extraction handle**, and a **clot capture as shown in Figure 9 and 10**.

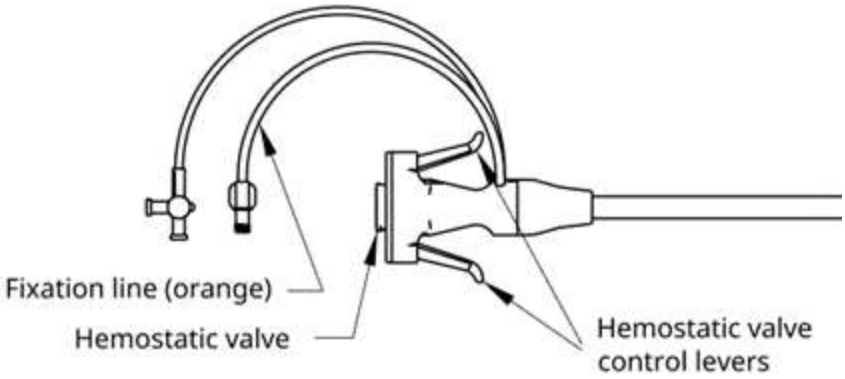


Figure 8: Vertex Catheter Handle Diagram

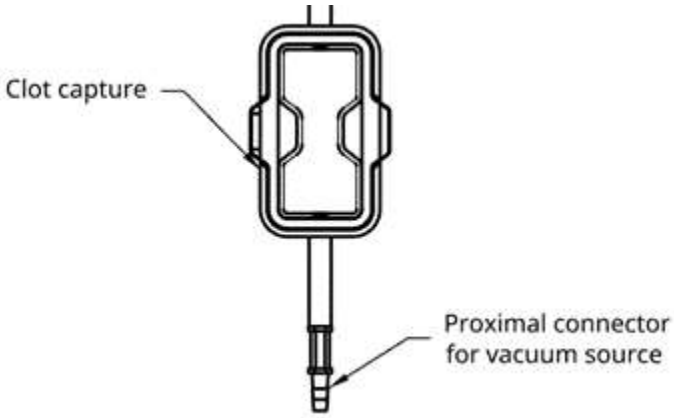


Figure 9: Extraction Set Clot Capture and Proximal Connector

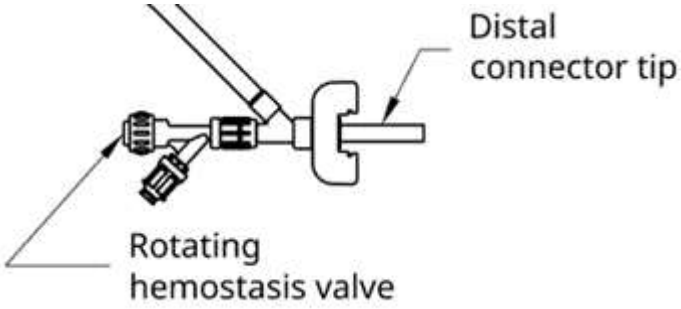


Figure 10: Extraction Set Distal Components

3.2 Indications for Use

The Vertex Pulmonary Embolectomy 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 Vertex Pulmonary Embolectomy System is intended for use in the peripheral vasculature and for the treatment of pulmonary embolism.

3.3 System Components

The Vertex Pulmonary Embolectomy System is supplied sterile and non-pyrogenic. The Vertex Pulmonary Embolectomy System is sterilized with ethylene oxide gas (EO). Device is intended for single use only and is not intended for re-sterilization or reuse. Please see table 3 for a list of contents on the system package.

Table 3: Vertex Pulmonary Embolectomy System Package Description

Vertex Catheter	Meridian Catheter	Meridian Extraction Set
• Vertex Catheter • Compatible Obturator	• Meridian Catheter • Compatible Obturator	• Extraction Set • Clot Capture Tray (3) • Clot Capture Lid (2)

The Vertex Catheter is introduced into the pulmonary arteries in a relaxed state using standard techniques over a guidewire through a compatible introducer sheath. When desired, the Vertex Catheter can be fixed in place by attaching an insufflator to the fixation line and pressurizing to a maximum of 6 ATM. Contrast may be injected through the Vertex or Meridian Catheters to aid in fluoroscopic visualization during the procedure. The Vertex Catheter may be relaxed and repositioned by de-pressurizing the insufflator. After aspiration is complete, the Vertex Catheter is relaxed, and all devices are removed from the patient.

3.4 Required Accessories (not included in package)

1. Compatible introducer sheath
2. 0.035” (0.89mm) guidewire
3. Inflation device or insufflator with a locking mechanism. Must have a minimum pressure rating of 6 ATM (608 kPa) and a minimum volume of 20 cc.
4. Luer lock syringe
5. Sterile saline

Commercially available vacuum pump. Must supply a minimum vacuum of -650 mmHg and a minimum flow rate of 40 L/min.

4. REGULATORY STATUS

The device is considered investigational and has not been approved for use in the European Union unless as part of a clinical study.

4.1 Device Label

The device to be used as part of this study is considered investigational. It has not been approved by any regulatory authority. It is required to be used per clinical investigation plan and as specified in the Instructions for Use document. The investigational devices will be identified with additional labeling indicating that device is dedicated exclusively for Clinical Investigation.

4.2 Release to Investigators

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

All investigational devices will be stored in a secure location, segregated from any commercial inventory to minimize the possibility of a study device being used in a non-study patient. Study devices will be labeled “Exclusively for Clinical Investigation”.

All unused investigational devices will be returned to Neptune Medical Inc at the end of the study.

5. STUDY PROCEDURE

Once all inclusion/exclusion criteria have been satisfied, including imaging assessments, the subject will proceed with the thrombectomy procedure using the Vertex Pulmonary Embolectomy System.

The suggested procedural steps for the use of the Vertex Pulmonary Embolectomy System are listed below. Refer to the study specific IFU and IB for more information on the appropriate use of the device for this Study. The Vertex Pulmonary Embolectomy System must be the only device used for pulmonary artery thrombectomy; additional adjunctive drugs may be used at the discretion of the Investigator. A Neptune Medical Inc representative will be present during the thrombectomy procedure.

NOTE: Hematocrit requirement (< 28%) must be confirmed prior to index procedure. Administer IV sedation or local anesthesia, as appropriate, to assure subject comfort and safety.

- Administer/continue to administer anticoagulation medications per standard institutional guidelines.
- Prepare Vertex Pulmonary Embolectomy System for use in accordance with IFU and IB.
- Access target area via femoral vein per standard institutional guidelines for thrombectomy procedures using a compatible introducer sheath (e.g., Gore DrySeal Flex Introducer Sheath).
- Obtain invasive pulmonary artery systolic and mean pressure (pre-procedure)
- Check hemoglobin at time of PA saturation
- Insert Vertex Catheter over compatible guidewire and through introducer sheath to desired location under fluoroscopic guidance.
- Fix Vertex Catheter in place by pressurizing insufflator to a maximum of 6 atm. If Vertex Catheter needs to be repositioned at any point, relax catheter by de-pressurizing insufflator prior to moving.
- Insert Meridian Catheter through Vertex Catheter to desired location under fluoroscopic guidance.
- At any point during procedure if aspiration is desired, remove accessories if needed and connect Extraction Set distal connector to desired catheter handle. With attached vacuum pump turned on, pulse extraction handle as needed to aspirate.
- If visualization or manipulation of aspirated thrombi is desired, evacuate residual blood from clot capture.
- After aspiration is complete, remove all devices from subject.
- A final angiogram will be performed when the procedure is complete.
- Obtain invasive pulmonary artery systolic and mean pressure (post-procedure).
- After removal of the Vertex Pulmonary Embolectomy System and the guidewire, continue to manage subject as medically appropriate.
- Complete the procedure per standard institutional guidelines for pulmonary artery thrombectomy procedures and transfer the subject to ICU (if appropriate) or post-surgical ward to monitor subject safety according to institutional guidelines.
- Continue to monitor for vital signs, oxygenation, and new symptoms.
- For symptomatic residual clot, distal embolization, or new PE, continue to treat with anticoagulation.
- Record adverse events/device deficiencies and technical complications as applicable.
- Post-procedure, the Investigator will review all images, clinically assessing the PE status and looking for evidence of vessel injury (perforation/dissection).
- Devices should be disposed of in accordance with applicable local regulations and site procedures following use.

The thrombectomy procedure using the Vertex Pulmonary Embolectomy System shall be aborted if the following occur in the opinion of the Investigator:

- Hemodynamic collapse
- Signs of vascular rupture

5.1 Procedural Screen Failure

5.1.1 Access Failures

There may be cases where the Vertex Pulmonary Embolectomy System is not used due to access failure. Access failure is defined as:

1) the guidewire cannot be introduced,

2) or vessel spasm precludes continuing the procedure.

If an adverse event occurs prior to discharge, subject will be followed for safety through discharge. A study exit form (CRF) is required for these Subjects.

5.1.2 Operative Screen Failures
The following subjects are considered operative failures:

- Any eligible patient in whom the Vertex Catheter is not able to be introduced into the pulmonary artery for any reason.
- Until any point prior to the introduction of the Vertex Pulmonary Embolectomy System, the procedure may be converted to another therapeutic treatment or discontinued without the patient receiving any investigational treatment.

No further information will be collected on this patient; a study exit form (CRF) is required for all these patients. Any patient that experiences an adverse event after venous puncture but in whom the Vertex Catheter is not inserted will be monitored through discharge for safety and information about AEs will be collected in CRF, if applicable.

5.1.3 Intent-To-Treat (ITT)
The Intent-To-Treat (ITT) population is defined as all enrolled patients who met the inclusion/exclusion criteria and who provide written informed consent, and in whom the Vertex Catheter is introduced past the pulmonic valve; when Vertex Catheter is introduced past the pulmonic valve, and in whom the Vertex Pulmonary Embolectomy System is not able to access a pulmonary embolus and will be monitored per clinical investigation plan until the end of the required follow up period of 30 days.

5.2 Adjunctive Treatment

Any use of thrombolytics during the procedure and up to 48-hours post-procedure will be considered a clinical investigation plan deviation and a treatment failure. The administration of thrombolytics to treat clinical deterioration will not be considered a clinical investigation plan deviation.

Adjunctive treatments will be considered as a clinical investigation plan deviation unless used to treat clinical deterioration. These adjunctive treatments will be recorded on the CRF.

Any use of adjunctive treatments for the purpose of reducing clot burden in the pulmonary artery (intra-procedure and up to 48 hours post procedure) will be considered a treatment failure.

6. STUDY OBJECTIVES

The Vertex Pulmonary Embolectomy System is a catheter-based mechanical thrombectomy device intended for use in the peripheral vasculature and for the treatment of pulmonary embolism. The Vertex Pulmonary Embolectomy System is designed to mechanically remove emboli and restore blood flow through the pulmonary arteries in patients experiencing acute PE.

The primary study objective is to evaluate the safety and effectiveness of the Vertex Pulmonary Embolectomy System for use in the removal of emboli in the treatment of acute intermediate risk pulmonary embolism.

6.1 Primary Endpoint - Safety

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

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

6.2 Secondary Endpoint - Safety
The study's secondary safety endpoints are:

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

**Adverse Events judged as possibly related, probably related or with causal relationship to Vertex Pulmonary Embolectomy System will be considered device-related.*

6.3 Primary Endpoint – Effectiveness
The study's primary effectiveness endpoint is the reduction in RV/LV ratio from baseline to 48 hours (± 8 hours or discharge, whichever occurs first) as assessed by Computed Tomography Angiography (CTA) and confirmed by qualified core laboratory.

6.4 Secondary Endpoint – Effectiveness

- Change in modified Miller Index Score between baseline and 48 hrs post procedure as assessed by CTA (core lab assessed)
- Procedural change in cardiac index
- Length of stay in the ICU associated with the index procedure
- Length of total hospital stay and post-index-procedure hospital stay
- Procedural reduction in pulmonary artery mean and systolic pressure
- Procedural reduction in Total Pulmonary Vascular Resistance
- Change in Dyspnea severity by mMRC score [Time Frame: at the 48-hour and 1-month visits]
- Change in Dyspnea severity by mMRC score [Time Frame: at the 48-hour and 1-month visits]

7. ENDPOINT DEFINITIONS

7.1 Device-Related Death
Device-related death is defined as any death directly related to the device not performing as expected. Device-related death could include death from:

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

7.2 Bleeding
The Bleeding Academic Research Consortium (BARC) bleeding definitions will be used in this study.

Type 0: no bleeding
Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3
Type 3a
Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding
Type 3b
Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents
Type 3c
Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
†Cell saver products are not counted.

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

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

7.2.2 Major Bleeding
The Bleeding Academic Research Consortium (BARC) Classification System Definitions will be used for this study, level 3b, 3c, 5a and 5b.

- 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents
- 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision.
- 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

†Overt bleeding was determined by the site investigator to be bleeding visible to the eye or detectable on an imaging study

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

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

Recurrence in this study is defined as a symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure. Based on the International Society on Thrombosis and Hemostasis (ISTH) guidance, "successful" means a clear clinical improvement of Subject symptoms and signs.[43] Symptomatic recurrent PE will be confirmed by CTA. "Symptomatic" means clinical symptoms and/or signs such as chest pains, dyspnea, hemoptysis, palpitations, or tachycardia.

7.4 Clinical Deterioration
Clinical deterioration is defined by hemodynamic or respiratory worsening and will include treatment-related events, such as;

- Unplanned endotracheal intubation,
- Unexpected requirement for mechanical ventilation,
- Arterial hypotension (>1 hour or requiring vasopressors) or shock,
- Cardiopulmonary resuscitation,
- Persistent worsening in oxygenation, and
- Emergency surgical embolectomy.

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

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

8. STUDY PROCEDURES

8.1 Overview of Study Flow
Subjects presenting with acute PE will be evaluated by the Investigator, in accordance with their institutional practices, to establish an appropriate treatment plan based on the patient's medical condition and available diagnostic screening procedures prior to recruitment in the SPIRARE I Clinical Study. Informed Consent will be obtained prior to proceeding to the treatment suite. A representative overview of the study flow is shown in Figure 11.

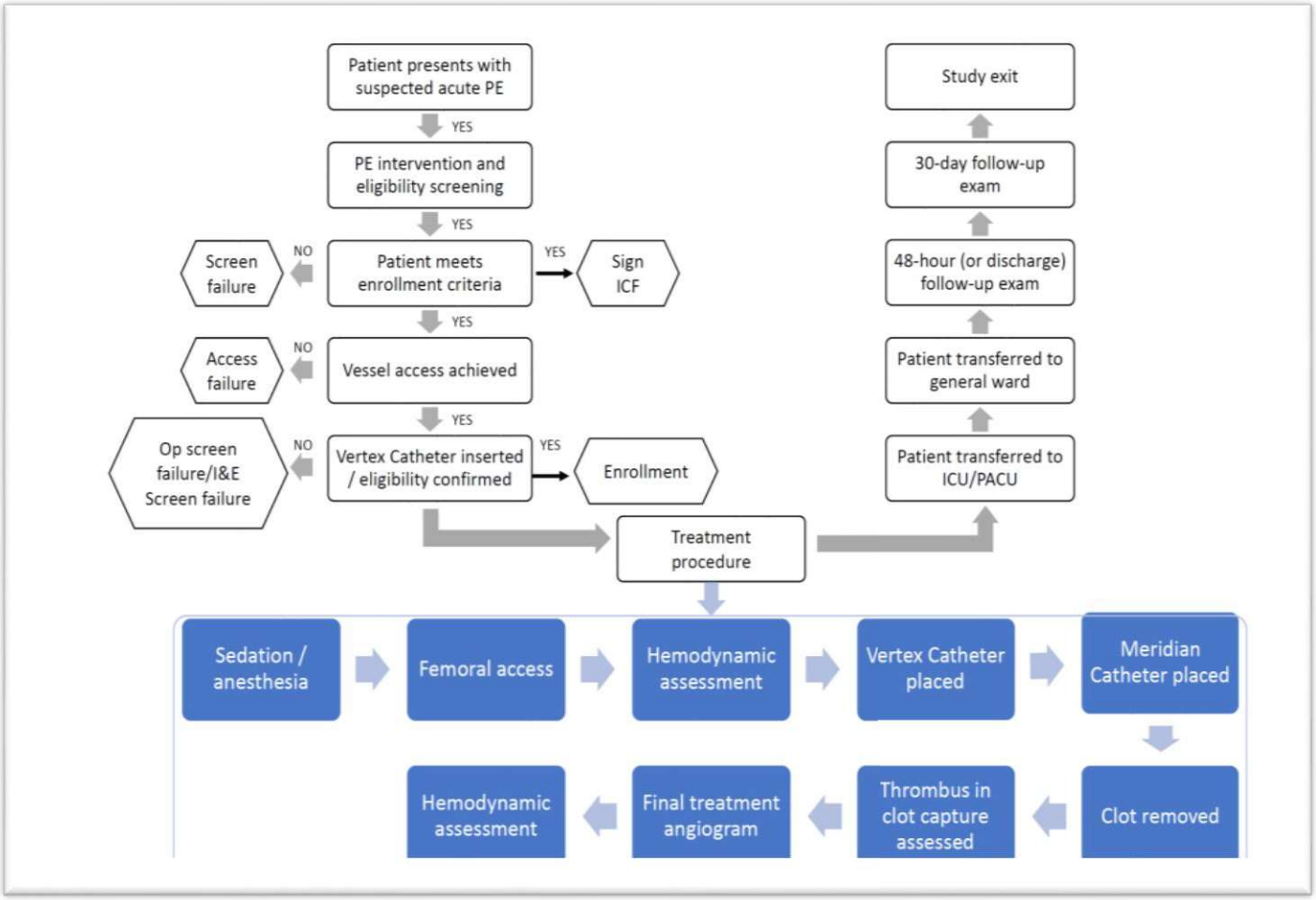


Figure 11: Representative Study Flow from Screening to Discharge

9. STUDY VISITS

The table of study procedures and follow up visits is presented below in Table 4. All scheduled exams listed in Table 4 must be performed at the designated time point and the results documented in the EDC. The following table details the clinical and laboratory procedures required from Screening through the 30-day follow-up visit. The majority of these tests and procedures are considered standard of care for all patients under treatment of clinically significant PE.

Table 4: Schedule of Assessments

Assessment/Method	Screening/ Baseline	Procedure Day 0	Post-Procedure	48 (± 8) Hours* Follow-up Day 2	30 (± 3) Days Follow-up Day 30~ (Clinic or Phone visit)
Informed Consent	X				
Demographics	X				
Medical/Surgical History	X				
Physical Examination/Vitals	X	X+	X	X	
Blood Labs (Hematocrit, Platelets, Sr creatinine, INR, BNP, Troponin, Serum lactate)	X		X		
Room Air SpO2	X			X	
mMRC dyspnea score	X			X	X
CT Angiography	X			X	
Echocardiogram	X			X	
Right heart Catheterization (Invasive Hemodynamic Assessment)		X	X		
Pulmonary Aspiration Thrombectomy		X			
Pregnancy Test	X=				
Major Trauma Injury Severity Score (ISS),	X]				
Concomitant Medications#	X		X	X	X
Assessment of AEs/DDs	X^	X	X	X	X

*or discharge; whichever occurs first
= Only for females of childbearing age only who are not surgically sterilized
] As applicable for subjects suspected of enduring trauma
+ Vitals only
#Relevant concomitant medications to be documented for the study are anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study
~ 30-day visit can be completed onsite or via televisit
^ Any adverse event/device deficiency occurring since subject signed ICF will be recorded in the subject's CRF.
Note: Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an adverse event further in the study. However, if that subject's condition deteriorates at any time during the study, it will be recorded as an AE.

9.1 Screening and Baseline Assessments
The following baseline assessments will be conducted at screening/baseline. Since most assessments are part of standard of care for acute PE, informed consent is not required prior to conducting these assessments.

1. Inclusion/Exclusion criteria
2. Demographics
3. Medical/Surgical History- Relevant medical and surgical history will be collected from all consented Subjects at the time of consent or prior to enrollment.
4. Physical Exam and Vital signs
5. CT Angiography
6. Echocardiogram
7. Right Heart Catheterization (Invasive Hemodynamic Assessment)
8. Laboratory - Blood tests are required for Subject inclusion/exclusion criteria evaluation. Study informed consent is not required in order to obtain blood tests as the required tests are a standard of care in assessing PE treatment. The following labs must be available to assess Subject eligibility for the study:
    a. Hematocrit (NOTE: hematocrit required within 6 hours of index procedure)
    b. Platelets
    c. Serum creatinine
    d. International normalized ratio (INR)
    e. B-type natriuretic peptide (BNP)
    f. Troponin
    g. Serum Lactate
9. Room Air SpO2
10. Major Trauma Injury Severity Score (ISS), as applicable
11. mMRC dyspnea score
12. Pregnancy Test
13. Concomitant Medications- relevant concomitant medication use during the study be documented at baseline, pre-procedure, procedure, and follow-up visits. Relevant medications for this study include *anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study.*

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

Any adverse event/device deficiency occurring since subject signed ICF will be recorded in the subject's CRF. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an adverse event further in the study. However, if that subject’s condition deteriorates at any time during the study, it will be recorded as an AE.

9.1.1. Computed Tomography Angiography (CTA)
Following imaging assessments will be conducted at baseline. Given the importance of imaging to Subject assessment, before and during the study, the Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer associated with the Study.

The Study requires a CTA be obtained for Subject screening to confirm pulmonary embolism, assess RV/LV dysfunction and determine the Modified Miller Score (MMS). The modified Miller index score is a quantitative tool used for anatomic quantification of thrombus burden and pulmonary arterial obstruction based on a computed tomographic angiogram. This will be measured by a qualified core laboratory. The modified Miller score (MMS) of 0–16 assigns an aggregate score to the affected segmental pulmonary arteries (nine on the right, seven on the left) occluded by thrombus. With increasing thrombus load in PE, there is CTA evidence of RV decompensation with an MMS threshold of 12. This suggests a “tipping point” beyond which RV decompensation is more likely to occur.

9.1.2 Echocardiogram
An echocardiogram will be conducted at Subject screening and at discharge or the 48-hour follow up (whichever occurs earlier). Please refer to the study imaging protocol for more details concerning the parameters of the echocardiogram.

9.1.3 Right Heart Catheterization
Once access is achieved, pulmonary artery systolic and mean pressures will be obtained and recorded prior to starting the Vertex Pulmonary Embolectomy System procedure. After the Vertex Catheter has been removed, a post-procedure invasive PA mean artery pressure and systolic pressure will be obtained. Cardiac Output, Cardiac Index and total pulmonary vascular resistance will be measured.

9.2 Procedure (Day 0)
The following assessments will be conducted during the procedure:

1. Vital Signs
2. Venous puncture for Vertex-Pulmonary Embolectomy Procedure
3. Right heart catheterization (pre-and post-procedure) for ruling out pulmonary hypertension and Invasive hemodynamic assessment- systolic and mean PA pressures. Cardiac Output, Cardiac Index and Total Pulmonary Vascular Resistance will be assessed
4. Vertex Pulmonary Embolectomy System Procedure: For procedural details please refer to section ***Section 4*** above. NOTE: Hematocrit requirement (< 28%) must be confirmed prior to index procedure.
5. Following data will be collected:
    - Procedure time
    - Thrombectomy time
    - Number of Devices used in Pulmonary Arteries
    - Use of Adjunctive treatment
    - Number of times pulmonic Valve re-crossed with the same device
    - Use of stiff guidewire
    - Number of aspirations, location
    - Fluoroscopy time
    - Radiation dosage
    - Contrast volume
6. Device Accountability
7. Concomitant medications (Pre procedure)
8. Adverse Events/Device Deficiencies
9. Clinical Investigation Plan Deviations

9.3 Follow Up Visits
9.3.1 48-Hour Follow-up Evaluation – Day 2: (± 8 Hours or discharge)
The following assessments will be performed at this clinic visit:

- Physical examination and vitals
- Room Air SpO2
- mMRC dyspnea score
- Repeat CTA and Echocardiogram consistent with baseline imaging study
- Adjunctive Treatment
- Record adverse events, as applicable
- Record concomitant medications
- Record clinical investigation plan deviations

9.3.2 30-Day Follow-up Evaluation- Day 30: (± 3 Days) (clinic or phone visit)
The following assessments will be performed at this visit:

- mMRC dyspnea score
- 30-day readmission rate
- PE recurrence rate
- Record adverse events, as applicable

- Record concomitant medications
- Record clinical investigation plan deviations
- Complete study Exit form (CRF)

9.4 Study Exit
Upon completion of the 30-day follow-up visit, the subject will exit the study. A Study Exit CRF/eCRF should be completed at this final follow-up visit. Following study exit, the subjects are followed according to standard of care by their medical team.

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

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

9.7 Study Discontinuation
Study Discontinuation by Ethic Committee/Regulatory Authority. The Regulatory Bodies may choose to discontinue the Study at any center(s) for which they granted approval if the:

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

9.7.1 Study Discontinuation by Sponsor
The Sponsor may choose to discontinue the Study should the Sponsor discover additional information during the Study that may cause harm to Subject safety. If the Study is terminated or suspended, the Sponsor will promptly inform all Investigators of the termination or suspension and the reason(s) for this. The EC will also be informed, either by the Sponsor or Investigator if a local EC is utilized, promptly and provided with the reason(s) for the termination or suspension. If applicable, Regulatory Authorities will be informed.

9.7.2 Withdrawal/Premature Discontinuation of Study Subject
Subjects may withdraw from the Study at any time (pior to study completion) upon written request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for following reasons: .

- any medical condition that, in the opinion of the Investigator, compromises patient's safety,
- withdrawal of consent for any reason, at any time,
- lost to follow-up (missed follow up visits, and documented unsuccessful three attempts to reach the patients by phone).

Withdrawal reasons will be reported in the eCRF dedicated to study termination.

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

9.8 Clinical investigation plan deviations
A clinical investigation plan deviation is defined as any change, divergence, or departure from the study design or procedures of a research clinical investigation plan that is under the Investigator's control and that has not been approved by the EC.

Principal Investigators and site staff will follow their patients according to this clinical investigation plan, which meet their routine clinical practices.

Investigators are not allowed to deviate from this CIP except under emergency situations when necessary to preserve the rights, safety or well-being of study patients. Use of waivers from the CIP is prohibited.

Nevertheless, deviations during the clinical evaluation may occur and efforts should be made to limit them. Deviations include but are not limited to follow-up visits outside of the routine visit window.

The Investigator is responsible for promptly reporting clinical investigation plan deviations to the EC in accordance with its internal regulation.

9.9 Study Assessments

9.9.1 Injury Severity Score

The injury severity score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an abbreviated injury scale (AIS) score and is allocated to one of six body regions. The highest AIS score in each body region is used. The three most severely injured body regions have their score squared and added together to produce the ISS score [XXIX]. The ISS score is virtually the only anatomical scoring system in use and correlates linearly with mortality, morbidity, hospital stay and other measures of severity (Figure 12). Major trauma is considered when ISS> 15.

Injury Severity Score (ISS)

Body Region
Head
Face
Neck
Thorax
Abdomen
Spine
Upper Extremity
Lower Extremity
External and other

Score	Abbreviated Injury Scale (AIS)
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Unsurviveable

All injuries are assigned from an internationally recognised dictionary that describes over 2000 injuries. Multiple injuries are scored by adding together the squares of the three highest AIS scores. The ISS can range from 1 to 75. Scores of 7 and 15 are unattainable because these figures cannot be obtained from summing squares. The maximum score is 75. By convention, a patient with an AIS of 6 in one body region is given an ISS of 75.

Figure 12. Injury Severity Score

9.9.2 Modified Medical Research Council (mMRC) dyspnea questionnaire
The mMRC is a patient reported outcome for the assessment of the perception of dyspnea. The scale begins at 0 (no dyspnea) to the highest perception of dyspnea (4). The specific text applied to the scale is listed in Appendix II.

The mMRC must be completed at screening/baseline, 48 hours and at 30 day follow up.

The difference in the score at follow-up visits relative to baseline will be calculated and reported.

10. RISK & BENEFIT ANALYSIS

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

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

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

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

10.1 Anticipated Risks

Potential Risks during the Interventional Procedure

The risks associated with the Vertex Pulmonary Embolectomy System are commensurate with large-bore endovascular venous interventions and catheter-directed embolectomies. Potential risks and complications include those resulting from anticoagulation and contrast dye, including bleeding, contrast-induced nephropathy, and anaphylactic reactions to iodine contrast. Potential vascular access complications include bleeding, hematoma, arteriovenous fistula, and pseudoaneurysm. The most serious complication resulting from catheter-directed procedures is perforation or dissection of a pulmonary artery, causing massive pulmonary hemorrhage and immediate death. The risk of perforation increases with smaller vessels. Under fluoroscopic guidance, the device is tracked over the guidewire into the pulmonary artery to the site of the pulmonary emboli. Use of fluoroscopic guidance for vascular access minimizes the risk of access failure and vascular complications, such as vessel perforation and vessel trauma. To further minimize the risk of perforation or dissection, confirm vessel diameter is appropriate for selected catheter. Other serious complications include pericardial tamponade, pneumothorax, cardiac rupture and cardiac arrest. Transient, periprocedural complications include arrhythmias when the catheter advances through the right heart, right heart block or bradycardia, worsening hypoxemia, and hemodynamic deterioration.

The Risk-Benefit analysis for Vertex considered the items below:

- A review of possible conflicting requirements;
- An evaluation of possible hazards that cause similar effects, the combination of which can possibly result in an enhanced effect;
- A review of warnings to ensure appropriate risk reduction and confirmation that there are no excessive warnings that can reduce the effect of a single warning; and
- A comparison between risks posed by the subject device of the analysis and other products manufactured by Neptune. This comparison considered available post-market surveillance and/or complaints data.

Under this process, the clinical safety and performance data of Vertex were compared to alternative therapies through published literature and clinical guidelines to demonstrate that the benefit-risk profile for Vertex is equivalent or non-inferior to other available non-operative, surgical, and medicinal therapies.

Based on the totality of this evaluation, it was concluded that, when used as directed, the clinical benefits for the patient outweigh any potential risk (overall residual risk).

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

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

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

Possible interactions with concomitant medical treatments

The clinical hazards associated with the use of the Vertex Pulmonary Embolectomy System are consistent with the known clinical hazards associated with aspiration thrombectomy procedures. All hazards have been identified appropriately. Clinically relevant information, such as precautions for the reduction of risks, has been considered in the device labeling to give adequate information to the user regarding safe use of the device. The clinical management of risks are well-established for thrombectomy procedures, including procedures facilitated by Neptune Medical for a clinical study.

Potential Risks from CT

High radiation exposure in cases of repeated examinations;

- Possible increase in risk of cancer
- Rise in serum creatinine levels

- Nephropathy

Table 5: Foreseeable Adverse Events

	Negligible	Minor	Serious	Critical
Rare (<1%) (Less than 1 in 100 people)	Bradycardia Adverse reaction to device materials Air embolism Drug reaction to contrast, thrombolytic or anticoagulation Foreign body embolism	Hemoglobinuria Vessel dissection/perforation	Neurological deficit Myocardial infarction Hemoptysis Cardiac tamponade Aneurysm Cardiac perforation Cardiac vessel blockage Hypo/hypertension Hypoxemia Pericardial effusion Peripheral nerve damage Pseudoaneurysm Retroperitoneal hemorrhage Stroke/transient ischemic attack Valvular disruption/injury Vasovagal reaction	Cardiogenic shock Hemodynamic instability Perforation of pulmonary arteries Vascular Injury Vessel stenosis
Uncommon (1-10%) (Between 1 and 10 in 100 people)		Access site complication/hematoma Arteriovenous fistula Bleeding/ blood loss Fever Fistulation General discomfort, tenderness or pain Hemolysis Infection Inflammatory response Vascular spasm Access site hematoma	Pulmonary infarction Respiratory failure Renal failure Distal embolism Embolism Nausea/vomitinD Organ impairment Pneumothorax Pulmonary edema Ventricular rupture Hemorrhage	Arrhythmias Death Right bundle branch block Tachycardia
Common (10-50%) (Between 10 and 50 in 100 people)				
Very Common (>50%) (Greater than 50 in 100 people)				

10.2 Risk Mitigation

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

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

10.3 Benefits

The purpose of the SPIRARE I Study is to assess the relative safety and efficacy of the Vertex Pulmonary Embolectomy System to safely and efficiently remove a sufficient amount of clot burden to achieve reduced RV afterload as indicated by a change in RV/LV ratio. In general, endovascular interventions (e.g., catheterization) are well-established in medical practice and are substantiated to minimize the risks to patients of: anesthesia complications, wound healing, bleeding, and infection typically associated with surgical interventions. However, endovascular approaches present additional risk of vessel injury and perforation that can lead to bleeding events that may require further intervention including surgery.

Unique to this study is the use of a large-bore catheter that is introduced in a relaxed state and selectively fixed after it has been placed through the right heart anatomy and into the pulmonary arteries. The ability to pass the catheter in a relaxed state may reduce hemodynamic complications associated with comparable stiffer large-bore catheters. The ability to conform the catheter to the anatomical pathway may also result in fewer adverse events compared to the use of conventional large-bore access sheaths by minimizing parasitic motion common to mother-daughter type configurations. Fixation may also aid in reducing overall clot burden by improving access to the branch vessels.

Surgical or systemic administration of thrombolytic agents carries significant risk especially when predisposing conditions or comorbidities exist. Patients may be hemodynamically unstable. Vertex Pulmonary Embolectomy System intervention offers the potential for an immediate reduction of right heart afterload though the removal of obstructive emboli within the pulmonary arteries. Fixation of the catheter and localizing control of aspiration may allow the operator to access a greater percentage of the clot burden which may benefit the goal of reliably, rapidly, and safely reducing right heart afterload. The Vertex Pulmonary Embolectomy System achieves clot removal without the use of thrombolytics. Information gained from the conduct of this Study may be of benefit to other persons with the same medical condition.

10.4 Warnings and Precautions

The following warnings and precautions are labeled for the Vertex Pulmonary Embolectomy System:

- Only physicians who have received appropriate training and are familiar with the principles, clinical applications, side effects, and hazards commonly associated with vascular interventional procedures should use this device.
- Adequate vessel access is required to introduce the Vertex and Meridian Catheters into the vasculature. Careful evaluation of vessel size, anatomy, tortuosity, and disease state (including calcification, plaque, and thrombi) is required to ensure successful introduction and subsequent withdrawal.
- Intended for single use only. Do not re-sterilize or reuse this device.
- Examine the catheter before use to verify it is not damaged.
- DO NOT fix Vertex Catheter to more than 6 ATM (608 kPa) of pressure. Over-fixation may rupture device and result in loss of performance. Device damage may also result in major bleeding, vessel damage, or serious injury to the patient, including death.
- Use before the “Use By” date specified on the product packaging.

Failure to abide by warnings in this labeling might result in damage to device coating, which may necessitate intervention or result in serious adverse events. For a detailed list of warnings and precautions, please refer to the Vertex Pulmonary Embolectomy System Instructions for Use.

10.5 Alternative Treatment

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

- Medical Therapy: Includes the use of anticoagulation therapy alone and/or systemic thrombolytics.
- Catheter-Directed Therapy: Pharmacomechanical delivery of intrapulmonary thrombolytics, with or without ultrasound assistance.

- Mechanical Thrombectomy Device: An alternate EMA-cleared catheter-based device designed to remove or dissolve blood clot.
- Surgical Embolectomy: Surgical removal of the pulmonary embolism.

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

10.6 Treatment

Patients will be observed during the procedure and post procedure for any adverse events and device effects which will be treated by qualified physicians who are adequately trained on study procedures and assessments. The 48-hour follow-up visit allows for monitoring of these patients and during this visit treatment of any adverse events and safety will be prioritized.

11. SAFETY

11.1 Safety Monitoring

Subject safety is of the utmost importance. Each Investigator has the responsibility for the safety of the Subjects under his/her care. For purposes of understanding data and relevant confounders, assessment of clinical outcomes and/or AEs/DDs thereof will be recorded.

11.2 Definitions

11.2.1 Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
(MDR Article 2(57))

NOTE:

a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures[3] involved

11.2.2 Adverse Device Event (ADE)
Any Adverse event related to the use of an investigational medical device or a comparator.

11.2.3 Anticipated Serious Adverse Device Effect (ASADE)
Any Serious Adverse Device Effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon Serious Adverse Device Effect occurred.

11.2.4 Device deficiency (DD)
Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
(MDR Article 2(59))

11.2.5 New Finding
New information discovered as the result of an inquiry/investigation/test based on the occurrence of the event. Follow-up from the event.

11.2.6 Serious Adverse Event (SAE)
Any Adverse Event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,
ii. permanent impairment of a body structure or a body function,
iii. hospitalisation or prolongation of patient hospitalisation,
iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

[3] For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect (MDR Article 2(58))

11.2.7 Serious Adverse Device Effect (SADE)
Any Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

11.2.8 Unanticipated Serious Adverse Device Effect (USADE)
Any Serious Adverse Device Effect, the nature, severity or outcome of which is not consistent with the reference safety information.

11.2.9 Serious Health Threat
Signal from any Adverse Event or Device Deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

NOTE 1 to entry: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.2.10 Unanticipated Adverse Device Effect (UADE)
An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study clinical investigation 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)).

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

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

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

11.4 Event Relationship
The following definitions will be used to assess the relationship of the adverse event to the investigational medical device/study procedure(s):

Not related: Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the (serious) adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the (serious) adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the (serious) adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the (serious) adverse event.

Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship: the (serious) adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the (serious) adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the (serious) adverse event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the (serious) adverse event.

11.5 Adverse Event Reporting

Subjects will be carefully monitored during the study for possible adverse events. Safety will be assessed by collecting adverse event/device deficiency data on each patient and will be captured in the CRFs. Any adverse event/device deficiency occurring since subject signed ICF will be recorded in the subject's CRF.

Note: Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an adverse event further in the study. However, if that subject’s condition deteriorates at any time during the study, it will be recorded as an AE.

Appropriate treatment will be initiated and the study follow-up will continue as completely as possible.

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a Serious Adverse Event.

Out of range (abnormal) laboratory value(s) should be captured as an AE(s) if clinically significant.

Ongoing AE should be reviewed and updated at each visit, if applicable. AE will continue to be recorded throughout the study including the follow-up until study exit.

The Investigator will document all observations and clinical findings of adverse events, including the nature, date of onset and stop date (if applicable), severity, seriousness, action(s) taken/treatment, outcome and relationship to the investigational medical device/study procedure(s), on the appropriate eCRFs in the EDC. Whenever possible, available source documentation should be provided to the Sponsor.

The Investigator is required to report Adverse Events/Device Deficiencies to the Sponsor within the following timeframes:

Type of event	Timeline for Reporting
SAE/SADE/UADE/ASADE/USADE	Immediately, but not later than **3 calendar days** after investigation site study personnel's awareness of the event
All other AEs/ADEs	In a timely manner, usually within **7 calendar days** after investigation site study personnel's awareness of the event
Device Deficiency	Immediately, but not later than **3 calendar days** after investigation site study personnel's awareness of the event
Serious Health Threat	At the earliest possible opportunity, but not later than within **24 hours** after investigation site study personnel's awareness of the event

Emergency contact for safety reporting:

CRO company:
Safety Department
E-mail: safety@kcri.org

Sponsor: Neptune Medical
E-mail: clinicalsafety@neptunemedical.com

As additional information concerning AEs/DDs becomes available, the Investigator will record it on the appropriate CRFs. Copies of source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports and patient summaries etc. are required for evaluation of the event. Copies of such documentation shall be obtained from the Investigator (de-identified as to the Subjects' identity) and provided to the Sponsor.

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

The Sponsor will comply with Medical Device Regulation (MDR) reporting requirements.
Reportable events will be reported to the applicable Regulatory Bodies of participating countries according to applicable local and national regulations.
In general, safety reporting to the Regulatory Bodies in European Economic Area (EEA) will be performed in accordance with MDCG 2020-10/1, unless specified otherwise.
The summary is provided below:

- the following events are considered reportable events in accordance with MDR Art. 80(2):
  a) any Serious Adverse Event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
  b) any Device Deficiency that might have led to a Serious Adverse Event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
  c) any new findings in relation to any event referred to in points a) and b).

- Reporting to the applicable Regulatory Bodies to be performed within the following timeframes:
  a) for all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
  This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

b) Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

12. STUDY ADVISORS

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

12.1 Imaging Core Laboratory

Medical Metrics Inc is the Core Lab designated for the SPIRARE I Clinical Study. The objectives of the Core Lab are to provide an unbiased assessment of the RV/LV ratio.

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

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

13. STATISTICAL DESIGN AND METHODS

13.1 Analysis Populations

The populations are defined as follows:

An enrolled patient is defined as all patients who met the inclusion/exclusion criteria and who provide written informed consent, meet the inclusion/exclusion criteria, and in whom the Vertex Catheter is introduced past the pulmonic valve.

The Intent-To-Treat (ITT) population is defined as all enrolled patients who met the inclusion/exclusion criteria and who provide written informed consent, and in whom the Vertex Catheter is introduced past the pulmonic valve; when Vertex Catheter is introduced past the pulmonic valve, and in whom the Vertex Pulmonary Embolectomy System is not able to access a pulmonary embolus.

All enrolled and ITT patients will be monitored per clinical investigation plan until the end of the required follow up period of 30 days.

This is a prospective, multicenter, single arm study designed to evaluate the safety and efficacy of the Vertex Pulmonary Embolectomy System for the aspiration of clot in patients with acute PE. The efficacy analysis will be conducted in the Intent-to-treat and per clinical investigation plan populations and the safety analysis will be conducted in all patients (enrolled, ITT, and procedural screen failures).

13.2 Statistical Analysis

The sample size for this clinical investigation plan is too small to permit a formal statistical analysis. Descriptive statistics will be used to summarize all safety and efficacy data. Trends, particularly in reported adverse events, will be noted and characterized. Demographics and Baseline Characteristics will be summarized.

Continuous variables, including age, height, and weight, will be summarized in terms of mean, median, standard deviation, minimum, and maximum. Categorical variables, including sex, ethnicity, will be summarized in terms of the number of observations available, frequencies and percentages of each possible value.

Results collected at multiple visits will be summarized at each visit for which they are collected as described in Table 4 Schedule of Assessments. Summaries for all measures will include all observed data for each visit.

13.3 Data Management

Data Management services may be performed by Neptune Medical Inc and/or designee.

13.3.1 Data entry

A web-based eCRF (Zelta™) is being used for data entry at each site. Data entry is performed by the Investigators and authorized designee. Only Investigators have the right to sign the pages for the patients they are responsible of.

Access to the eCRF is protected by an identification system with personal login and password using a secure connection (https). Furthermore, all the connections and/or modifications of data are saved in an audit trail.

Each authorized user has allocated rights which can restrict his access to functionalities or pages of the online eCRF. Before the first connection, eCRF Completion Guidelines to be provided to each site. These guidelines include descriptions of the functionalities of the eCRF.

13.3.2 Data Check and cleaning

All data will be validated thanks to edit checks defined and programmed by KCRI (i.e. range checks, inconsistencies). Furthermore, manual queries can be placed in the eCRF by specific user roles (e.g. Data Managers, Monitors), as a result of data review and/or source data verification (SDV). For details about data cleaning and the different roles involved, refer to the Data Management Plan (DMP).

13.3.3 Software validation

MerativeTM is a vendor EDC software hosted on a cloud server. The software has an installation validation (IQ) and can be requested at the sponsor.

13.3.4 Data Retention

All data are saved on a dedicated cloud server by Merative in the USA and a regular back up of the server is done. For details about the backup schedule, refer to the Service Agreement with Merative.

According to MDR source documents will be archived at Neptune Medical Inc and Investigator with a minimum of 10 years after the device is placed on the market the last time. The Investigator will maintain the records of the investigation including the source data, correspondence, the study protocol with all amendments, all correspondence with the local Competent Authority and responsible Ethics Committee, including the approval. Further the budget agreement, the clinical study agreement, investigational device accountability records, individual patient records, and signed informed consent forms as compiled in the Investigator Site File and Investigator Office File.

The files may be discarded only upon notification from Neptune Medical Inc. To avoid error, the Investigator should contact Neptune Medical In before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

14. ETHICAL CONDUCT OF STUDY

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

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- The Declaration of Helsinki concerning medical research in humans (59th WMA General Assembly, Seoul, October 2008)
- Medical Device regulation 2017/745,
- ISO 14155 standards,
- MDCG 2020/10-1
- General Data Protection Regulation (GDPR)
- REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices

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

15. SITE SELECTION & TRAINING

15.1 Site Selection

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

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

15.2 Site Training

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

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

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

15.3 Study Initiation

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

- EC and RA approval for the Clinical Investigation Plan
- EC and Sponsor approved study-specific Informed Consent Form for the study
- Investigator(s') curriculum vitae (CV)
- Financial Disclosure(s) for the PI and Sub-I(s)
- Signed Confidentiality Disclosure Agreement (CDA)
- Signed Clinical Trial Agreement (CTA) for the site and Investigator
- Training Log documentation to verify the appropriate study staff has been trained on the clinical investigation plan, device, CRFs and study conduct

16. ETHICS COMMITTEES

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

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

Any amendment or modification to the clinical investigation plan should be sent to the EC. The EC should also be informed of any event likely to affect the safety of Subjects or the conduct of the Study.

16.1 Informed Consent Form (ICF)

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

16.2 Case Report Forms (CRF)

A cloud-based Electronic Data Capture (EDC) system will be used to document study data.

Electronic Case Report Forms (eCRFs) will be developed to collect all Study-related information and data points. Neptune Medical will provide access to eCRFs for each Subject enrolled in the Study to each investigational site. The appropriate eCRF will be completed after each Study visit. EDC and eCRF completion guidelines and training will be provided to the sites in addition to online support.

17. STUDY MONITORING

Neptune Medical Inc (the "Sponsor") is responsible for ensuring that adequate monitoring at each site is completed to ensure the rights and safety of Subjects is protected, and the quality and integrity of the data collected and submitted is in compliance with Title 21 CFR Part 812 Subpart C, CIP, ISO 14155:2020 and the current/latest version of the Declaration of Helsinki, to verify completed CRFs match the hospital records and to resolve any discrepancies. Appropriately trained personnel (Monitors) appointed by the Sponsor will conduct monitoring visits according to the Monitoring Plan. Monitors will consist of Sponsor clinical staff and/or qualified contract services (e.g., CRO) appointed by the Sponsor.

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

compliance, and any suspected inconsistency in data that requires investigation. Risk-based monitoring will be undertaken for the study.

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

17.1 Direct Access to Source Documents

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

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

17.2 Confidentiality of Protected Health Information

The Sponsor complies with the principle of patient's right to protection against invasion of privacy. Data collection and processing for study patients will be minimized to the required data to fulfill the objectives defined for this study. Throughout this trial, all data will be identified only by an identification number. The data will be blinded in all data analyses. The patient must be informed and consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, etc.) and relevant Health regulatory agency will have direct access to personal medical data to assure a high-quality standard of the study.

"Protected health information" will be treated and maintained in compliance with the directive 95/46/EC (European Directive for data protection law), the General Data Protection Regulation (GDPR) and applicable local laws on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

The duration of storage time of personal data at the investigational sites will be in accordance with national regulations.

17.3 Compliance to the Clinical investigation plan

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

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

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

17.4 On-Site Audits

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

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

17.5 Record Storage and Retention

The study Sponsor will maintain hard or electronic copies of correspondence, data, shipment of devices, adverse events/device deficiencies, and other records related to the clinical trial. Clinical sites will maintain study records for ten (10) years after study completion or in accordance with GCP and local EC requirements.

Data related to this study will be stored according to the regulations pertaining to MDR and ISO 14155:2020 instructions for documents retention.

It is the responsibility of the investigator and the study staff to maintain a comprehensive and centralized filing system of all relevant study documentation which may include:

Source Documents – which substantiate the data entered in the electronic Case Report Forms for all required tests and procedures.

Subject Identification Log – a list correlating all subject names, appropriate identifying information, etc., to the Sponsor-assigned subject number.

Screening Log– which should reflect the reason any subject was screened for the study and found to be ineligible.

Monitoring Visit Log – which lists dates of monitor/Sponsor visits.

EC/ Correspondence – includes approval letter(s), and reporting of events considered reportable based on established reporting requirements or other correspondence with the EC.

Sponsor Correspondence –letters, e-mails, or faxes sent to the investigator or study coordinator at the investigational site.

Site Correspondence - letters or fax sent to the Sponsor from the investigator or study coordinator at that site.

Signed Informed Consent for each subject

Informed Consent Log – lists version of consent(s) signed by each subject screened and enrolled into the study

Device Accountability Log – includes a list of any devices received by the site, used in a case and/or returned to the Sponsor.

All Study Documentation pertaining to the conduct of the study must be kept on file by the investigator for a minimum of ten (10) after being notified by the Sponsor that the study is closed.

In compliance with current regulatory guidelines regarding the monitoring of clinical studies, it is requested that the investigator permit the study monitor to review and duplicate information in the subject's medical record that is directly related to the study. This information may include relevant study documentation, including the subject's medical history, to verify eligibility, laboratory test results to verify transcription accuracy, CTA, Echo and Ultrasound reports, admission and discharge summaries for hospital or outpatient admissions occurring while the subject is participating in the study, charges and billing, and autopsy reports for deaths occurring during the study (if available).

As part of the required content of informed consent, the subject must be informed that his/her medical record will be reviewed and, possibly, duplicated by the Sponsor, or the Sponsor's authorized representative or government regulatory authorities. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the patient subject is entered into the study.

It is required that a copy of all records (e.g., informed consent documents, source documents, safety reports, study device dispensing record, etc.) which support case report forms for this study, be retained in the files of the responsible investigator for a period of time as defined per local regulations following notification by the sponsor that all investigations (not merely the investigator's portion) are completed, terminated and/or discontinued. The investigator will take measures to prevent accidental or premature destruction of these documents which will be located in adequate conditions and limited access. If the principal investigator retires, relocates, or for other reasons

withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Neptune Medical Inc must be notified in writing of the name and address of the new custodian.

17.6 Financing and Insurance

Neptune Medical Inc has a study specific insurance policy taken out in compliance with national legal requirements.

The study is financed by Neptune Medical Inc, 1828 El Camino Real, Suite 508, Burlingame, CA 94010

The Investigators, study personnel and the center will receive remuneration for conducting the study in accordance with the signed contract between the Sponsor, Site and the Principal Investigator.

Neptune Medical Inc will not make any payment to patients for their participation in the study.

17.7 Vulnerable Population

No vulnerable patients will be enrolled in this study.

17.8 Amendments to the CIP

Essential modifications in the CIP require re-approval of the RAs and ECs prior continuation of the study according to these modifications. Any modifications or supplements will generate a revision of the CIP and shall be indicated in the document history. The rationale for CIP revision shall be described.

17.9 Data Ownership

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

17.10 Clinical Investigational Report (CIR)

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to ISO 14155 guidelines and submitted to all involved sites, ECs and RA.

18. CONFIDENTIALITY

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

19. PUBLICATION POLICY

The Sponsor will collaborate with all Investigators interested in potential publication of study results. The Sponsor requests that no publication, abstract, or presentation is submitted or given by the Investigator or other personnel involved in the study prior to the release of any formal study publication, unless written consent by the Sponsor is provided. The Sponsor requests 30 days to review and comment on any prepublication or presentation manuscript to make modifications to the publication necessary to protect its proprietary information and to ensure the accuracy of any references to Neptune Medical, their trademarks, trade names, or technical information relating to the study.

The Sponsor will have access to all anonymized data on safety and intraprocedural and effectiveness data collected during the study. The Sponsor will be allowed to prepare a company report comprising these data. Such a report will be regarded as confidential but may be submitted to regulatory authorities for registration and approval purposes.

20. REFERENCES

I. Marshall PS, Mathews KS, Siegel MD. Diagnosis and management of life-threatening pulmonary embolism. J Intensive Care Med. 2011;26:275–294.

II. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008;28:370–372.

III. https://www.nhlbi.nih.gov/news/2020/study-death-rate-lung-clots-rise-after-years-decline#:~:text=Pulmonary%20embolisms%20and%20DVT%20kill,States%20from%201999%20to%202018.

IV. Turetz M, Sideris AT, Friedman OA, Triphathi N, Horowitz JM. Epidemiology, Pathophysiology, and Natural History of Pulmonary Embolism. Semin Intervent Radiol. 2018;35(2):92-98. doi:10.1055/s-0038-1642036

V. Smith S B, Geske J B, Kathuria P et al. Analysis of national trends in admissions for pulmonary embolism. Chest. 2016;150(01):35–45.

VI. Inari Medical. Investor Presentation. May 4, 2022. https://ir.inarimedical.com/static-files/ac353660-0c6a-493e-9607-8e78b5d8a9ba

VII. Keller K, Beule J, Balzer JO, Dippold W. D-Dimer and thrombus burden in acute pulmonary embolism. Am J Emerg Med. 2018 Sep;36(9):1613-1618. doi: 10.1016/j.ajem.2018.01.048. Epub 2018 Jan 17. PMID: 29371044.

VIII. Alisha Jamil, Hillary Johnston-Cox, Steven Pugliese, Ashwin S. Nathan, Paul Fiorilli, Sameer Khandhar, Mitchell D. Weinberg, Jay Giri, Taisei Kobayashi. Current interventional therapies in acute pulmonary embolism, Progress in Cardiovascular Diseases. Volume 69, 2021 Pages 54-61. https://doi.org/10.1016/j.pcad.2021.11.009

IX. Grau E, Tenías JM, Soto MJ, Gutierrez MR, Lecumberri R, Pérez JL, Tiberio G; RIETE Investigators. D-dimer levels correlate with mortality in patients with acute pulmonary embolism: Findings from the RIETE registry. Crit Care Med. 2007 Aug;35(8):1937-41. doi: 10.1097/01.CCM.0000277044.25556.93. PMID: 17581488.

X. Sista AK, Kuo WT, Schiebler M, Madoff DC. Stratification, Imaging, and Management of Acute Massive and Sub-massive Pulmonary Embolism. Radiology. 2017 Jul;284(1):5-24. doi: 10.1148/radiol.2017151978. PMID: 28628412.

XI. Eric Secemsky, Yuchiao Chang, C. Charles Jain, Joshua A. Beckman, Jay Giri, Michael R. Jaff, Kenneth Rosenfield, Rachel Rosovsky, Christopher Kabrhel, Ido Weinberg. Contemporary Management and Outcomes of Patients with Massive and Sub-massive Pulmonary Embolism. The American Journal of Medicine. Volume 131, Issue 12, 2018. https://doi.org/10.1016/j.amjmed.2018.07.035.

XII. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and sub-massive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011 Apr 26;123(16):1788-830. doi: 10.1161/CIR.0b013e318214914f. Epub 2011 Mar 21. Erratum in: Circulation. 2012 Aug 14;126(7):e104. Erratum in: Circulation. 2012 Mar 20;125(11):e495. PMID: 21422387.

XIII. Azari A, Beheshti AT, Moravvej Z, Bigdelu L, Salehi M. Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: Short and long-term prognosis. Heart Lung. 2015 Jul-Aug;44(4):335-9. doi: 10.1016/j.hrtlng.2015.04.008. PMID: 26077690.

XIV. Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. Thromb Res. 2014 Dec;134(6):1265-71. doi: 10.1016/j.thromres.2014.10.004. Epub 2014 Oct 13. PMID: 25457585.

XV. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Áinle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019 Oct 9;54(3):1901647. doi: 10.1183/13993003.01647-2019. PMID: 31473594.

XVI. American College of Cardiology. Management PE. Jan 2020. https://www.acc.org/latest-in-cardiology/articles/2020/01/27/07/42/management-of-pe

XVII. Robert S. Zhang, Muhammad H. Maqsood, et al. Efficacy and Safety of Anticoagulation, Catheter-Directed Thrombolysis, or Systemic Thrombolysis in Acute Pulmonary Embolism. JACC. Volume 16, Issue 21, 2023, Pages 2644-2651.

XVIII. Percy ED, Shah R, Hirji S, Tartarini RJ, Yazdchi F, Harloff M, Kaneko T, Pelletier MP. National Outcomes of Surgical Embolectomy for Acute Pulmonary Embolism. Ann Thorac Surg. 2020 Aug;110(2):441-447. doi: 10.1016/j.athoracsur.2020.02.024. Epub 2020 Mar 19. PMID: 32199827.

XIX. Weinberg AS, Dohad S, Ramzy D, Madyoon H, Tapson VF. Clot Extraction With the FlowTriever Device in Acute Massive Pulmonary Embolism. J Intensive Care Med. 2016 Dec;31(10):676-679. doi: 10.1177/0885066616666031. Epub 2016 Sep 21. PMID: 27601482.

XX. Edelman JJ, Okiwelu N, Anvardeen K, Joshi P, Murphy B, Sanders LH, Newman MA, Passage J. Surgical Pulmonary Embolectomy: Experience in a Series of 37 Consecutive Cases. Heart Lung Circ. 2016;25:1240–1244.

XXI. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, Conti A, Agnelli G, Berni G. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000 Jun 20;101(24):2817-22. doi: 10.1161/01.cir.101.24.2817. PMID: 10859287.

XXII. 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. 2022 Jul;37(7):877-882. doi: 10.1177/08850666211036446. Epub 2021 Aug 16. PMID: 34397286.

XXIII. Greenfield LJ, Kimmell GO, McCurdy WC 3rd. Transvenous removal of pulmonary emboli by vacuum-cup catheter technique. J Surg Res. 1969 Jun;9(6):347-52. doi: 10.1016/0022-4804(69)90079-1. PMID: 5769435.

XXIV. Toma C, Jaber WA, Weinberg MD, Bunte MC, Khandhar S, Stegman B, Gondi S, Chambers J, Amin R, Leung DA, Kado H, Brown MA, Sarosi MG, Bhat AP, Castle J, Savin M, Siskin G, Rosenberg M, Fanola C, Horowitz JM, Pollak JS. Acute outcomes for the full US cohort of the FLASH mechanical thrombectomy registry in pulmonary embolism. EuroIntervention. 2023 Feb 20;18(14):1201-1212. doi: 10.4244/EIJ-D-22-00732. PMID: 36349702; PMCID: PMC9936254

XXV. Sista AK, Horowitz JM, Tapson VF, Rosenberg M, Elder MD, Schiro BJ, Dohad S, Amoroso NE, Dexter DJ, Loh CT, Leung DA, Bieneman BK, Perkowski PE, Chuang ML, Benenati JF; EXTRACT-PE Investigators. Indigo Aspiration System for Treatment of Pulmonary Embolism: Results of the EXTRACT-PE Trial. JACC Cardiovasc Interv. 2021 Feb 8;14(3):319-329.

XXVI. Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, Khandhar S, Amin R, Weinberg M, Engelhardt T, Hunter M, Holmes D, Hoots G, Hamdalla H, Maholic RL, Lilly SM, Ouriel K, Rosenfield K; FLARE Investigators. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv. 2019 May 13;12(9):859-869.

XXVII. 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 Nov;20(11):1431-40.

XXVIII. Chechi T, Vecchio S, Spaziani G, Giuliani G, Giannotti F, Arcangeli C, Rubboli A, Margheri M. Rheolytic thrombectomy in patients with massive and submassive acute pulmonary embolism. Catheter Cardiovasc Interv. 2009 Mar 1;73(4):506-13.

XXIX. Baker SP, O'Neill B, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14:187-196.

Appendix I
List of Investigative Sites

Country	Site name and address:	Principal Investigator
Poland	Krakowski Szpital Specjalistyczny im. Św. Jana Pawła II, Prądnicka 80, 31-202 Kraków	**Prof. Krzysztof Bartuś**
Austria	AKH-Vienna, Medical University of Vienna, Internal Medicine II, Cardiology, Anna Spiegel CTR Level 6, Währinger Gürtel 18-20, A-1090 Vienna	**Prof. Irene Lang**

Appendix II
Modified Medical Research Council (mMRC) Dyspnea Scale

mMRC Dyspnea Scale

Grade	**Degree of Breathlessness Related to Activities**
Grade 0	No breathlessness except with strenuous exercise
Grade 1	Breathlessness when hurrying on the level or walking up a slight hill
Grade 2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
Grade 3	Stops for breath after walking about 100 yards or a few minutes on the level
Grade 4	Too breathless to leave the house or breathless when dressing or undressing

Adapted from Fletcher CM, Elmes PC, FaECairn MB et al. (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal* 2:257–66.