Clinical Protocol Title	**R**ecombinant tPA by **E**ndovascular Administration for the treatment of **S**ubmassive pulmonary embolism using pharmaco-mechanical **C**atheter directed thrombolysis for the red**U**ction of thrombus burd**E**n - **The RESCUE Study**
Protocol Number	THRO-CLIN-2019-01
Study Phase	Phase III – Pivotal Study
Device Phase	Pre-market
Study Sponsor	Thrombolex, Inc. 75 Britain Drive New Britain, PA 18901
Current Protocol Version	4.0
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Steering Committee	Anthony J. Comerota MD, FACS, FACC Kenneth Rosenfield MD, MSCAI, FACC Akhilesh K. Sista MD, FSIR, FAHA Victor Tapson MD, FCCP, FRCP
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Chief Scientific Officer
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Approval Date
August 18, 2020

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1.0 PROTOCOL SYNOPSIS

STUDY NAME	**R**ecombinant tPA by **E**ndovascular Administration for the treatment of **S**ubmassive pulmonary embolism using pharmaco-mechanical **C**atheter directed thrombolysis for the red**U**ction of thrombus burd**E**n - **The RESCUE Study**
PROTOCOL NO.	THRO-CLIN-2019-01
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STEERING COMMITTEE	Anthony J. Comerota MD, FACS, FACC Kenneth Rosenfield MD, MSCAI, FACC Akhilesh K. Sista MD, FSIR, FAHA Victor Tapson MD, FCCP, FRCP
STUDY DEVICE	The Bashir™ Endovascular Catheter (BEC) is a device intended for the localized infusion of therapeutic agents into the pulmonary artery and peripheral vasculature. Two sizes of BECs will be used in this study.
STUDY OBJECTIVE	To demonstrate the efficacy and safety of the Bashir™ Endovascular Catheter for the administration of pharmaco-mechanical catheter directed therapy using low dose r-tPA for the treatment of acute submassive pulmonary embolism.
POPULATION	Patients 18 to ≤ 75 years of age who present with symptoms of acute submassive PE within 14 days of onset of symptoms will be considered for this study.
STUDY DESIGN	Prospective, non-randomized, multi-center study.
SAMPLE SIZE	Up to 125 will be enrolled and treated; the subjects enrolled and treated per site will not exceed 20 subjects.
SITES	Up to 20 sites will be qualified to participate in this study.
THROMBOLYTIC ADMINISTRATION	**Pulse Sprays:** r-tPA 2mg in 20cc 0.9% NaCl divided into two (2) 10cc syringes to administer in two (2) pulse sprays, 10cc each, through the infusion port with 10cc syringes. Unilateral PE: 2mg total in 20cc administered in two (2) 10cc syringes. Bilateral PE: 4mg total in 40cc administered in two (2) 10cc syringes into each PA for a total of four (4) syringes, two (2) into each PA. **Infusion:** Unilateral PE: r-tPA 5mg in 500cc 0.9% NaCl infused at 1.00mg/hr at an infusion rate of 100cc/hr, through the Bashir™ Endovascular Catheter until r-tPA mixture has completely infused. Total r-tPA dose (pulse spray and infusion) is 7mg. Bilateral PE: r-tPA 5mg in 500cc 0.9% NaCl infused at 1.00mg/hr at an infusion rate of 100cc/hr bilaterally through each Bashir™ Endovascular Catheter, until r-tPA mixture has completely infused, for a total r-tPA dose of 1.0mg/hr through each catheter. Total r-tPA dose (pulse spray and infusion) for bilateral dosing is 14mg.

1.0 PROTOCOL SYNOPSIS (CONTINUED)

ANTICOAGULANT DOSAGE AND ADMINISTRATION	**Pre-procedure:** There is a choice of anticoagulation to be administered according to the investigator's standard of care. 1. If the investigator's standard of care is to use heparin, unfractionated heparin (UFH) will be administered by IV infusion to maintain therapeutic anticoagulation. 2. If the administration of low molecular weight heparin (LMWH), such as enoxaparin (Lovenox®), is the investigator's standard of care, administer 1mg/kg sub-Q every 12 hours. **BEC Procedure:** Choose one of the two scenarios below according to the investigator's standard of care: 1. If heparin was administered pre-procedure or patient received LMWH 1mg/kg SQ >12 hours prior to the BEC procedure, start BEC procedure with subject on heparin infusion in the IR suite / cath lab. Once r-tPA infusion is started, decrease heparin infusion dose to five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. 2. If LMWH was administered ≤ 12 hours pre-procedure, start BEC procedure without heparin in the IR suite / cath lab, until patient is 8 hours post last dose of LMWH. Then start infusion of UFH at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. **Post-BEC Procedure:** Heparin infusion at the completion of the BEC procedure and during the r-tPA infusion: 1. Continue heparin administration through the side arm of the sheath at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. If bilateral BECs are in place, the heparin infusions must be administered into each sheath. Administer half (or approximately half) the dose prescribed by the investigator into the side arm of each sheath to equal the prescribed dose. 2. If subject has not reached 8 hours post last dose of LMWH in the IR suite / cath lab, then in the ICU start dose of UFH at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. **Post r-tPA Infusion:** Once r-tPA infusion is complete, increase UFH dose to target aPTT within therapeutic range (aPTT suggested 60-80 sec). Replace r-tPA infusion with standard heparinized saline through the basket infusion line connector of the BEC(s) at 30cc/hour to maintain patency until removal. **Sheath Removal:** Stop UFH for at least one (1) hour prior to sheath removal, unless the operator believes that the UFH, in the best interest of the patient, should not be stopped prior to and during sheath removal. Remove sheaths according to standard of care. **Anticoagulation Post-Sheath Removal:** Re-start anticoagulation within one (1) hour post sheath removal with LMWH 1mg/kg SQ q 12 hours or UFH at therapeutic doses for 24 hours post sheath removal. After 24 hours post sheath removal, physicians can start therapeutic anticoagulation according to their standard of care. If physicians choose to use DOACs then patients should be properly loaded according to the current guidelines.

1.0 PROTOCOL SYNOPSIS (CONTINUED)

PRIMARY EFFICACY ENDPOINT	1. Reduction in RV/LV diameter ratio as measured by contrast enhanced chest CT (CTA) within 48 hours after the completion of r-tPA treatment.
PRIMARY SAFETY ENDPOINT	1. Major bleeding, as defined by International Society of Thrombosis and Hemostasis (ISTH), within 72 hours of initiation of r-tPA infusion ISTH major bleeding in non-surgical study subjects is defined as having a symptomatic presentation and: a. Fatal bleeding; and/or b. Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or c. Bleeding causing a fall in hemoglobin level of 2.0g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.
SECONDARY ENDPOINTS	1. Device Success: The number of devices with therapy delivered without a device failure. 2. Refined Modified Miller Score as measured on contrast enhanced chest CT (CTA) within 48 hours after the completion of the r-tPA infusion compared to baseline as measured by core lab. 3. All-cause mortality at hospital discharge through 30-day follow-up. 4. SAEs through 30-day follow-up. 5. AEs through 30-day follow-up. 6. UADEs through 30-day follow-up. 7. Recurrent PE through 30-day follow-up. 8. Clinically Relevant Non-Major bleeding: Any sign or symptom of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: a. Requiring medical intervention by a healthcare professional. b. Leading to hospitalization or increased level of care. c. Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation. 9. Technical procedural complications. 10. Systolic PA pressure measured at completion of infusion after BEC(s) removal and compared to baseline. 11. Cardiac output (CO by Modified Fick calculation) and cardiac index (CI) following completion of the r-tPA infusion compared to the baseline. Please refer to Terms and Definitions section for the Modified Fick calculation to be done in the IR suite / cath lab at baseline and the ICU after BEC removal).

1.0 PROTOCOL SYNOPSIS (CONTINUED)

ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Willing and able to provide informed consent; 2. Age 18 to ≤ 75 years of age; 3. PE symptom duration ≤ 14 days. 4. Filling defect in at least one main or lobar pulmonary artery as determined by CTA; 5. RV/LV diameter ratio ≥ 0.9 by CTA as determined by the investigative site; 6. Willing and able to comply with all study procedures and follow-up.
	Exclusion Criteria 1. CVA or TIA within one (1) year; 2. Head trauma, active intracranial, or intraspinal disease ≤ one (1) year prior to inclusion in the study; 3. Active bleeding from a major organ within one (1) month prior to inclusion in the study; 4. Intracranial condition(s) that may increase the risk of bleeding (e.g., neoplasms, arteriovenous malformations, or aneurysms); 5. Patients with bleeding diatheses; 6. Hematocrit < 30%; 7. Platelets < 100,000/μL; 8. INR > 1.5 if currently on warfarin (Coumadin®); 9. aPTT > 50 seconds in the absence of anticoagulants; 10. Major surgery ≤ 14 days prior to inclusion in the study; 11. Serum creatinine > 2.0mg/dL; 12. Clinician deems high-risk for catastrophic bleeding; 13. History of heparin-induced thrombocytopenia (HIT Syndrome); 14. Pregnancy; 15. SBP < 90 mmHg > 15 minutes within two (2) hours prior to BEC procedure and is not resolved with IV fluids; 16. Any vasopressor support; 17. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR) during this hospitalization at treating institution and/or referring institution; 18. Evidence of irreversible neurological compromise; 19. Life expectancy < one (1) year; 20. Use of thrombolytics or glycoprotein IIb/IIIa inhibitor within 3 days prior to inclusion in the study; 21. Use of non-vitamin K oral anti-coagulants (NOACs), such as rivaroxaban (Xarelto®), apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa®) within 48 hours prior to inclusion in the study; 22. Profound bradycardia requiring a temporary pacemaker and/or inotropic support; 23. Previous enrollment in this study; 24. Morbidly obese patient who by the judgement of the investigator is high risk for bleeding; *Continued next page*

1.0 PROTOCOL SYNOPSIS (CONTINUED)

ELIGIBILITY CRITERIA (CONTINUED)	25. BMI > 45kg/m^2; 26. Absolute contraindication to anticoagulation; 27. Uncontrolled hypertension defined as SBP > 175mmHg and / or DBP > 110mmHg with pharmacotherapy within two (2) hours prior to inclusion in the study; 28. Currently participating in another study; 29. Any arterial line placement; 30. Current positive COVID diagnosis, or ≤ 8 weeks negative of COVID, or > 8 weeks from positive COVID test and with current symptoms, or current active viral pneumonia on chest CT scan. 31. In the opinion of the investigator, the subject is not a suitable candidate for the study.
SUBJECT PARTICIPATION	Duration of participation will be from time of informed consent through 30-day follow-up.
STUDY DURATION	It is estimated that the study duration will be 24 months.
CEC/DSMB CHAIRPERSON	Gregory Piazza, MD, MS Brigham and Women's Hospital Boston, MA
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3.0 TERMS AND DEFINITIONS

TERM	DEFINITION
AE	Adverse Event
aPTT	Activated partial thromboplastin time
BEC	Bashir™ Endovascular Catheter
BNP	Brain Natriuretic Peptide is made inside the pumping chambers of the heart when pressure builds up from heart failure. The test is an important assessment to diagnose heart failure quickly.
BSA	$0.024265 \times (\text{Height in cm})^{0.3964} \times (\text{Weight in kg})^{0.5378}$
CBC	Complete blood count
CEC	Clinical events committee
CFV	Common femoral vein
CI	Cardiac Index: Hemodynamic parameter that relates the cardiac output (CO) from right or left ventricle in one minute to body surface area (BSA), thus relating heart performance to the size of the individual. The unit of measurement is liters per minute per square meter ($L/min/m^2$). CI = CO/BSA.
CO	Cardiac output
COVID-19	Novel Coronavirus Disease 2019
CMP	Complete metabolic panel
CTA	Computerized tomography angiography
CTEPH	Chronic thromboembolic pulmonary hypertension
CVA	Cerebrovascular accident
DOAC	Direct-Acting Oral Anticoagulant
DSMB	Data safety monitor board: Panel of physicians experienced in the treatment of PE with mechanical thrombolysis will review all adverse events in this study.
DUS	Duplex ultrasound - a type of ultrasound used to visualize the vasculature. This is a study requirement to assess the ability to access the PA(s) from the CFV.
F2F	Face-to-face
GTT	Drip
Modified Fick Calculation	$CO = O_2$ Consumption (VO_2) ml/min = L/min $(CaO_2 - CvO_2) \times 10$ $VO_2 = 125 \times BSA$ $CaO_2 = (1.36 \times Hgb \times SpO_2)$ $CvO_2 = (1.36 \times Hgb \times SvO_2)$ This Modified Fick calculation is required in this protocol. Substitute CaO_2 with SpO_2 as indicated above to eliminate the need for an arterial puncture.

3.0 TERMS AND DEFINITIONS (CONTINUED)

TERM	DEFINITION
HIT	Heparin induced thrombocytopenia
Hr	Hour
Hrs	Hours
IJ	Internal jugular
INR	International normalized ratio
LCFV	Left common femoral vein
LMWH	Low molecular weight heparin
NOAC	Non-vitamin K oral anticoagulants; such as rivaroxaban (Xarelto®), apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa®).
PAD	Pulmonary artery diastolic pressure
PaO_2	Partial pressure of arterial oxygen
PAP	Pulmonary artery pressure
PAS (PASP)	Pulmonary artery systolic pressure
PE	Pulmonary embolism
PMCDT	Pharmaco-mechanical catheter directed thrombolysis
Procedure Start Time	Procedure start time refers to the PMCDT (BEC) procedure and is defined as the injection of local anesthetic at the access site prior to sheath placement in the IR suite / cath lab.
RCFV	Right common femoral vein
Recurrent PE	Recurrent PE is defined as symptomatic and objectively confirmed with contrast-enhanced chest CT or invasive contrast pulmonary angiography.
Refined Modified Miller Score (RMMS)	Like the Modified Miller (MM) score, the Refined Modified Miller score (RMMS) regards each lung as having 10 segmental arteries, and the degree of obstruction of the segmental pulmonary arteries is measured using an ordinal scale. In contrast to the MM, however, the RM score allows for a finer distinction of partial obstruction in seven major arteries; the main pulmonary artery, left and right pulmonary artery, left and right interlobar arteries, left and right basal trunks. Partial obstruction is classified into three categories based upon cross-sectional diameter reduction: 0.5 for 1–33%, 1.0 for 34–66%, and 1.5 for 67–99% obstruction. As in the MM scoring system, the weighted score of the major supplying artery is compared with the sum of its tributaries, and the larger number is recorded. For example, if thrombus obstructed the lumen of a basal trunk vessel by 50% (score =1.0 x 7), but its four segmental tributaries were fully occluded (score = 2.0 x 4), the higher value of 8 would be recorded as the RMM score. A cumulative score is calculated by summing the scores for all arteries. Similar to the MM score, the RMM score can range from 0 to 20 per lung, for a maximum of 40 bilaterally.[25]

3.0 TERMS AND DEFINITIONS (CONTINUED)

TERM	DEFINITION
RV/LV	Right ventricular / left ventricular
SAE	An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and will be collected when the patient outcome is: Death Life-threatening - Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient. Hospitalization (initial or prolonged) - Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event). Disability or Permanent Damage - Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life. Congenital Anomaly/Birth Defect - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child. Required Intervention to Prevent Permanent Impairment or Damage (Devices) - Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product. Other Serious (Important Medical Events) - Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.
SaO_2	Arterial oxygen saturation
S_pO_2	Arterial oxygen saturation measured by pulse oximetry
Submassive PE	A normotensive patient with PE and evidence of RV dysfunction
S_vO_2	Venous oxygen saturation drawn from the pulmonary artery

3.0 TERMS AND DEFINITIONS (CONTINUED)

TERM	DEFINITION
TIA	Transient ischemic attack
Troponin	Cardiac troponins are the most sensitive and the most specific biochemical markers showing myocardial injury. Elevated troponin can also be seen in acute pericarditis, myocarditis, acute PE, severe cardiac failure, sepsis and acute renal failure as well as in myocardial infarction. In acute PE, the mechanic load of the right ventricle is increased because of the increased pulmonary vascular resistance following pulmonary artery obstruction. That can lead to acute right ventricular dilatation. The dilatation and hypokinesia of the right ventricle may cause severe myocardial ischemia and increase the troponin levels. Increased serum Troponin levels support the diagnosis of severe PE.
UADE	According to 21 CFR 812.3(s) an unanticipated adverse device effect means any serious adverse effect on health or safety of 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 investigational plan or application(including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
UFH	Unfractionated heparin
USAT	Ultrasound assisted thrombolysis
VTE	Venous thromboembolism - a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

4.0 BACKGROUND AND RATIONALE

4.1 Clinical Problem

Acute venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and acute pulmonary embolism (PE). PE occurs when a deep vein thrombus breaks loose and embolizes to the pulmonary artery. Pulmonary embolism is the third leading cause of cardiovascular death after myocardial infarction and stroke and is a major global health problem.[1,2]

Raskob et al (2014) conducted a literature search and review and found that there is a strong and consistent association between an increase in incidence of VTE and increasing age. They found the annual incidence increased from between 2 and 7 per 1,000 population for those 79 and younger to between 3 and 12 per 1,000 population for those aged 80 and older. This finding has major implications for the treatment of the elderly in the US healthcare system.[2] It is important to note that 60 percent of the VTE events are associated with hospitalization.[3] The number of deaths from VTE in the USA has previously been reported to be approximately 300,000 annually.[3,4] Clinically, study subjects may present with DVT or PE, or both. With many of the known risk factors, advanced age, immobility, surgery, obesity, increasing in our society, this number only continues to grow. Because there is no national surveillance program for VTE, the precise number with VTE of all types is unknown.[5,6]

Patients who present with PE may be classified into low risk, intermediate risk (submassive) or high risk (massive) PE. Both massive and submassive PE cause right ventricular (RV) dysfunction, while massive PE in addition causes systemic hypotension. Typical diagnostic studies include contrast enhanced computerized tomography (CT) to diagnose the PE, echocardiography to assess right and left ventricular function, and cardiac biomarkers, such as troponin I, and BNP to assess the degree of myocardial ischemia/strain associated with the PE. Patients categorized as having a low-risk PE do not have evidence of hemodynamic compromise or RV dysfunction. Low risk PE patients are not included in this study for obvious reasons.[7]

4.2 Current Treatment Options

Anticoagulant therapies are administered to symptomatic patients while their workups are being completed for a definitive diagnosis of massive or submassive PE. For the treatment of massive and submassive PE, both systemic administration and catheter-directed administration of thrombolytic therapies have been utilized.[8-10] However, systemic administration of thrombolytics carries a prohibitively high risk of bleeding: Up to 7% intracranial bleeds and up to 20% major bleeding rates; hence the attraction of delivering thrombolytics in much lower dosage directly into the clot to treat this potentially life-threatening condition.[11]

Devices for percutaneous treatment of patients in whom systemic thrombolytic therapy is absolutely contraindicated have been developed and utilized. The percutaneous devices include manual thrombus fragmentation using a balloon dilatation catheter or a pigtail (off-the shelf technologies). More recently, catheters specifically created for thrombus fragmentation that produce greater fragmentation of the clot compared to off-the-shelf technologies mentioned

previously, without aspirating the clot; aspiration or suction thrombectomy devices to decrease thrombus burden; rheolytic thrombectomy where a saline jet is directed into the clot and the clot and saline are aspirated, have been introduced.[7-10,12-14] However, there are also hazards associated with rapid clot fragmentation including hemodynamic collapse due to the distal embolization of thrombus and release of vasoactive substances.

Over the past several years a device received 510(k) clearance for its ultrasound-facilitated, catheter directed low-dose fibrinolysis using r-tPA (EKOS, Bothell WA). With this technology, the EKOS ultrasound device was used to deliver t-PA in patients with massive and submassive PE at 1mg/hour over 24 hours (unilateral PE), and 2mg/hr over 12 hours (bilateral PE).[15]

More recently, studies have reported that the ultrasound component of the EKOS device does not contribute to the effectiveness of the treatment of submassive and massive pulmonary embolism. Kuo et al (2015) found in a real-world registry, for CDT that incorporated USAT, there was no advantage in patients treated with USAT vs standard CDT. These data suggest that CDT may be performed effectively without the added cost associated with USAT.[16] In a subgroup analysis comparing patients treated with EKOS to those treated with standard infusion catheters, Bloomer et al (2017) reported a study for the Safety of CDT for massive and submassive PE: Results of a multi-center registry and Meta-analysis. Bloomer et al found in a subgroup analysis comparing patients treated with EKOS to those treated with standard infusion catheters, that there were similar PA pressure changes after CDT and similar complication rates. CDT is associated with a low major complication rate.[17]

Tafur et al (2016) conducted a Systematic Review and Meta-Analysis of Modern Literature. They concluded from their study current clinical evidence does not show that USAT is superior to other CDT methods.[18]

Overall, CDT decreased PASP, decreased RV to LV diameter ratio, and reduced the Modified Miller Index scores. The goal of CDT is to substantially reduce thrombus burden, as assessed by the Modified Miller Index on CTA, which remains high with currently available catheters, with or without USAT.

While it is critical to reduce RV/LV ratio, it is of great importance to both short-term and long-term patient outcomes to decrease the thrombus burden as much as is feasible. Even a small reduction in the clot burden can translate into a marked improvement in RV function and improve acute survival. However, much more effective reduction in the residual clot burden is required to reduce the long-term complications of PE, including disabling post-PE syndrome and chronic thromboembolic pulmonary hypertension (CTEPH).[7]

4.3 Study Rationale

While the medical community continues to focus on prevention of VTE, half of all VTE patients have unprovoked VTE. Therefore, the treatment options for patients who present with DVT and/or acute PE must continue to evolve to increase efficacy, decrease side effects, limit long-term complications, and provide an improved quality of life for these patients. This study is focused on the treatment of patients with acute submassive PE with an interventional device designed to increase the exposure of the thrombus burden to endogenous and exogenous

thrombolytics, thus this increased exposure has the potential to greatly decrease the thrombus burden.

The Bashir™ Endovascular Catheter has been designed to administer therapeutic agents in the peripheral vasculature. Because of the unique design of the catheter, with its six expandable infusion limbs, the Bashir™ Endovascular Catheter has the ability to: 1. Create a much larger central channel for blood flow, thereby utilizing the body's own endogenous fibrinolytic agents to lyse the clot, and 2. Greatly enhance the radial dispersion of a catheter-administered thrombolytic agent throughout the thrombus. Expansion of the multiple arms of the basket in the infusion catheter causes fissuring of the clot. The net result is that a greater surface area of clot is exposed to both endogenous and exogenously administered lytic agents, thereby promoting clot dissolution.

This study will utilize the Bashir™ Endovascular Catheter and the Bashir Endovascular Catheter with a short basket (Bashir™ S-B endovascular catheter) to administer catheter directed thrombolysis in patients with submassive PE who have consented and meet all eligibility criteria. The Bashir™ and Bashir™ S-B endovascular catheters represent a new methodology for localized catheter-based delivery of thrombolytics. The thrombolytic to be used in this study is r-tPA (Genentech Corporation, South San Francisco, USA).[19] The dosing of the thrombolytic in the past has been much greater than what is proposed in this study. The SEATTLE II study administered a total of 24 mg of r-tPA over 12 hours for bilateral PE and 24mg over 24 hours for unilateral PE. The incidence of major bleeding in the SEATTLE II study was 10 percent.[20] The design of the Bashir Endovascular Catheter with the multiple infusion limbs creating a basket-like formation when expanded, provides an immediate channel for blood flow through the thrombus and a greater surface area in the thrombus for the endogenous and exogenous thrombolytics to take effect, as described above.

Because of the rationale stated previously, a reduced dose of thrombolytic can be administered over a reduced period of time due to an increased exposure of the clot to endogenous and exogenous thrombolytics for clot dissolution. The OPTALYSE study, using the EKOS catheter, was conducted to assess the outcomes with lower dose r-tPA administration for the treatment of acute submassive PE. Four groups were administered lower doses of r-tPA over a shorter period of time. While each group showed a statistically significant reduction in RV/LV ratio at 48 hours post-procedure, the reduction in residual clot burden was noticeably lower (6%) in patients treated with the smallest dose of r- tPA for the shortest time period (4/8 mg r-tPA over 2 hours) compared to those treated with the highest dose for the longest duration (26% reduction in clot burden; 12/24 mg r-tPA over 6 hours). This illustrates the discordance between reduction in RV/LV diameter ratio and reduction in clot burden, as well as a dose response relationship. between the dose of r-tPA administered and the reduction in clot burden.[30] It is much easier to achieve the former than the latter with low doses of r-tPA for shorter periods of time. There is clearly also a lot of room for improvement if 74% of the clot burden still remains after the highest dose of infusion in the OPTALYSE study.[21]

We hypothesize that the dose of r-tPA may be reduced using the Bashir™ Endovascular Catheter from what was administered in the SEATTLE II study, i.e. 24mg over 12 hours (bilateral PE) or 24 hours (unilateral PE), because of its unique features described previously, as well as our experience in the First- in-Man study just completed with the BEC in patient with acute submassive pulmonary embolism (see below).[20] We therefore propose to utilize the following regimen: r-tPA 2mg in 20cc administered, 1.0mg in two 10cc increments into the PA for a total of 2 pulse sprays into the infusion basket. This will be done for each PA if the subject has bilateral pulmonary embolisms. The pulse sprays will be followed by a 5mg infusion at 1.00mg/hr until complete for unilateral PE, and 5mg infusion into each pulmonary artery for bilateral PE, at 1.0mg/hr until complete. This is a total of 10.0mg over approximately five hours (pulse spray 1.0mg x 2 sprays = 2mg plus infusion at 1.0mg/hr x 5 hours = 7mg for unilateral PE). For bilateral PE, we propose to administer the same pulse spray and same infusion dose into each PA for a total of 14mg administered. This is a substantially lower dose and a shorter duration of treatment compared to SEATTLE II for the treatment of PE in a similar patient cohort.

4.4 First-in-Man Study Results

The first-in-man study has been completed. Nine subjects were enrolled, treated, and followed through 30-day follow-up. Patients received 2 X 1mg pulse sprays of r-tPA into each affected pulmonary artery followed by a total of 10mg r-tPA over 8 hours. The total dose of r-tPA for unilateral PE was thus 12mg and for bilateral PE 14mg. Through 30-day follow-up there were no deaths, BEC or r-tPA related major bleeding, or device related adverse events. After 48 hours the RV/LV ratio decreased from 1.52 ± 0.26 to 0.97 ± 0.06 (p = .0009: 95% CI = 0.33 to 0.82: 36.7% reduction) as assessed by an independent core lab (Medical Metrics, Houston, TX). Thrombus burden measured by Modified Miller Index as assessed by the independent core lab (Medical Metrics, Houston, TX) decreased from 25.4 ± 5.3 to 16.0 ± 4.0 (p = .0005: 95% CI = 5.5 to 13.4: 37.1% reduction). BEC CDT appears safe, preliminary evidence shows that this platform technology leads to significant reduction in RV/LV ratio and thrombus burden. The study protocol permitted to enroll up to ten (10) subjects. The sponsor stopped enrollment on December 3, 2019 due to the consistent results shown across the sites after nine (9) subjects were enrolled.

5.0 INVESTIGATIONAL DEVICE

The Bashir™ Endovascular Catheter (BEC) and the BEC Short Basket (S-B) are devices intended for the localized infusion of therapeutic agents into the pulmonary artery and peripheral vasculature. The distal infusion segment of the device contains an expandable radial array of conduits with a total of 48 laser drilled orifices used for the delivery of the therapeutic agents at multiple cross-sectional points of the target vessel location. The infusion segment can be expanded and collapsed by the actuator (slider) located on the handle at the proximal end of the device. The infusion line connector is also located on the handle.[22] The difference between the BEC and the BEC S-B is solely in the length of the basket. In its unexpanded state, the basket of the BEC 12.5cm long and the BEC S-B basket is 10cm long. The choice of device used will be at the physician's discretion based on the patient's anatomy.

Figure 1. Bashir Endovascular Catheter

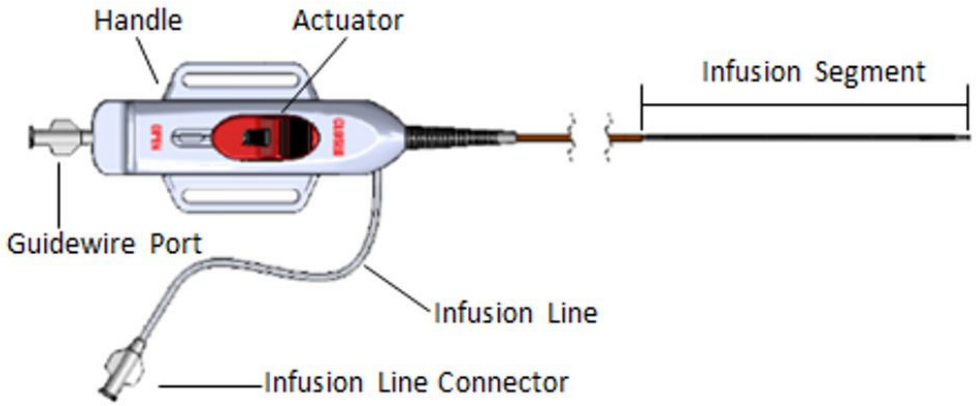

Figure 2. Bashir Endovascular Catheter with Basket Expanded

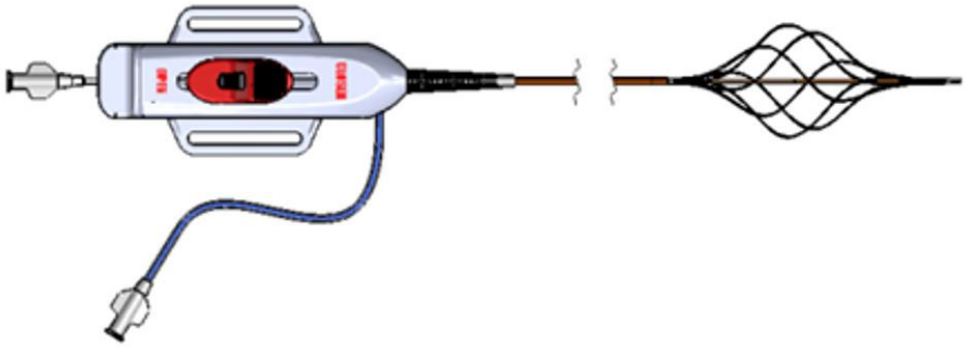

Table 1. Bashir™ Endovascular Catheter Dimensions

Bashir Endovascular Catheter	
French Size	7F (2.3mm)
Effective Length	92.5cm (36.44 in)
Infusion Segment Length	12.50cm (4.94 in)
Infusion Basket Diameter	45mm Maximum
Bashir Endovascular Catheter Basket Length Unexpanded	12.50cm
Bashir Endovascular Catheter – Short Basket	
French Size	7F (2.3mm)
Effective Length	92.5cm (36.44 in)
Infusion Segment Length	10.0cm (3.94 in)
Infusion Basket Diameter	42mm Maximum
Bashir Endovascular Catheter Short Basket Length Unexpanded	10.0cm

6.0 STUDY DESIGN

6.1 Study Objective

To demonstrate the efficacy and safety of the Bashir™ and Bashir™ S-B Endovascular Catheters for the administration of pharmaco-mechanical catheter directed therapy using low dose r-tPA for the treatment of acute submassive pulmonary embolism.

6.2 Endpoints

6.2.1 Primary Efficacy Endpoint

Reduction in RV/LV diameter ratio as measured by CTA within 48 hours after the completion of r-tPA treatment.

6.2.2 Primary Safety Endpoint

Major bleeding, as defined by International Society of Thrombosis and Hemostasis (ISTH), within 72 hours of initiation of r-tPA infusion. ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and:

a. Fatal bleeding; and/or
b. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or
c. Bleeding causing a fall in hemoglobin level of 2.0g/dL (1.24mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.[27]

6.2.3 Secondary Endpoints

1. Device Success: The number of devices with therapy delivered without a device failure.
2. Refined Modified Miller Score as measured on CTA within 48 hours after the completion of the r-tPA infusion compared to baseline as measured by core lab. [25]
3. All-cause mortality at hospital discharge through 30-day follow-up.
4. SAEs through 30-day follow-up.
5. AEs through 30-day follow-up.
6. UADEs through 30-day follow-up.
7. Recurrent PE through 30-day follow-up.
8. Clinically Relevant Non-Major bleeding: Any sign or symptom of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
    a. Requiring medical intervention by a healthcare professional.
    b. Leading to hospitalization or increased level of care.

c. Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation. [27]

9. Technical procedural complications.
10. Systolic PA pressure measured at completion of infusion after BEC(s) removal and compared to baseline.
11. Cardiac output (CO by Modified Fick calculation) and cardiac index (CI) following completion of the r-tPA infusion compared to the baseline. Please refer to Terms and Definitions section for the Modified Fick calculation to be done in the IR suite / cath lab at baseline and the ICU after BEC removal).

6.3 Eligibility Criteria

The population to be enrolled in this study includes patients 18 to 75 years of age who present with symptoms of acute submassive PE within 14 days of onset of symptoms will be considered for this study.

6.3.1 General Inclusion Criteria

All answers must be YES to the inclusion criteria below:

1. Willing and able to provide informed consent;
2. Age 18 years of age to ≤ 75 years of age;
3. PE symptom duration ≤ 14 days;
4. Filling defect on at least one main or lobar pulmonary artery as determined on CTA;
5. RV/LV diameter ratio ≥ 0.9 by CTA as determined by the investigative site;
6. Willing and able to comply with all study procedures and follow-up.

6.3.2 General Exclusion Criteria

All answers must be NO to the exclusion criteria below:

1. CVA or TIA within one (1) year;
2. Head trauma, active intracranial, or intraspinal disease ≤ one (1) year prior to inclusion in the study;
3. Active bleeding from a major organ within one (1) month prior to inclusion in the study;
4. Intracranial condition(s) that may increase the risk of bleeding (e.g., neoplasms, arteriovenous malformations, or aneurysms);
5. Patients with bleeding diatheses;
6. Hematocrit < 30%;
7. Platelets < 100,000/μL;
8. INR > 1.5 if currently on warfarin (Coumadin®);
9. aPTT > 50 seconds in the absence of anticoagulants;
10. Major surgery ≤ 14 days prior to inclusion in the study;
11. Serum creatinine > 2.0mg/dL;

12. Clinician deems high-risk for catastrophic bleeding;
13. History of heparin-induced thrombocytopenia (HIT Syndrome);
14. Pregnancy;
15. SBP < 90 mmHg > 15 minutes within two (2) hours prior to BEC procedure and is not resolved with IV fluids;
16. Any vasopressor support;
17. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR) during this hospitalization at treating institution and/or referring institution;
18. Evidence of irreversible neurological compromise;
19. Life expectancy < one (1) year;
20. Use of thrombolytics or glycoprotein IIb/IIIa inhibitor within 3 days prior to inclusion in the study;
21. Use of non-vitamin K oral anti-coagulants (NOACs), such as rivaroxaban (Xarelto®), apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa®) within 48 hours prior to inclusion in the study;
22. Profound bradycardia requiring a temporary pacemaker and/or inotropic support;
23. Previous enrollment in this study;
24. Morbidly obese patient who by the judgement of the investigator is high risk for bleeding;
25. BMI > 45kg/m^2;
26. Absolute contraindication to anticoagulation;
27. Uncontrolled hypertension defined as SBP > 175mmHg and / or DBP > 110mmHg with pharmacotherapy within two (2) hours prior to inclusion in the study;
28. Subject is currently participating in another study;
29. Any arterial line placement;
30. Current positive COVID diagnosis, or ≤ 8 weeks negative of COVID, or > 8 weeks from positive COVID test and with current symptoms, or current active viral pneumonia on chest CT scan.
31. In the opinion of the investigator, the subject is not a suitable candidate for the study.

6.4 Study Duration

6.4.1 Enrollment

It is estimated that up to 20 sites will be qualified to participate; they will enroll and treat up to 125 subjects (to achieve 100 evaluable subjects) over an estimate of 24 months. There may be an unlimited number of subjects consented for this study to achieve completion of 100 evaluable subjects. A maximum of 125 subjects will be enrolled, treated, and complete the study through 30-day follow-up. The subjects enrolled and treated per site will not exceed 20 subjects.

6.4.2 COVID-19 Impact Assessment Form - Enrollment

A COVID-19 Impact Assessment Form will be completed to assess if study investigators and other site personnel are unable to be on site to manage enrollment, and having subjects at the institution places them at risk, and if there is a known risk that follow up may not occur as planned. This form shall be submitted to the CRO as soon as possible. The CRO will review the Impact Assessment Form with Thrombolex Inc. and communicate an appropriate plan according to the site's level of operation. Enrollment will be suspended if a site cannot enroll in accordance with the study protocol. All actions regarding suspension and activation will be documented. The site IRB will be sent all related communications.

The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted.

6.4.3 Follow-up

The follow-up for each subject will be completed at 30-days post-hospital discharge.

6.4.4 COVID-19 Impact Assessment Form - Follow-Up Visits

The COVID-19 Impact Assessment Form identifies aspects of the follow-up visits that can be completed and how (i.e. via telephone, or video conference). The CRO will review the Impact Assessment Form with Thrombolex, Inc. and generate site specific follow-up protocols to be implemented. This will ensure that alternate follow-up visit plans are consistent for the site and in accordance with the COVID-19 Impact Assessment. The COVID-19 Impact Assessment Form, if completed by site(s) due to necessary changes in study conduct, the changes will be in effect until clinical research operations are restored.

All actions related to COVID-19 will be documented. If a follow-up visit under the COVID-19 does not meet protocol requirements, the visit will be reported as a protocol deviation and tracking of visits where protocol requirements cannot be met conducted under COVID-19 will be documented.

The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate

which trial participants were impacted and how those trial participants were impacted.

6.4.5 Complete Study Period

It is estimated that this study will require up to 24 months to complete enrollment and follow-up.

6.4.6 Subject Participation

Each subject will participate in this study for approximately 30 days from consent through 30-day follow-up.

7.0 METHODOLOGY

7.1 Pre-Procedure Testing Within 48 Hours Pre-Procedure

7.1.1 Laboratory Tests

1. **CMP, CBC, Cardiac Biomarkers Troponin and BNP** – These tests will be drawn within 48 hours pre-procedure.
2. **aPTT** – Drawn within 48 hours pre-procedure. If the investigator's standard of care is to use heparin, unfractionated heparin will be administered, and aPTT is to be drawn prior to the BEC procedure.
3. **International Normalized Ratio (INR)** – INR will be drawn within 48 hours pre-procedure for patients who are on warfarin (Coumadin®) and must be ≤ 1.5 to be eligible for enrollment. Patients who are on warfarin who have consented for the study and have an INR ≤ 1.5, warfarin will be discontinued during the heparin infusion and the r-tPA infusion and restarted prior to hospital discharge.

7.1.2 Imaging

1. **Contrast Enhanced CT of Chest (CTA)** – A chest CTA will be performed within 48 hours pre-procedure. The CTA is used to determine the pre-procedure Refined Miller Score by core lab analysis. The CTA will be used by the study site to determine eligibility into the study ensuring the RV/LV diameter ratio is ≥ 0.9 by CTA. *CTA will be sent to the core lab for analysis.* [25]
2. **Lower Extremity Venous DUS** – A duplex ultrasound is required within 48 hours pre-procedure to verify patency of the common femoral vein (CFV) for femoral access. The right CFV or the left CFV may be used for access, whichever is patent. If both of the CFVs are not patent, an internal jugular (IJ) vein may be used for access. IJ may also be used if that is the operator's preference.

7.1.3 Assessments

1. **Physical Examination** – The physician will perform a physical exam within 48 hours prior to the procedure to ensure the subject meets eligibility criteria.
2. **RV/LV Diameter Ratio** – The RV/LV ratio will be measured within 48 hours pre-procedure by CTA to ensure the subject meets the eligibility criteria of an axial RV/LV ratio ≥ 0.9, as determined by the investigative site. The independent core lab protocol will be followed for data acquisition. *The CTA will be sent to the core lab for analyses.*
3. **12-Lead Electrocardiogram (ECG)** – A 12-lead ECG will be performed prior to the procedure.

7.1.4 Anticoagulation

Pre-procedure: There is a choice of anticoagulation to be administered according to the investigator's standard of care.

1. If the investigator's standard of care is to use heparin, unfractionated heparin (UFH) will be administered by IV infusion to maintain therapeutic anticoagulation.
2. If the administration of LMWH, such as enoxaparin (Lovenox®), is the investigator's standard of care, administer 1mg/kg sub-Q every 12 hours.

BEC Procedure: Choose one of the two scenarios below according to the investigator's standard of care:

1. If heparin was administered pre-procedure or patient received LMWH 1mg/kg SQ >12 hours prior to the BEC procedure, start BEC procedure with subject on heparin infusion in the IR suite / cath lab. Once r-tPA infusion is started, decrease dose of heparin to five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. ACTs may be checked if standard of care.
2. If LMWH was administered pre-procedure, start BEC procedure without heparin in the IR suite / cath lab, until patient is 8 hours post last dose of LMWH. Then start dose of UFH at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. ACTs may be checked if standard of care.

Post-BEC Procedure: Heparin infusion at the completion of the BEC procedure and during the r-tPA infusion:

1. Continue heparin administration through the side arm of the sheath at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. If bilateral BECs are in place, then one-half of the dose of the heparin infusion must be administered into each sheath for a total prescribed dose. Administer half (or approximately half) the dose prescribed by the investigator into the side arm of each sheath to equal the prescribed dose.

2. If subject has not reached 8hrs post last dose of LMWH in the IR suite / cath lab, then in the ICU start dose of UFH at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr.

Post r-tPA Infusion: Once r-tPA infusion is complete, increase UFH dose to keep aPTT within therapeutic range (aPTT suggested 60-80 sec). Replace r-tPA infusion with standard heparinized saline at 30cc/hr on an infusion pump through the basket infusion line connector of the BEC(s) to maintain patency until removal of the BEC(s).

Sheath Removal: Stop UFH for at least one (1) hour prior to sheath removal, unless the operator believes that the UFH, in the best interest of the patient, should not be stopped prior to and during sheath removal. Remove sheaths according to standard of care.

Anticoagulation Post-Sheath Removal: Re-start anticoagulation within one (1) hour post sheath removal with LMWH 1mg/kg SQ q12hrs or UFH at therapeutic doses for 24hrs post sheath removal. After 24hrs post sheath removal, physicians can start therapeutic anticoagulation according to their standard of care. If physicians choose to use DOACs then patients should be properly loaded according to the current guidelines.

7.1.5 Data Collection

The following data will be collected and documented in the CRF in addition to the required pre-procedure testing.

1. **Informed Consent** – Required for all study subjects prior to any testing that is not the standard of care. Please note that the screen failure rate is unknown for this study. Patients may be consented until up to 125 subjects have been enrolled and treated per protocol. Therefore, more subjects will be consented than are treated in order to reach the minimum of 100 subjects included in the analysis. The subjects enrolled and treated per site will not exceed 20 subjects.
2. **Demographics and Medical History** – Recorded once Informed Consent has been obtained.
3. **Eligibility Criteria** – All inclusion criteria must be met, and all exclusion criteria must not be met to enroll in this study.
4. **Medications** – All antiplatelet, anticoagulant, cardiac meds, and NSAIDs will be recorded within 48 hours pre-procedure, at baseline.
5. **Refined Modified Miller Score (RMMS) –** Refined Modified Miller Score (RMMS) will be calculated by the core lab at baseline. The CTA will be sent to the core lab for RMI analysis.[25]

8.0 IR SUITE / CATH LAB STUDY PROCEDURES

Should the study subjects meet all eligibility criteria for inclusion into the study, continue with the following procedures that take place in the IR suite / cath lab.

8.1 Required Accessories and Supplies

8.1.1 Accessories to be provided by the IR suite / cath lab

1. Introducer Sheath(s) - 7F or greater and of appropriate length. The sheath selected must reach the target site and allow for retraction to expose the infusion basket. A 75cm length or less straight tip sheath, e.g. Flexor® Raabe Guiding Sheath (Cook Medical, Inc.) or equivalent for femoral access is recommended for most. ***The sheath length must be long enough to reach the clot and must not exceed 75cm.*** A shorter sheath of appropriate length may be utilized for IJ access and the ***sheath used must be able to reach the clot.***
2. Ultrasound for ultrasound guided access *is required* for both IJ and CFV access.
3. Micropuncture kit for IJ and CFV venous access is required for both IJ and CFV access.
4. Guidewire - .018in x 300cm in length minimum (Hi-torque Steelcore® Peripheral Guide Wire Abbott Vascular or equivalent).
5. 7F Swan-Ganz catheter with 0.035in guidewire lumen (Arrow® or equivalent) or an angled pigtail catheter.
6. 3-way stopcock(s) – with Luer-lock connectors (2 for unilateral / 4 for bilateral procedures).
7. Infusion pump(s) and IV tubing for r-tPA infusion(s).
8. Heparinized saline for flushing.
9. 0.9% NaCl intravenous (IV) infusion bag 500cc for r-tPA pulse spray mixture.
10. Sterile water for injection, USP (Do not use bacteriostatic water, USP for injection) – for 2.2mg vial Cathflo™ Alteplase (r-tPA) mixture (Genentech, Inc., South San Francisco, CA).
11. r-tPA vial(s) for pulse sprays.
    a. **Unilateral PE**: One (1) 2.2mg vial of Cathflo™ Alteplase (r-tPA) for pulse spray use.
    b. **Bilateral PE**: Two (2) 2.2mg vials of Cathflo™ Alteplase (r-tPA) for pulse spray use.
12. 10cc syringes to administer pulse spray r-tPA
    a. **Unilateral PE:** Two (2) 10cc syringes for injecting the pulse sprays.
    b. **Bilateral PE:** Four (4) 10cc syringes for injecting the pulse sprays
13. Heparinized saline at 500 units/500cc .9% NaCl or 100 units/500cc .9% NaCl or .45% NaCl or other standard of care heparinized saline concentration, or normal saline without heparin intravenous (IV) pressure infusion bag(s) with transducer tubing if the BEC will be used to monitor PA pressures in the ICU.

14. r-tPA Infusion:
    a. **Unilateral PE**: Obtain three (3) 2.2mg vials of Cathflo™ Alteplase (r-tPA) for continuous infusion to be started in the IR suite / cath lab for a total of 5mg for one infusion. *Mixture requirements are in section 8.3.*
    b. **Bilateral PE**: Obtain five (5) 2.2mg vials of Cathflo™ Alteplase (r-tPA) for continuous infusion to be started in the IR suite / cath lab for a total of 5mg for each infusion for two infusions. *Mixture requirements are in section 8.3.*

8.1.2 Procedure Supplies Provided by the Sponsor

1. Bashir™ and Bashir™ S-B Endovascular Catheters

8.2 Baseline Hemodynamic Readings

The following readings will take place using the Swan-Ganz or angled pigtail catheter in the IR suite / cath lab prior to placement of the Bashir™ Endovascular Catheter(s).

1. PA Pressures measured using a Swan-Ganz catheter or angled pigtail: PAS / PAD / PA Mean
2. S_pO_2 – Pulse Oximeter Arterial Oxygen Saturation
3. S_vO_2 – Mixed Venous Oxygen Saturations (from tip of a pigtail catheter or Swan-Ganz Catheter PA port)
4. CO – Modified Fick Calculation
5. CI – Calculation

8.3 r-tPA Administration - Prepare Pulse Spray(s) and Infusion(s) prior to opening the Bashir Endovascular Catheter (BEC).

8.3.1 Reconstitution of r-tPA Pulse Spray Mixture

1. Obtain a 2.2mg vial of r-tPA (1mg/ml) provided by the site.
2. Mix the lyophilized powdered r-tPA with 2.2ml sterile water for injection (as stated in the r-tPA information sheet) to obtain 1mg/ml. Do **not** use bacteriostatic sterile water for injection.
3. Aspirate exactly 1mg (1ml) into a 3cc syringe (for accuracy).
4. Inject 1.0mg (1ml) of r-tPA mixture into a 10cc syringe, and aspirate 0.9% NaCl to have a maximum of 10cc of diluent and drug mixture in the syringe.
5. Repeat step 1 through 4 above x 1.
6. This equals two (2) 10cc pulse spray doses (1.0mg/10cc in one 10cc syringes per pulse spray) with 1.0mg r-tPA per dose - Total of 2.0mg of r-tPA for unilateral PE).
7. If treating bilateral PE, repeat steps 1 through 5 above, for a total of 4.0mg, 2.0mg per PA. This equals four (4) 10cc pulse spray doses (1.0mg/10cc in one 10cc syringes per pulse spray).

Table 2. r-tPA Doses and Mixtures for Pulse Sprays and Infusions through the BEC

Pulse Sprays						
	No. of 2.2mg Cathflo™ r-tPA Vials Required	**Diluent: Sterile Water for Injection**	**Total Diluent Required 0.9% NaCl**	**Total Dose per Syringe**	**Total Syringes for Pulse Sprays**	**Total Pulse Spray Dose**
Unilateral PE	1	2.2ml per vial to have 1mg/ml	Total of 20cc including r-tPA	1.0mg in each 10cc syringe	Two 10cc syringes	2.0mg
Bilateral PE	2	2.2ml in 1 vial for 1mg/ml	Total of 40cc including r-tPA	1.0mg in each 10cc syringe	Four 10cc syringes	4.0mg

Infusion(s)				
	No. of 2.2mg Cathflo™ r-tPA Vials Required	**Total Diluent Required 0.9% NaCl**	**Infusion Rate**	**Total Infusion Dose**
Unilateral PE	3	500cc total including r-tPA mixture x 1 bag	100cc/hr = 1.0mg/hr x 1 infusion until complete	5.0mg
Bilateral PE	5	500cc total including r-tPA mixture x 2 bags	100cc/hr = 1.0mg/hr per infusion x 2 infusions (1 into each BEC) until complete	10.0mg

8.3.2 Reconstitution of r-tPA IV Infusion Mixture

a. Unilateral PE

i. Obtain a 500cc bag of 0.9% NaCl for infusion.
ii. Aspirate 5cc of 0.9% NaCl from the 500cc IV bag to have a total diluent of 495cc.
iii. Mix three (3) vials (2.2ml injected into 2.2mg vials) of r-tPA with sterile water for injection until the lyophilized powder is dissolved, for a total of 6.6mg of r-tPA. (Do NOT use bacteriostatic water for injection).
iv. Aspirate 5ml (5mg) into a syringe from vials.
v. Verify 5ml are aspirated into the syringe.
vi. Inject the 5mg solution of r-tPA into the IV bag for infusion. The IV bag has a total of 5mg of r-tPA in 500cc of diluent.

b. Bilateral PE

i. Obtain two (2) 500cc bags of 0.9% NaCl for infusion.
ii. Aspirate 5cc of 0.9% NaCl from each 500cc IV bag to have a total diluent of 495cc in each bag.

iii. Mix five (5) vials (2.2ml injected into 2.2mg vials) of r-tPA with sterile water for injection until the lyophilized powder is dissolved, for a total of 10mg of r-tPA (1mg/ml).
iv. Aspirate 5ml (5mg) dose into a syringe from vials.
v. Verify 5ml are aspirated into the syringe.
vi. Inject the 5mg solution of r-tPA into one IV bag for infusion. The IV bag has a total of 5mg of r-tPA in 500cc of diluent.
vii. Repeat steps iv through vi for second IV bag.

9.0 BASHIR™ ENDOVASCULAR CATHETER INVESTIGATIONAL PROCEDURE

Please refer to the Instructions for Use for complete instructions on preparation, use, and handling of the Bashir™ and the Bashir™ S-B Endovascular Catheters (BECs).

9.1 Baseline Readings - Summary of Procedure Steps

1. It is recommended that the patient's blood pressure is under control prior to the investigational procedure.
2. Obtain venous access using ultrasound guidance and micropuncture needle. Ultrasound guidance and use of micropuncture needle is mandatory for both CFV and IJ access.
3. Place 7F sheath(s) in the RCFV or access point of choice (CFV or IJ). CFV or IJ access is operator's choice.

9.2 Choose one of the two anticoagulation options below according to the investigator's standard of care:

1. If heparin was administered pre-procedure or patient received LMWH >12 hours prior to the BEC procedure, start BEC procedure in the IR suite / cath lab while on heparin. Once r-tPA infusion is started, decrease dose of heparin to five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr.
2. If LMWH was administered ≤ 12 pre-procedure, start BEC procedure without heparin in the IR suite / cath lab, until patient is eight (8) hours post last dose of LMWH. Then start dose of UFH at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. ACTs may be checked if standard of care.

9.3 Summary of Procedure Steps

1. Using a .035in exchange length wire, insert the wire into a sheath and advance it up to the right atrium.
2. Insert the Swan-Ganz or angled pigtail catheter over the wire and advance it up to the right atrium.
3. Remove the guidewire.
4. Float the Swan-Ganz catheter or angled pigtail into the pulmonary artery and record baseline hemodynamic data

5. Insert the exchange length guidewire, or equivalent, into the Swan-Ganz or angled pigtail catheter. Remove the Swan-Ganz or angled pigtail catheter.
6. Exchange the Swan-Ganz Catheter, or angled pigtail, for a long 7F or greater sheath (CFV access) or 7F sheath (IJ access) which is placed into the PA where the thrombus is located.
7. Remove the guidewire and the dilator carefully from the PA making sure that the sheath does not jump forward.

9.3.1 Intra-procedure Data Collection Requirements

1. Hemodynamic readings
2. AEs / SAEs
3. Times of pulse sprays administration
4. Time the r-tPA infusion(s) started
5. Time of heparin infusion(s) started
6. Technical complications
7. Medications (antiplatelet, anticoagulant, cardiac medications, and NSAIDs only)
8. Equipment used
9. Blood pressure and heart rate, at start of procedure

9.4 Bashir Endovascular Catheter Use – Procedure Steps

1. **Prepare all r-tPA solutions and IV infusion mixtures in Section 8.3** prior to opening the Bashir™ Endovascular Catheter (BECs). The Bashir™ S-B Endovascular Catheter may be preferred for smaller patients or for treatment of thrombus in the left pulmonary.
2. Prepare the relevant BEC(s) for use:
   a. Ensure that the infusion basket of the BEC can be expanded and collapsed by moving the actuator on the handle backward and forward while depressing the white button.
   b. With the basket expanded, flush the basket infusion port with standard flush solution. Observe for flush solution exiting the infusion holes of the basket. Collapse the basket.
   c. Flush the wire lumen of the BEC observing that flush solution exits the tip of the catheter.
3. Using a .018in x 300cm length steel core non-hydrophilic guidewire, introduce the wire into the central lumen of the long sheath.
4. Backload the BEC onto the 0.018in guidewire and advance towards the long sheath. DO NOT insert the BEC into the sheath.
5. Attach a three-way stopcock to the infusion basket port of the BEC.
6. Commence r-tPA infusion via the stopcock on the basket infusion line connector using an infusion pump. Start the infusion through the BEC PRIOR TO inserting the catheter into the sheath. This is to maintain patency during catheter insertion, advancement, and positioning in the patient.

7. Advance the BEC into the target PA and retract the sheath to expose the basket segment.
8. Do NOT aspirate back from the basket infusion line connector to back bleed. Only maintain forward flow by infusing the r-tPA at the prescribed rate 100cc/hr for unilateral PE and bilateral PE, as stated in Table 2.
9. Keeping the wire in the central wire lumen expand the infusion basket of the BEC.

9.5 Pulse Spray of r-tPA for Unilateral and Bilateral PE

a. **Unilateral PE**: With the catheter in the target PA, and after verifying that the basket portion of the catheter has exited the sheath under fluoroscopy, and with the guidewire in place, expand the basket of the catheter to the desired diameter making sure that the infusion limbs are expanded to less than the diameter of the vessel wall.
b. Turn stopcock off to the infusion and administer 10ml (1.0mg r-tPA in 10ml) of pulse spray, from the 1st syringe of two syringes, into the thrombus at a steady rate over 10-15 seconds.
c. Under fluoroscopy, with the guidewire in place, collapse the basket and re-expand the basket.
d. Repeat this with the second 10cc syringe (1.0mg r-tPA in 10ml) over 10-15 seconds.
e. As soon as the pulse sprays are administered, turn the stopcock open to the r-tPA infusion to restart the r-tPA via the infusion port of the BEC.

Please note: Even if the clot appears to be primarily unilateral, the default should be to use a second BEC in the contralateral pulmonary artery if there is any substantial clot on the contralateral side.

f. **Bilateral PE**: Repeat, using a second BEC, steps a-e for bilateral PE.
g. Once pulse sprays are complete, the basket(s) should remain expanded.
h. Remove the guidewire(s), attach a 3-way stopcock and connect fluid or cap off the line. (See specifics at 9.9.3).

Please note that the BEC is to be placed in the optimal location to treat the PE. It is NOT to be used to selectively cannulate multiple branches of the pulmonary vasculature in multiple locations to administer the r-tPA.

9.6 r-tPA Infusion – Prior to Departing the IR Suite / Cath Lab

1. **For unilateral PE:** The total r-tPA infusion is 5mg at 1.0mg/hr. Using an IV pump at 100cc/hr, infuse the 500cc of 0.9% NaCl with the 5mg r-tPA at 1.0mg/hr until infusion is complete (approximately 5 hours).
2. **For bilateral PE:** The r-tPA infusion is 5mg at 1.0mg/hr into each BEC. Using two (2) IV pumps at 100cc/hr, infuse the 500cc of 0.9% NaCl x 2 simultaneously for 1.0mg/hr into each PE until complete (approximately 5 hours), for a total infusion dose of 10mg.

9.7 Anticoagulation Post-BEC Procedure

Heparin infusion at the completion of the BEC procedure and during the r-tPA infusion

1. Continue heparin administration through the side arm of the sheath at five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr. If bilateral BECs are in place, the heparin infusions must be administered into each sheath. Administer half (or approximately half) the dose prescribed by the investigator into the side arm of each sheath to equal the prescribed dose.
2. If subject has not reached 8hrs post last does of LMWH in the IR suite / cath lab, then in the ICU start dose of UFH to five (5) to eight (8) units/kg/hr up to a maximum of 1,000 units/hr.

9.8 Maintaining Patency Through the Central Lumen of the BEC(s) During Transport to ICU

To maintain patency of the central lumen (guidewire lumen) of the BEC(s) during transport to the ICU, follow hospital standard protocol during transport to ICU, unless the BEC central lumen is not going to be used for PA pressure monitoring in the ICU and it is capped off.

9.9 Preparation in IR Suite / Cath Lab for Transfer to ICU

1. Suture sheaths in place.
2. Secure r-tPA and heparin drips to maintain infusions in the ICU.
3. The BEC central lumen (guidewire lumen) may be used to monitor PA pressures in the ICU.
   a. Option #1: Connect fluid to central lumen (guidewire lumen) at hospital standard of care dose and rate (e.g. heparinized saline at 500 units/500cc .9% NaCl or 100 units/500cc .9% NaCl or .45% NaCl or other standard of care saline concentration, or normal saline without heparin) using pressure tubing to the stopcock to maintain patency until removal of the BEC(s). Using this set-up provides the option of monitoring the PA pressures in the ICU during the r-tPA infusion.
   b. Option #2: If the central lumen of the BEC(s) is/are not going to be used for monitoring pressure in the ICU, the central lumen may be capped off prior to leaving the IR Suite / Cath Lab.
4. Securing the device(s):
   a. For CFV Access: tape device to thigh. Then follow step "5" below.
   b. For Right IJ Access: Cover the catheter with a sterile sleeve (such as the sleeve that comes with a Swan-Ganz catheter) tape device to left pectoral area with the shaft of the catheter placed posterior to the neck. Then follow step "5" below. Do the opposite for Left IJ access.
5. Place a strong adhesive dressing, such as Tegaderm™ (3M™, St Paul, MN) or equivalent tape over the handle and the actuator (slider) to make sure the handle and actuator (slider) are secure and cannot be moved.

6. For femoral access, a knee brace is recommended to prevent the patient from bending his/her knee when the BEC is in place.

10.0 POST-PROCEDURE PATIENT MANAGEMENT AND TESTS

The study subject will be admitted to the intensive care unit (ICU) where nursing staff are experienced in the care of patients treated for pulmonary embolisms.

10.1 r-tPA Infusion – Intensive Care Unit

1. **r-tPA Infusion:** Maintain the r-tPA Infusion through the infusion line on the side of the handle of the BEC in the ICU for approximately five (5) hours from start of the infusion in the IR suite / cath lab. The infusion should run at the rate prescribed in this protocol until the infusion is complete. *See section 8.3*

10.2 Post-r-tPA Infusion:

1. **Maintain BEC Infusion Basket Patency:** Once the r-tPA infusion is complete, maintain patency through the infusion basket of the BEC(s) by replacing r-tPA infusion with heparinized saline (per hospital standard of care e.g. 500 units/500cc .9% NaCl or 100 units/500cc .9% NaCl or other standard of care heparinized concentration) using an infusion pump, at 30cc/hr, until the BEC(s) is / are removed. Please note this solution must be heparinized.
2. **Anticoagulation Post-r-tPA infusion:** At the completion of r-tPA infusion, increase heparin dose to therapeutic doses with target aPTT in therapeutic range (suggested 60-80sec).
3. **Physical Exam:** A physical exam is required to be performed as soon as possible after the completion of the r-tPA infusion.

10.3 The Completion of r-tPA Infusion in the ICU

1. The BEC catheter(s) will be removed as soon as possible at the end of infusion only by an operator trained and approved to place and remove the study device. Collapse the basket(s) of the BEC(s).
2. Remove the BEC by retracting the catheter(s) carefully into the sheath(s) and then removing them from the body. Do not remove the sheath(s) at this time.
3. Please note: If pressurized tubing set-up was used to monitor the pressure through the central lumen of a BEC in the ICU, aseptically remove the tubing from the port at the back of the BEC and set aside for using for step 5a below.
4. Back bleed the sheath(s) and flush with heparinized saline.
5. Attach pressure tubing to the side arm of the sheath(s) and record the following:
   a. Final hemodynamic parameters (PAS, PAD, PA Mean) – record from each PA if bilateral PE with bilateral sheaths in place.
   b. S_pO_2 – Pulse oximetry oxygen saturation.
   c. S_vO_2 – Mixed venous oxygen saturation.
   d. CO – Calculate using the Modified Fick formula.

e. CI – Calculate using the Modified Fick formula.

6. After BEC removal, the long sheath may be exchanged for a short sheath once the hemodynamic parameters have been recorded if the sheaths are not removed at the completion of the r-tPA infusion (after the effects of the r-tPA have worn off).

10.4 Sheath Removal

1. **Sheath removal:** Stop UFH for at least one (1) hour prior to sheath removal, unless the operator believes that the UFH, in the best interest of the patient, should not be stopped prior to and during sheath removal. Remove sheaths according to standard of care.
2. **Anticoagulation Post-Sheath Removal:** Re-start anticoagulation within one (1) hour post sheath removal with LMWH 1mg/kg SQ q12hrs or UFH at therapeutic doses for 24 hours post sheath removal. After 24 hours post sheath removal, physicians can start therapeutic anticoagulation according to their standard of care. If physicians choose to use DOACs then patients should be properly loaded according to the current guidelines.

11.0 TESTS REQUIRED 24 HOURS AFTER COMPLETION OF THE R-TPA INFUSION

11.1 Laboratory Tests and Other Tests

1. **BMP, CBC, Cardiac Biomarkers Troponin and BNP** – These tests will be drawn 24 hours (±8 hours) after completion of the r-tPA infusion.

11.2 Assessments

1. **Physical Examination** – The physician will perform a physical examination at the end of the infusion and 24 hours after completion of r-tPA infusion.
2. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through 24 hours.

11.3 Data Collection

The following data will be collected and documented in the CRF in addition to the required pre-procedure testing.

1. **Medications** – All antiplatelet, anticoagulant, cardiac medications, and NSAIDs will be recorded that are administered within 24 hours following the infusion.
2. **Laboratory Test Results** – Tests performed above will be documented in the CRF.

12.0 TESTS REQUIRED 48 HOURS AFTER COMPLETION OF THE R-TPA INFUSION

12.1 Imaging

1. **CTA** – A CTA will be performed at 48 hours (±8 hours) after the completion of the r-tPA infusion.

12.2 Assessments

1. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through discharge.

12.3 Data Collection

1. **Medications** – All antiplatelet, anticoagulant, cardiac medications, and NSAIDs will be recorded that are administered within 48 hours following the infusion.
2. **RV/LV Diameter Ratio** – This will be measured and calculated by CTA at 48 hours (±8 hours) following completion of the r-tPA infusion.

13.0 ASSESSMENTS REQUIRED 72 HOURS FOLLOWING START OF R-TPA INFUSION

13.1 Assessments

1. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through discharge.

   Please note the primary safety endpoint assessment for bleeding within 72 hours will be assessed through 72 hours (-4 / +12 Hours) following initial administration of the r-tPA infusion in the IR suite / cath lab.

13.2 Data Collection

1. **Medications** – All antiplatelet, anticoagulant, cardiac medications, and NSAIDs will be recorded that are administered within 72 hours following the infusion.
2. **If Subject has been discharged Prior to 72 Hour Visit** – If the study subject is discharged from the hospital prior to the 72-hour visit, the assessment may be conducted over the phone.
3. **COVID-19 Impact** - A COVID-19 Site Impact Assessment Form will be completed and submitted to the CRO prior to visits to be impacted by COVID-19.

14.0 ASSESSMENTS REQUIRED JUST PRIOR TO HOSPITAL DISCHARGE

14.1 Assessments

1. **Physical Examination** – The physician will perform a physical examination within eight (8) hours prior to discharge.
2. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through discharge.

15.0 30-DAY FOLLOW-UP VISIT POST PROCEDURE

15.1 Assessments

1. **Physical Examination –** The physician will perform a physical exam at 30-day follow-up visit (±7 days).
2. **AEs/ SAEs** – All adverse events will be recorded at the 30-day follow-up visit.
3. **COVID-19 Impact** – If, as referenced in section 6.4.4 of this protocol, the subject is unable to attend the 30-Day Follow-Up Visit in person due to COVID-19, the assessment may be done over the phone or by video conference. Documentation of the visit and how it was impacted by COVID-19 must be documented on the CRF. Any visit-related procedure that is not completed for the 30-Day Follow-up Visit under this COVID-19 amendment will be reported as a deviation. **Data Collection**

1. **Medications** – All antiplatelet, anticoagulant, cardiac medications, and NSAIDs post-discharge will be recorded at this visit.

16.0 ANTICIPATED ADVERSE EVENTS

The following events are anticipated adverse events in subjects who are treated for pulmonary embolism. An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

The signs, symptoms, and sequelae of an underlying adverse event (linked pathophysiologically to the AE) should not be reported as separate adverse events. All adverse events, of any type, are to be recorded on an Adverse Event case report form.

Table 3 lists the anticipated adverse events identified for the Bashir™ and the Bashir™ S-B Endovascular Catheters (BECs).

Table 4 lists the anticipated adverse events identified for the r-tPA infusion.

Table 5 lists the anticipated adverse events identified for the pulmonary embolism procedure.

Table 3. Anticipated Adverse Events Related to the Investigational Device[22]

Adverse Event	Definition
Allergic reactions	Any exaggerated immune response to a foreign antigen regardless of mechanism
Hematoma at access site	Blood collects under the skin in the area where the physician accessed the femoral artery to perform the treatment, and results in bruising (ecchymosis)
Hemorrhage	A profuse discharge of blood from a ruptured blood vessel resulting in a decrease in hemoglobin
Intimal damage	Trauma to the intimal lining of the vessel
Ischemia	Inadequate blood supply to an organ or part of the body or heart muscles
Pain and tenderness	Discomfort in an area that is impacted by the device
Vascular thrombosis	A formation of a blood clot in an artery or vein
Vessel perforation	A hole or tear in an artery or vein
Vessel spasm	A temporary tightening (constriction) of the muscles in the wall of one of the arteries that supplies blood flow

Table 4. Anticipated Adverse Events Related to r-tPA Infusion[15,19]

Adverse Event	Definition
Fever	Elevated temperature above normal
Hematuria	Blood in the urine
Hematoma	Collection of blood under the skin
Hemoptysis	Coughing up blood
Hypotension	Sustained low blood pressure, below normal (Usually indicative of MAP< 60 mmHg)
Mucosal bleeding	Bleeding in the mouth
Pleural effusion	Fluid accumulation around the lung
Pulmonary edema	Fluid accumulation in the tissue and air spaces of the lungs
Pulmonary re-embolization	Sudden blockage of a major pulmonary artery
Thromboembolism	Obstruction of a blood vessel by a clot that has become dislodged

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Table 5. Anticipated Adverse Events Related to the Procedure[23]

Adverse Event	Definition
Access site pseudoaneurysm	Sometimes called a false aneurysm, occurs when a blood vessel wall is injured, and the blood is contained by the surrounding tissues
Anemia	Deficiency of red blood cells
Arrhythmia	Abnormal heart rhythm
Bleeding requiring blood transfusion	Any loss of blood that may or may not require medical intervention
Cardiac arrest	Permanent or temporary cessation of organized heart function requiring emergency CPR, cardioversion, or defibrillation
Death	The permanent end of vital processes in a cell or tissue
Ecchymosis	Bruising
Hematuria	Blood in the urine
Hemodynamic instability	Blood pressure requires vasopressor support.
Heparin induced thrombocytopenia	Caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF4), activating the platelets and promoting a prothrombotic state
Infection	Bacteria in the blood or at the access site
Pain at access site	Discomfort at site of catheter insertion
Perforation	A hole or tear in a vessel
Pneumothorax	A presence of air or gas in the cavity between the lungs and the chest wall, causing collapse of the lung
Pulmonary infarct	Death of a portion of lung tissue caused by an interruption of blood supply
Shock	A life-threatening medical condition of low blood perfusion
Skin necrosis (if on warfarin)	A condition in which skin and subcutaneous tissues die due to long term treatment with warfarin

17.0 ADVERSE EVENT REPORTING

17.1 Serious Adverse Events

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and will be collected when the patient outcome is:

1. Death
2. Life-threatening - Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.
3. Hospitalization (initial or prolonged) - Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.
   Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

4. Disability or Permanent Damage - Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
5. Congenital Anomaly/Birth Defect - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Required Intervention to Prevent Permanent Impairment or Damage (Devices) - Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
7. Other Serious (Important Medical Events) - Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

17.2 Unanticipated Adverse Device Effect

Unanticipated adverse device effect is any serious adverse effect on health or safety, 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

17.3 Adverse Event Documentation

All adverse events (AEs) including those categorized as anticipated, life threatening, serious, unexpected, and suspected are to be reported on the case report form.

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17.4 Adverse Event Relatedness

Table 6. Adverse Event Categories of Study Device or Drug Relatedness

Relatedness Term	Relatedness Definition
Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration or use of device and cannot be explained by concurrent disease or other drugs or chemicals. The event must be pharmacologically or phenomenologically definitive.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug or use of device, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possibly Related	There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication or use of device). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Not Related	The adverse event is completely independent of study drug administration or use of device, and/or evidence exists that the event is definitely related to another etiology.

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Table 7. Adverse Event Categories of Procedure Relatedness

Relatedness Term	Relatedness Definition
Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to the interventional procedure.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after the interventional procedure.
Possibly Related	There is some evidence to suggest a causal relationship (e.g, the event occurred within a reasonable time after interventional procedure). However, other factors may have contributed to the event (e.g, the participant's clinical condition, other concomitant events).
Not Related	The event is completely independent of the interventional procedure, and/or evidence exists that the event is definitely related to another etiology.

17.5 Investigator SAE Reporting Requirements

An SAE occurring during the study or within 30 days of stopping the treatment must be reported to the study safety monitor. Any such SAE due to any cause, whether or not related to the study medication, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event.

The investigator must send a preliminary report of any such SAE to the project manager via the EDC system within 24 hours or if this is not possible via email or fax using an SAE Report Form, or at a minimum by telephone.

The event must be recorded on the electronic SAE CRF page. Preliminary reports of SAEs must be followed by detailed descriptions, including clear pseudonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. All photocopies should be redacted to remove study subjects' personal details and annotated with the patient's unique study identifiers. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug. Appropriate remedial measures should be taken to treat the SAE, and the response to treatment should be recorded. Study subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator.

18.0 REGULATORY REQUIREMENTS

The following are requirements of the sponsor and of the investigators.

18.1 Investigator Responsibilities

The following responsibilities are required for investigators participating in this study:

An investigator is responsible for ensuring that the investigation is conducted according to the signed agreement, the protocol, and applicable FDA regulations, for protecting the rights, safety and welfare of subjects under the investigator's care and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50. Specific responsibilities include:

1. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the protocol and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in 21 CFR 812 subpart E.
2. Awaiting approval: an investigator may determine whether potential subjects would be interested in participating in an investigation but shall not request the written informed consent of any subject to participate and shall not allow any subject to participate before obtaining FDA and IRB approval.
3. Compliance: an investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, any applicable FDA regulations and any conditions of approval impose by an IRB or FDA.
4. Supervising Device and Drug Use: an investigator shall permit an investigational device and drug to be used only with subjects under the investigator's supervision and shall not supply an investigational device to any person not authorized under FDA regulation to receive it.
5. Financial Disclosure: an investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to comply with 21 CFR 54 and shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
6. For FDA approved and IRB approved protocols, a PI Agreement is required to be reviewed and signed by the principal investigator prior to commencement of enrollment. PI Agreements are required to be signed after FDA and IRB approval of subsequent protocol amendments.
7. A Sub-I Agreement is required to be completed and signed by the sub-investigator prior to the Sub-I's commencement of enrollment.
8. Disposing of Device and Drug: upon completion or termination of the investigator's part of an investigation, return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

9. Investigator Records and Reports: participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:
    a. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
    b. Records of receipt, use or disposition of a device that relate to:
        i. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
        ii. The names of all persons who received, used, or disposed of each device.
        iii. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
10. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including; for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
    a. Documents showing evidence of informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
    b. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    c. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
11. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
12. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
13. The Principal Investigator is required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation, when necessary:
    a. Withdrawal of IRB approval (within 5 working days)
    b. Progress report, if applicable (annually)
    c. Deviations from the protocol (Not permitted unless to protect the health, safety, welfare of the patient)
    d. Informed consent deviations (within 5 working days)
    e. Final report

14. Core Lab Data Acquisition: Provide core labs with recorded media according to the core lab protocols within the specified timeframe in the core lab instruction manual. Independent core lab for CTA:

    Syntactx, LLC
    Richard Ouriel
    SVP, Clinical Services
    4 World Trade Center
    150 Greenwich Street, Floor 44
    New York, NY 10007
    Phone: 212-878-6885
    Email: rouriel@syntactx.com

    Publication: The Principal Investigator shall not create any publication related to this study without the express written permission of the sponsor. Should the principal investigator wish to publish or present the results of single-center results from this study, the principal investigator agrees to collaborate with the principal investigators participating in this study and provide the sponsor with an abstract, manuscript, and/or presentation for review 60 days prior to submission for publication or presentation. Once initial results are published, the site principal investigator may publish single-center results in collaboration with the sponsor.

    The sponsor retains the right to delete from the manuscript confidential information and to object to suggested publication and/or its timing (at the device manufacturer's sole discretion).

18.2 Sponsor Responsibilities

1. General Duties
   a. Submitting the IDE application to FDA.
   b. Obtaining both FDA and IRB approvals for the investigation before shipping the devices and drugs to any investigator.
   c. Obtaining FDA approval and IRB approval for a supplemental application before beginning that portion of the investigation.
   d. Selecting qualified investigators.
   e. Ensuring proper monitoring.
   f. Ensuring sites adhere to patient informed consent being documented and obtained.
2. Selection of Investigators
   a. Assure selection of investigators qualified by training and experience
   b. Shipping the investigational device only to participating investigators
   c. Obtaining a signed investigator's agreement containing:
      i. Investigator's curriculum vitae
      ii. Statement of investigator's relevant experience, including dates
      iii. Location, extent, and type of experience

iv. If an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination

v. Statement of the investigator's commitment to:
   - Conduct the investigation in accordance with the agreement, the investigational plan, 21 CFR Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA
   - Supervise all testing of the device involving human subjects
   - Ensure that the requirements for informed consent are met (21 CFR Part 50)

3. Providing investigators with the necessary information to conduct the investigation including, but not necessarily limited to:
   a. The Protocol
   b. Final Report from Protocol THRO-CLIN-2018-01
   c. IFUs
   d. Case Report Form
   e. Informed Consent
   f. FDA Letter to Commence the Study
4. Refer to Section 17 for Safety Reporting Requirements

18.3 Record Retention

Subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the investigational site for a minimum of two years or in line with the institutional document retention policy (if longer) after the completion/termination of this study or when it is no longer needed to support a marketing application, whichever is later. The Principal Investigator must contact Thrombolex, Inc. before destroying or archiving off-site any records and reports pertaining to this trial to ensure that they no longer need to be retained on site. Thrombolex, Inc. reserves the right to have all documents shipped to its office at the end of the two-year retention period at its own cost.

18.4 Emergency Circumstances

If emergency circumstances unrelated to the study should occur, Thrombolex, Inc. will follow the FDA guidance on how to manage the ongoing investigation during such crisis.[31]

19.0 DEVICE AND DRUG ACCOUNTABILITY

19.1 Bashir™ Endovascular Catheter Packaging for the IR Suite / Cath Lab

The Bashir™ Catheters are packaged to provide protection during transportation and to facilitate introduction into the sterile environment. The shaft of the Bashir Catheter

is inserted into a protective tube, mounted to a 0.3" wide x 46.5" long; .020" HDPE is inserted into a peel-pouch is shipped in a dispenser box.

19.2 Device Accountability

A packing slip will accompany all devices in each shipping box, 1 slip for multiple catheters. The site will retain the packing slips in their regulatory binder. The site should document each device and device disposition on the device accountability log provided to the site by the CRO.

19.3 Drug Accountability

The study drug is commercially available and is to be purchased by the institution. The site should document each vial and drug disposition in the case report form for each study subject.

20.0 STATISTICAL CONSIDERATIONS - ENDPOINTS, HYPOTHESES, AND ANALYTICAL METHODS

20.1 Power and Sample Size Calculation

The study will enroll up to 125 patients with the goal to have 100 evaluable subjects (after accounting for a 20% attrition rate of subjects who are enrolled and treated) in a prospective, non-randomized, multi-center study. The following assumptions were used to determine the required sample size for the study:

- This study would have an attrition rate of subjects enrolled and treated no greater than 20%.
- A mean reduction of 28% in the primary efficacy endpoint (RV/LV diameter ratio) after 48 hours in BEC-treated patients. It will be compared to the performance goal of 20% reduction in RV/LV diameter ratio after 48 hours.
- A standard deviation (SD) on the scale of percent change for the primary efficacy endpoint (RV/LV ratio) of 25%.
- An interim analysis will be conducted once data on 60 participants have been collected, in order to obtain preliminary efficacy results using the primary efficacy endpoint. To constrain the overall type I error rate, an O'Brien-Fleming alpha spending function will be utilized, in which a stringent type I error rate of alpha=0.0038 will be used for the interim analysis, leaving alpha=0.0212 for the final analysis, when study data are complete.

Alpha values for interim and final analyses were obtained from the R package ldbounds function bounds(), which calculates alpha given the type of spending function, timing of the interim analyses, and overall type I error desired. The parameters used to obtain these alpha values were O'Brien-Fleming spending function, single interim analysis at 60% of total sample, and overall alpha of 0.025 (one-sided).

The sample size needed for 80% power to test the primary efficacy hypothesis in the final analysis is 83 subjects, based on the assumptions stated above, and alpha = 0.0212.[6] This estimate is based on a one-sided one-sample t-test of mean percent change from baseline to 48-hour assessment, comparing the percent change in RV/LV ratio that is predicted in this study with a 20% reduction.

20.2 Endpoints, Hypotheses, and Analytical Methods

20.2.1 Primary Efficacy Endpoint:

The primary efficacy endpoint is reduction in the chest CT-measured RV/LV diameter ratio assessed by contrast enhanced chest CT from baseline within 48 ± 6 hours of initiation of treatment.

20.2.2 Hypothesis:

The predicate device for Bashir Endovascular Catheter is the EkoSonic Endovascular System (EKOS, Bothell, WA). The SEATTLE II Study reported a reduction in RV/LV diameter ratio of -0.42 ± 0.36 (mean ± SD) in 115 patients who underwent a within-window CT measurement of RV/LV diameter ratio. We hypothesize that RV/LV diameter ratio measured at 48 hours compared with measured ratio at baseline will be reduced on average by more than 20%.

20.2.2.1 Analytical methods: A change score *d* will be calculated:

$$\boldsymbol{d = \frac{R_{48} - R_0}{R_0}}$$

that expresses the change as a proportion of the baseline value, where R_0 and R_{48} are $\frac{\text{RV}}{\text{LV}}$ at time 0 and 48 hours post-treatment, respectively. A larger decrease from baseline will result in a change score with a greater magnitude and a negative sign. The change score will be compared to the benchmark value of 20% in a one-sided hypothesis test:

$$\boldsymbol{H_0: d \geq -0.2}$$

$$\boldsymbol{H_A: d < -0.2}$$

The distribution of the change score will be examined to assess whether the normality assumption is met, using both graphical methods (Q-Q plots and histograms) as well as multiple hypothesis tests of normality (Shapiro-Wilk, Kolmogorov-Smirnov, Anderson-Darling, and Cramer-von Mises). Multiple hypothesis testing methods will be employed to assess normality because the choice of the most powerful test depends on the distributional qualities of the data; if the different tests do not result in the same conclusion, more weight will be given to the method that is best suited to the observed distributional qualities of the data (*e.g.,* heaviness of tails). If the data are determined to be normal based on these methods, a t test will be done; if not, a one-sample Wilcoxon

signed rank test (the non-parametric alternative to the one-sample t test) will be done. In addition, the t-test will be presented for the primary endpoint analysis regardless of the normality of the test results.

The test will be performed twice: once at the interim analysis (with α=0.0038) and once at the final analysis (with α=0.0212). If the p-value is less than α at either analysis, then the test will be considered statistically significant.

20.2.3 Primary Safety Endpoint:

The primary safety endpoint is major bleeding within 72 hours of procedure initiation of r-tPA infusion (the start of the infusion). Bleeding events are classified by the International Society of Thrombosis and Hemostasis (ISTH).

20.2.4 Hypothesis:

The comparator device for Bashir Endovascular Catheter is the EkoSonic Endovascular System (EKOS, Bothell, WA), and results from the study evaluating the safety and efficacy of this device were the basis for the performance goal of 14.9% proposed for this study. The SEATTLE II Study reported a 10% (standard error=2.45%) of moderate to severe bleeding in treated subjects within 72 hours of the treatment initiation. The hypothesis is that the bleeding rate in this study will not exceed 10% + 2*SE = 14.9%. A one-sided, one-sample exact test of a binomial proportion *p* will be used to test the hypotheses below.

$$\boldsymbol{H_0: p \geq 0.149}$$

$$\boldsymbol{H_A: p < 0.149}$$

The hypothesis test for the primary safety endpoint will not be done at the interim analysis, but only at the end of the study. This test will have a type I error rate of 0.025.

20.2.5 Secondary Endpoints:

Descriptive statistics will be generated for the secondary endpoints listed below. For continuous measures (e.g., Modified Miller Index comparing 48 hours post therapy to baseline), the mean and 95% confidence limits will be calculated, along with the median, standard deviation and range. For frequency outcomes (e.g., device success), results will be reported as the overall frequency of occurrence as well as the percentage of subjects.

1. Device Success: The number of devices with therapy delivered without a device failure.
2. Refined Miller Score as measured on contrast enhanced chest CT (CTA) within 48 hours after the completion of the r-tPA infusion compared to baseline as measured by core lab.
3. All-cause mortality at hospital discharge through 30-day follow-up.

4. SAEs through 30-day follow-up.
5. AEs through 30-day follow-up.
6. UADEs through 30-day follow-up.
7. Recurrent PE through 30-day follow-up.
8. Clinically Relevant Non-Major bleeding: Any sign or symptom of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
   a. Requiring medical intervention by a healthcare professional.
   b. Leading to hospitalization or increased level of care.
   c. Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.
9. Technical procedural complications.
10. Systolic PA pressure measured at completion of infusion after BEC(s) removal and compared to baseline.
11. Cardiac output (CO by Modified Fick calculation in Protocol) and cardiac index (CI) following completion of the r-tPA infusion compared to the baseline.

20.2.6 Poolability, Subgroup, and Sensitivity Analysis

To assess poolability by study site, analyses will be done that test whether study site is a predictor of the primary efficacy and safety outcomes. Two regression models will be fit: a linear regression model having RV/LV diameter ratio as the dependent variable, and a logistic regression model having whether major bleeding occurred (as defined by ISTH within 72 hours of initiation of r-tPA infusion) as the dependent variable. Each model will include site as an independent variable and test the hypothesis that study site was a significant predictor of each dependent variable. If the hypothesis tests show that site is not a significant predictor of either outcome, it will be concluded that the study sites do not differ substantially in terms of outcome, and the data from sites will be pooled for analysis of all primary and secondary endpoints.

For the primary endpoints, descriptive statistics by site will be listed: the mean ± standard deviation, minimum, and maximum RV/LV diameter ratio, and the proportion of patients experiencing major bleeding, will be calculated for each study site and presented in a table to facilitate site comparisons.

If the hypothesis tests reveal site differences for either outcome, analyses will be performed to compare study sites in terms of participant baseline characteristics (*e.g.,* demographics, medical history) as well as other variables that could influence clinical outcome such as eligibility criteria. Analyses of primary and secondary endpoints will be conducted separately for each study site, and the results of the site comparisons will be used to inform how to interpret site-specific results.

Subgroup analyses will be performed to determine if RV/LV diameter ratio and the proportion of patients experiencing major bleeding differ by demographic variables age,

race, and gender. Summary statistics (mean ± standard deviation, minimum, and maximum RV/LV diameter ratio, and the proportion of patients experiencing major bleeding) will be calculated for each demographic subgroup and presented in a table to facilitate group comparisons. Regression models will be fit (linear regression for RV/LV diameter ratio, logistic regression for major bleeding) having each primary endpoint as the dependent variable and demographic group as the independent variable. A separate regression model will be fit for each combination of endpoint and demographic variable to formally test the hypothesis of subgroup differences in each primary endpoint.

Sensitivity analyses will be undertaken to assess the impact of missing data for the primary endpoints. The methods for this analysis are described in detail in Section 8 of the Statistical Analysis Plan (THRO-STAT-2019-01), "Handling of Dropouts and Missing Data." If subjects become COVID-19 positive after enrollment and during the study, a subgroup analysis will be performed. Refer to Statistical Analysis Plan (SAP) (THRO-STAT-2019-01) for additional details.

20.3 Analysis Populations

All enrolled subjects who receive the study treatment will be included in the Intent-to-Treat (ITT) population. The ITT will consist of subjects who both provide informed consent to participate and have the BEC (or first of two BECs for bilateral PE) introduced into the sheath. The modified ITT (mITT) population are evaluable subjects defined as members of the ITT who have data available to assess the primary efficacy endpoint of reduction in RV/LV ratio as measured by contrast-enhanced chest CT (CTA) at screening and RV/LV ratio as measured by contrast-enhanced CTA at 48 hours after completion of r-tPA treatment. The patients comprising the mITT population are evaluable patients. Members of the ITT population who remain in the study long enough to complete the 30-day follow-up period will comprise the Per-Protocol (PP) population.

The mITT population will be used to analyze the primary efficacy endpoint. The ITT population will be used to analyze the primary safety endpoint, as well as all secondary safety and device endpoints that do not require 30 days of follow-up (*e.g.,* device success, clinically relevant non-major bleeding, technical procedural complications). The PP population will be used to analyze secondary endpoints that require 30 days of follow-up: all-cause mortality, SAEs, AEs, UADEs, and recurrent PE through 30-day follow-up).

Up to 125 subjects, in up to 20 sites, will be enrolled and treated, with the objective to have at least 100 subjects complete the 30-day follow-up period, and be included in the primary efficacy analysis. Each site will have an enrollment cap such that no more than 20% (n=20) of participants are enrolled at a single site.

21.0 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will be selected to review the study conduct, feasibility data, and safety data and will review all types of adverse events reported in this study and adjudicate as required. The independent DSMB shall have the final adjudication for the events. A data safety charter will be established and will be approved by the DSMB. Qualifications for the DSMB members, at a minimum, shall include current experience with catheter directed thrombolysis for the treatment of submassive pulmonary emboli, management of the patient post-treatment and extensive research experience. Adherence to the study stopping criteria in this protocol will also be included in the DSMB meetings in addition to following the charter.

The DSMB shall have CEC responsibilities as well. This hybrid committee include CEC responsibilities that include providing an independent expert review of data on clinical events based on protocol-specific definitions. The CEC review ensures that events critical to the analysis of study results are assessed in a uniform manner. This facilitates reliable pooling of data within a trial and with predicate trials and improves the validity of comparisons with published data. In addition to study endpoints, the CEC will provide assessment of other events or areas of concern at the request of the DSMB or Sponsor (e.g., device malfunction or failure, serious anticipated adverse events versus serious unanticipated adverse events). Member selection will be based on:

- Balanced composition;
- Relevant expertise;
- Complete independence from the Sponsor and conduct of the trial;
- Evaluation and documentation of any Conflict of Interest; and
- Commitment to flexible schedules for the duration of the project life cycle.

22.0 STUDY STOPPING RULES

22.1 General Study Stopping Rules

The Sponsor, DSMB, IRBs, regulatory authorities, or the principal investigators may make recommendations to terminate the study if the safety and well-being of the subjects are in jeopardy.

If the study is terminated or suspended, prompt notification will be provided to all parties involved in the conduct of the study.

Patient enrollment may be paused or terminated early if the Sponsor or DSMB, and/or CEC determines that the potential benefits of the investigational device are unlikely to outweigh the risks associated with continuation of the trial.

22.2 Study Stopping Rules Related to Safety

22.2.1 Intracranial Hemorrhage

If three (3) patients undergoing the investigational procedure experience an unprovoked intracranial hemorrhage, confirmed by independent CEC/DSMB adjudication, and did not have a protocol violation such that he/she cannot be considered as representative of the intended patient population, the study shall be paused for re-evaluation, and may be stopped.

22.2.2 Bleeding

Should severe bleeding occur in 12 study subjects, the study will be paused, and the pharmacotherapy dosage and administration will be re-evaluated.

22.2.3 Ad Hoc Criteria for CEC/DSMB Meetings

1. If there are two (2) intracranial bleeds or eight (8) major bleeds within the first 60 subjects, an ad hoc meeting will occur for adjudication of the events.
2. An ad hoc meeting will take place if any untoward event that, in the opinion of the chair, warrants an ad-hoc meeting.

22.3 Device Study Stopping Rules

22.3.1 Device Related SAEs

Should it be suspected that a device caused a serious adverse event, the serious adverse event will be adjudicated by the independent DSMB and the device shall be returned to the manufacturer. A root cause analysis shall be performed. The DSMB will determine if the study should be stopped, temporarily suspended, or continued after each such event.

22.3.2 Device Malfunctions and Non-conformances

There are device malfunctions, or non-conformances, that may impact the patient and prevent treatment with an investigational device. Upon commencement of enrollment, if there are device failures that prevent a total of five (5) subjects across two or more study sites (e.g. site 01 has three (3) device malfunctions, and site 05 has two (2) device malfunctions) from being treated in this study, the study shall be paused for re-evaluation of the device. A root cause analysis will be performed to determine the cause(s) of the device failures and a corrective and preventative action will be implemented.

22.4 Study Safety Reporting Requirements

Reporting requirements for IDE studies will be followed. The representative that will provide any necessary reports to FDA is the following:

Diane Horwitz, PhD
Eminence Clinical Research, Inc.
Principal Regulatory Consultant
dhorwitz@ecr-inc.com
Phone: (703) 307-2921

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23.0 VERSION CONTROL

Add to table below for each protocol amendment

PROTOCOL THRO-CLIN-2019-01		
VERSION	**SUMMARY OF THE CHANGE**	**RATIONALE**
0.0	Original for FDA Review Edited per FDA request to add in the following sentence: enrollment will not be stopped at the interim analysis of n=60 patients and full enrollment is planned for the study.	N/A
1.0	Edited per FDA request to add in the following sentence: enrollment will not be stopped at the interim analysis of n=60 patients and full enrollment is planned for the study. [The rev number of this protocol reverts to the draft revision numbering in case there are additional changes to be made per FDA request. The final version approved by FDA will be changed to 1.0 once all final FDA requested changes are made and the IDE approval letter is received.]	Make FDA requested changes and additional editorial changes.
2.0	Enrollment capped at 20% of sample size per FDA request, statistical changes made per FDA IDE approval letter February 6, 2020, and administrative changes.	Implement changes in protocol according to recommendations in FDA IDE approval letter dated February 6, 2020. Administrative changes were done to add clarification.
3.0	Protocol amendment due to COVID-19, patient follow-up plan and Impact Assessment Form. Revise AE relatedness definitions and separate evaluation of device/drug from procedure events. Address FDA recommendations in IDE approval letter for S001 dated April 2, 2020.	New FDA Guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic; capture more detail related to AE relatedness.
4.0	The protocol was amended after the CEC/DSMB kick-off meeting. The CEC/DSMB members asked for guidance from the steering committee to change the study stopping rules from percentages to patient numbers and to add ad hoc criteria for when the CEC/DSMB chairperson would call an ad hoc meeting.	CEC/DSMB first meeting required changes to the stopping rules, criteria for ad hoc meetings, and to include emphasis on not cannulating arterial branches with the BEC at any time, add COVID-19 exclusion, and administrative changes were made.

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25.0 APPENDICES

APPENDIX 25.1 REQUIRED STUDY PROCEDURES

Test	Pre-Procedure	Procedure	Post-Procedure	End of r-tPA Infusion	24 Hrs Post-r-tPA Completed	48 Hrs Post- r-tPA Completed	72 Hrs Post- r-tPA Initiated	Before Dis-charge	30-day Follow-up
Visit Window	≤ 48 Hrs of procedure				±8 Hrs	±8 Hrs	-4 / +12 Hrs	-8 Hrs	±7 Days
Informed Consent	X								
Demographics and Medical History	X								
Physical Examination	X			X	X			X	X[7]
12 Lead ECG	X								
CBC, INR[1]	X				X				
aPTT	X[2]		X	X					
CMP	X								
BMP					X				
Cardiac Biomarkers: Troponin, BNP	X				X				
Lower Extremity Venous DUS	X								
Contrast Enhanced CTA of the Chest	X					X			
RV/LV Diameter Ratio with each CTA	X					X			
Eligibility Criteria	X	X							
Anticoagulation[3]	X	X	X	X	X				
Ultrasound Guided Access		X							
IR / Cath Lab: Invasive Hemodynamic Data[4]		X							
IR / Cath Lab: r-tPA Pulse Sprays Administration		X							
Bashir™ Endovascular Catheter(s) and r-tPA Use[5]		X	X	X					
ICU: PAS / PAD / Mean PA from Sheath(s)				X					
ICU: Mixed venous SvO_2 from Sheath				X					
r-tPA Infusion		X	X						
CO/CI by Modified Fick Method		X		X					
Medications (antiplatelet, anticoagulant, cardiac meds, and NSAIDs)	X	X	X	X	X	X	X[6]	X	X
AEs / SAEs		X	X	X	X	X	X[6]	X	X
Contrast Enhanced Chest CTs to Core Lab	X					X			
COVID-19 Site Impact Assessment Form[7]									

[1] INR is only required at baseline for patients on Coumadin (warfarin) and must be ≤ 1.5 prior to enrollment. If patient is eligible for the study, Coumadin will be discontinued temporarily for study purposes.

[2] Pre-procedure suggested aPTT be maintained at therapeutic dose. Suggested aPTT during r-tPA administration decrease dose of UFH to 5-8 units/kg/hr up to a maximum of 1,000 units/hr.

[3] Refer to protocol section 7.1.4.

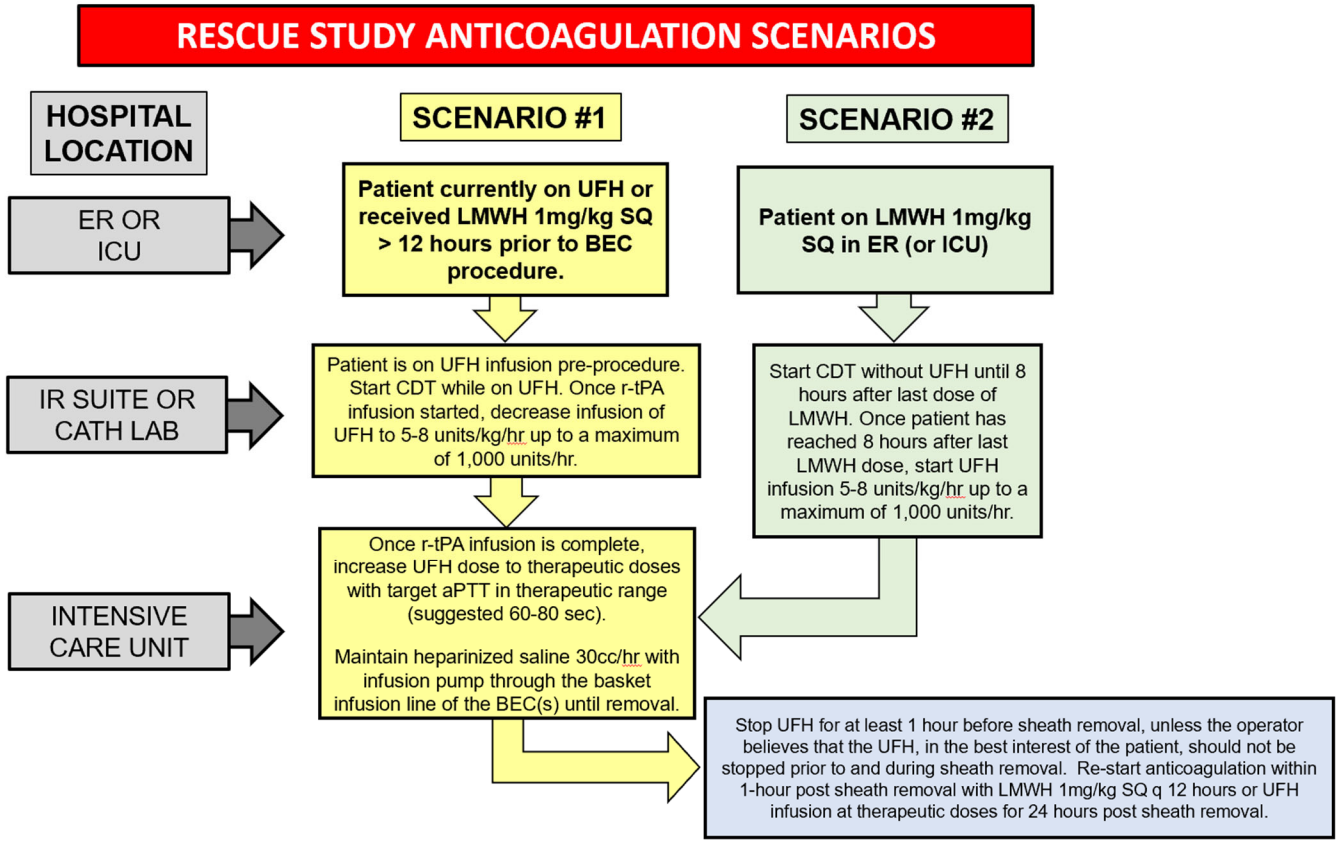
[4] Required: PAS, PAD, PA Mean, CO, CI, S_pO_2, S_vO_2 / at baseline, & post-infusion in the ICU. Swan-Ganz or angled pigtail may be used. CO= Modified Fick calculation.

[5] IV solution must be mixed according to protocol and infuse at the prescribed rate into target PA, or both PAs if bilateral PE. Infusion is to be administered over approximately 5 hours.

[6] If a study subject is discharged from the hospital prior to the 72-hour visit, a telephone follow-up in lieu of F2F follow-up will be conducted to verify that an AE and/or a change in medication has not occurred. If either of these have occurred, additional detail will be collected over the phone and documented.

[7] If the study subject is unable to attend the visit in person, or in the event any study required test is omitted due to COVID-19, a protocol deviation form will be completed.

APPENDIX 25.2 RESCUE STUDY ANTICOAGULATION SCENARIOS



APPENDIX 25.3 INFORMED CONSENT FORM

(The informed consent form is an appendix to the protocol and is provided separately in MS Word® format for site to edit according to IRB requirements)

APPENDIX 25.4 CASE REPORT FORM

(The case report form is an appendix to the protocol and is provided separately as a template for the electronic data capture database)

APPENDIX 25.5 CORE LAB PROTOCOLS

(The core lab protocols are an appendix to the protocol and is provided separately.)

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APPENDIX 25.6 COVID-19 CONTINGENCY PLAN

STEP 1 Evaluate Impact to the Study

The Impact Assessment Form will be completed by each site and submitted to the CRO representative. The investigational site operations will be evaluated to determine impact of the COVID-19 Pandemic. The Impact Assessment Form will be reviewed with the sponsor.

STEP 2 Alternate Study Plans

The CRO representative will review the Impact Assessment Form with the sponsor and will contact the site to confirm the site's proposed appropriate alternative plan under the following conditions:

1. **Patient enrollment activities cannot be conducted in full compliance with the current protocol.**
   If the impact affects the ability to complete any of the required activities for study enrollment, the site will not be activated, or enrollment will be suspended if the site was previously activated, until full operations can be restored. A Suspension of Study Due to COVID-19 Notice will be issued to the site. The investigator will submit the notice to the participating IRB.

2. **Patient follow-up cannot be conducted in full compliance with the current protocol.**
   If the impact affects the follow-up visits for patients who have already been enrolled and treated with the study device, follow-up should be completed according to the protocol if possible. The Impact Assessment Form will be completed and submitted to the CRO representative. Based on the information given in the Impact Assessment Form, a follow-up plan for the site should be provided by the site on the Impact Assessment Form to the CRO. Additionally, the investigator will submit the completed Impact Assessment Form to the participating IRB.

STEP 3 Restoration of Clinical Research Operations

1. **Resuming Clinical Research Operations**
   As soon as the site can confirm that clinical research operations have resumed, or a due date is defined for resumption, the site will notify the CRO representative.

2. **Activation Letter**
   The CRO, with approval from the study sponsor, will issue an Activation Letter or Addendum to the Suspension of Study Due to COVID-19 Notice with an effective date. This will restore the site to resume active status and return to all activities as defined per the protocol.

RESCUE STUDY COVID-19 SITE IMPACT ASSESSMENT FORM

SECTION 1 GENERAL IMPACT ASSESSMENT- ANSWER ALL QUESTIONS			
Site Name:		**Site Number:**	
Investigator Name:			
Are any enrollment activities per the study protocol impacted?	☐ No ☐ Yes If yes, site may not be activated, or new enrollment may be suspended until full operation can be restored.		
Are any follow-up activities per the protocol impacted?	☐ No ☐ Yes If yes, complete section 2 below		
Are monitoring activities impacted?	☐ No ☐ Yes If yes, complete section 3 below		
Are any enrolled subjects impacted?	☐ No ☐ Yes If yes, complete section 4 below		
Record an effective date when full operations will resume: ☐ N/A	_____/_____/20_____ (mm/dd/yyyy)		
Comments:			

SECTION 2 IMPACT ON FOLLOW-UP ASSESSMENTS – ANSWER ALL QUESTIONS **Describe what follow-up assessments are impacted or cannot be conducted and if there is an alternate method to utilize (i.e. telephone, video conference or other)**		
Assessment	**Affected?**	**If YES, Explain Alternate Modified Plan**
24 Hours Post r-tPA Completion	☐ No ☐ Yes ☐ N/A	
48 Hours Post r-tPA Completion	☐ No ☐ Yes ☐ N/A	
72 Hours Post r-tPA Initiated	☐ No ☐ Yes ☐ N/A	
Hospital Discharge	☐ No ☐ Yes ☐ N/A	
30-Day Follow-up	☐ No ☐ Yes ☐ N/A	

Site Name:		Site Number:	

Assessment	Affected?	If YES, Explain Alternate Modified Plan
Concomitant Medications	☐ No ☐ Yes ☐ N/A	
AE/SAE/UADE	☐ No ☐ Yes ☐ N/A	

SECTION 3
IMPACT ON DATA MONITORING – ANSWER ALL QUESTIONS

Assessment	Affected?	If YES, Explain Impact / Limitations
Are there any impacts affecting monitoring at the site? (Obtaining access to the source documentation)	☐ No ☐ Yes	
Has a remote monitoring plan been implemented at the site as an alternative to on-site monitoring?	☐ No ☐ Yes	

SECTION 4
LIST OF ENROLLED SUBJECTS IMPACTED

Subject #	Plan

Person Completing Form Printed Name:		Signature & Date:	___/___/20___
Physician Printed Name:		Signature & Date:	___/___/20___

APPENDIX 25.7 RISK OVERVIEW

RISK OVERVIEW

1. DESCRIPTION OF THE POPULATION

Age 18 years of age to ≤ 75 years of age, have a filling defect in at least one main or lobar pulmonary artery as determined on contrast enhanced chest CT Scan (CTA), RV/LV diameter ratio ≥ 0.9 by contrast enhanced chest CT scan (CTA) as determined by the investigative site. They must not have had a CVA or TIA within one (1) year, head trauma, active intracranial, or intraspinal disease within one (1) year prior to inclusion in the study, any active bleeding from a major organ within one (1) month prior to inclusion in the study, an intracranial condition(s) that may increase the risk of bleeding, a bleeding diatheses, a hematocrit less than 30, platelet count less than 100,000/µL, INR greater than 1.5 if currently on warfarin (Coumadin®), and each patient cannot have an aPTT greater than 50 seconds in the absence of anticoagulants. Please see section 6.3 for a complete list of eligibility criteria.

2. OVERVIEW OF EFFICACY

The Bashir™ Endovascular Catheter is intended for the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. A First-in-man study was recently completed for the treatment of subjects with submassive pulmonary embolism. The study included administration of r-tPA through the BEC in the form of pulse sprays followed by an infusion over eight hours. Subjects with unilateral embolism were administered a 2mg pulse spray through the basket of the BEC into the pulmonary artery (PA) followed by an infusion of 10mg over approximately eight hours for a total dose of 12 mg. Subjects with bilateral embolisms were administered 2mg pulse sprays into each pulmonary artery followed by an infusion of 5mg of r-tPA into each PA over eight hours for a total of 14mg. Nine subjects were enrolled and treated. After 48 hours the RV/LV ratio decreased from 1.54 ± 0.26 to 0.97 ± 0.06 (p = .001: 95% CI = 0.33 to 0.82: 36.7% reduction) as assessed by an independent core lab (Medical Metrics, Houston, TX). Thrombus burden measured by Modified Miller Index as assessed by the independent core lab (Medical Metrics, Houston, TX) decreased from 25.4 ± 5.3 to 16.0 ± 4.0 (p = .001: 95% CI = 5.5 to 13.4: 37.1% reduction).

Table 1. Independent Core LAB RV/LV Diameter Ratio

Independent Core Lab RV/LV Diameter Ratio at 48 hours After Completion of r-tPA Infusion By Contrast Enhanced Chest CTA Compared to Baseline				
Baseline	**48 hours**	**Difference (Baseline – 48 hrs)**	**95% CI of difference**	**T-test p-value**
Mean ± SD (n) Median [Range]	Mean ± SD (n) Median [Range]	Mean ± SD (n) Median [Range]	N=8	
1.54 ± 0.27 (8) 1.48 [1.21-1.98]	0.97 ± 0.06 (8) 0.96 [0.87-1.05]	0.57 ± 0.29 (8) 0.56 [0.18 - 1.02]	0.33 – 0.82	0.001

Table 2. Independent Core Lab Modified Miller Index Scores

Independent Core Lab Modified Miller Index Scores at 48 hours After Completion of r-tPA Infusion By Contrast Enhanced Chest CTA Compared to Baseline				
Baseline	**48 hours**	**Difference (Baseline – 48 hrs)**	**95% CI of difference**	
Mean ± SD (n) Median [Range]	Mean ± SD (n) Median [Range]	Mean ± SD (n) Median [Range]	N=9	**T-test p-value**
25.4 ± 5.3 (9) 28.0 [18.0 – 33.0]	16.0 ± 4.0 (9) 15.0 [11.0 – 22.0]	9.4 ± 5.1 (9) 8.0 [4.0 – 18.0]	5.5 – 13.4	0.001

This first-in-man experience showed excellent efficacy results in all study subjects evident by the results from the independent core lab analyses for reduction in RV/LV diameter ratio and Modified Miller Index Scores.

3. OVERVIEW OF SAFETY

In the First-in-Man study mentioned above, the study results revealed an excellent safety profile for the BEC. There were no adverse events or serious adverse events related to the device and there were no adverse events or serious adverse events related to the r-tPA.

4. POTENTIAL RISKS AND RISK MITIGATION

A. Potential Risks to Research Subjects

The potential risks in the RESCUE study related to the device can be categorized in the following way in Table 3 below. These include basic safety, device related SAEs, device related AEs, procedure related complications due to the investigation, risks associated with the study itself, and risks from false-positive or false negative results for diagnostics. The last category is not applicable, as the RESCUE study is the delivery of a therapy.

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Table 3. Definitions of Types of Risks

Risk Types	Definition
Basic Safety	Protection against physician hazards, which should be addressed and mitigated with a reasonable level of certainty.
Device Related SAEs	Events attributable to the investigational use of the device which produce an injury that is life threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
Device Related AEs (non-serious)	Events attributable to the investigational use of the device which do not produce an injury or illness that is life-threatening, does not result in permanent impairment or damage to the body, or does not require medical or surgical intervention to prevent permanent harm to the body.
Procedure-related Complications Due to the Investigation	This includes not just the device use, but risks related to the investigation itself to which the subject would otherwise not be exposed, e.g. risk of anesthesia during procedures involving an investigational device.
Risks associated with the study itself	Risks the subject may be exposed to that do not directly result from use of the device and would not be expected as part of usual care outside of the investigational setting. Examples include additional procedures (such as medical imaging) for ascertainment of study endpoints.
Risk from false-positive or false-negative results for diagnostics	N/A – The BEC is not a diagnostic device.

A description and analysis of the risks to research subjects related to the device and the study are listed below for each category in Table 3 above.

Basic Safety: Physician hazards may include exposure to blood and body fluids, which is standard for any invasive procedure in the interventional lab. Physicians and staff wear personal protective equipment to prevent exposure. This is not unique to the investigational device in the RESCUE study. There is no electrical power required for this device, so electrical safety issues are not relevant.

Device Related SAEs or Device Related AEs (Non-Serious): Device related SAEs may include allergic reactions, hematoma at access site, hemorrhage, intimal damage, ischemia, pain and tenderness, vascular thrombosis, vessel perforation, and vessel spasm. These adverse events will be categorized as serious only if one of the following conditions applies:

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and will be collected when the patient outcome is:

1. Death
2. Life-threatening - Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.
3. Hospitalization (initial or prolonged) - Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.
   Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
4. Disability or Permanent Damage - Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
5. Congenital Anomaly/Birth Defect - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Required Intervention to Prevent Permanent Impairment or Damage (Devices) - Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
7. Other Serious (Important Medical Events) - Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Procedure Related Complications Due to the Investigation: These complications are unrelated to the BEC and may include access site pseudoaneurysm, anemia, arrhythmia, bleeding requiring blood transfusion, cardiac arrest, death, ecchymosis, hematuria, hemodynamic instability, heparin induced thrombocytopenia, infection, pain at access site, perforation, pneumothorax, pulmonary infarct, shock, skin necrosis (if on warfarin).

Risks Associated with the Study Itself: The risks associated with the study itself are discussed below. The additional risks are not expected to be above standard of care.

B. Risk Mitigation and Risk Minimization

1. **Basic Safety:** There is no expected increase in basic safety concerns. The sites selected are highly experienced in the protection from blood borne pathogens and the use of the BEC does not increase this risk. Additionally, regarding radiation exposure for the staff and physicians, the procedure times are short compared to some interventional procedures. The procedure time in the First-in-Man study from local anesthetic to last wire out of the patient was a mean of 57 minutes (with a range of 43 minutes to 72 minutes).

2. **Device Related SAEs:** Allergic reaction – Staff monitor the subject for reactions and medicate the study subject accordingly.
   Hematoma at access site – This is potentially due to the venous stick technique. We are minimizing the potential for a hematoma by requiring the use of ultrasound guidance at the time of obtaining access either in the femoral vein or the internal jugular vein.
   Hemorrhage – We are preventing hemorrhage by only selecting physicians in the study who are experienced in PM-CDT and hemodynamic monitoring. Having this expertise prior to study site selection will minimize the possibility of hemorrhage due to perforation. Additionally, the dose of r-tPA is less than the dose in other studies. The RESCUE protocol requires a certain heparin dose and lovenox dose. This is to prevent over anti-coagulation in the study subjects.
   Intimal damage – There is the potential for intimal damage with any interventional procedure within the vasculature. This is minimized by the use of the long sheaths and the assessment under fluoroscopy of the basket expanding in the pulmonary vasculature.
   Ischemia may be minimized by shorter procedure times, shorter time to improved ventilation and perfusion in the pulmonary embolism patient.
   Vascular thrombosis is prevented with anti-coagulation.
   Vessel perforation is prevented by choosing experienced operators who have extensive experience with catheter-based therapies and PM-CDT.
   Vessel spasm may occur but can be minimized with highly experienced operators. The potential for spasm is much less in venous treatment than with arterial treatment.

3. **Procedure-Related Complications:** The procedure-related complications listed above will be mitigated by selecting experienced operators, lab staff, and research staff. In the First-in-Man study use in the pulmonary artery, the device was inserted through a long sheath that was placed in the pulmonary artery prior to the BEC insertion. This allows for easy insertion from the sheath outside of the patient into the right side of the heart and the pulmonary artery within the sheath. The physicians place the device in the interventional lab by advancing it through the sheath, and by viewing the radiopaque infusion basket under fluoroscopy. The entire basket is made of nitinol components; therefore, the entire basket is radiopaque under fluoroscopy. This same technique will be used in the RESCUE study. This minimizes the possibility of the BEC causing damage to the vasculature when being inserted through the vasculature.

4. **Risks Associated with the Study Itself:** The CTA imaging is a requirement for the primary endpoint analysis. Site staff will be trained on the image acquisition protocol and they will be qualified in advance to ensure they have the proper imaging equipment to perform the tests. Both of these requirements should help reduce the exposure that could result from redoing study-required imaging. If the 48-hour CTA is not standard of care, one extra CTA would be required for the study subject, a small increase in radiation exposure. The in-lab imaging is standard of care for the practicing interventionalist.

C. Summary

Overall, the actions taken to mitigate risks include the following:

1. Select qualified sites and investigators that meet strict criteria;
2. Provide detailed didactic and hands-on device training;
3. Ensure all investigators inspect the device and prep the device and test it for functionality before use;
4. Provide core lab requirement training;
5. Support study procedure as needed with procedure and research experts to guide physicians and staff.

5. POTENTIAL BENEFITS

The potential benefit from BEC treatment of pulmonary embolism is effective treatment for the condition, as reduction in clot burden has been demonstrated by RV/LV ratio reduction and decrease in refined Modified Miller Score in the First-in-Man study. Additionally, there may be a lower bleeding risk with the BEC because of low r-tPA dose and shorter infusion times compared to what was required in SEATTLE II. The design of the BEC creates multiple channels where blood can flow to increased exposure of the clot surface area to fluid, endogenous lytics, exogenous lytics (e.g., r-tPA), thus potentially having a greater reduction in clot burden than other PM-CDT devices that create only a single channel. This benefit remains to be seen in a larger population; therefore, the RESCUE study is being conducted.

6. CONCLUSIONS

As demonstrated in the First-in-Man study, the potential benefits outweigh the risks of treating patients with the BEC.