Clinical Protocol Title	**First – In – Man Study to Assess the Safety and Feasibility of The Bashir™ Endovascular Catheter for the Treatment of Acute Pulmonary Embolism**
Protocol Number	**THRO-CLIN-2018-01**
IND Number	140347
Study Phase	Phase I – First-in-Man Study
Drug Development Phase	Post-Market - FDA approved drug administered in this study
Study Sponsor	Thrombolex, Inc. 75 Britain Dr, New Britain, PA 18901
Current Protocol Version	6.0
Version Date	September 14, 2019
Previous Version	5.0
Principal Investigators	Kenneth Rosenfield MD – Interventional Cardiologist Akhilesh Sista MD – Interventional Radiologist
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Approval Date
September 16, 2019

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1.0 PROTOCOL SYNOPSIS

STUDY NAME	First – in – man study to assess the safety and feasibility of the Bashir™ Endovascular Catheter for the treatment of acute pulmonary embolism.
PROTOCOL NO.	THRO-CLIN-2018-01
PROTOCOL DATE	September 14, 2019
SPONSOR	Thrombolex, Inc. New Britain, PA
CO-PRINCIPAL INVESTIGATORS	Kenneth Rosenfield MD – Interventional Cardiologist Akhilesh Sista MD – Interventional Radiologist
STUDY DEVICE	The Bashir™ Endovascular Catheter is a device intended for the localized infusion of therapeutic agents into the pulmonary artery and peripheral vasculature.
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 basket infusion port with 10cc syringes. Unilateral PE: 2mg total in 20cc administered in two (2) 10cc syringes. Bilateral PE: 4 mg 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 10mg in 750cc 0.9% NaCl infused at 1.27mg/hr at an infusion rate of 95cc/hr, through the Bashir™ Endovascular Catheter until complete. Total r-tPA dose (pulse spray and infusion) is 12.0mg. Bilateral PE: r-tPA 5mg in 500cc 0.9% NaCl infused at 0.65mg/hr at an infusion rate of 65cc/hr bilaterally through each Bashir™ Endovascular Catheter, until complete for a total r-tPA dose of 1.3mg/hr, 0.65mg per hour through each catheter. Total r-tPA dose (pulse spray and infusion) is 14.0mg.
ANTICOAGULANT DOSAGE AND ADMINISTRATION	Pre-procedure: Unfractionated heparin will be administered IV to prolong the aPTT pre-procedure (suggested range 60-80 seconds). Note: Use of enoxaparin (Lovenox®) is permitted pre-procedure for the treatment of PE. If Lovenox is given, then catheter directed thrombolysis procedure is to start no sooner than 12 hours after the last Lovenox dose was administered**.** Procedure: Heparin infusion will be discontinued upon arrival in the IR/Cath lab. ACT will be monitored in IR/Cath Lab and heparin boluses administered to achieve ACT ≥ 200 seconds. During r-tPA Infusion: Heparin infusion will be restarted post-procedure and administered through the side arm of each sheath to prolong the aPTT (suggested range 40-60 seconds). Post r-tPA Infusion: Upon completion of r-tPA infusion, maintain patency through the BEC by replacing r-tPA with heparinized saline TKO using the infusion pump. Starting 45 minutes (± 15 minutes) after the r-tPA completion, administer Lovenox 1mg/kg sub-Q every 12 hours (±30 minutes) through the completion of the 48-hour CTA.

1.0 PROTOCOL SYNOPSIS (CONTINUED)

POPULATION	Patients 18 years of age or older 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.
STUDY OBJECTIVE	Assess the safety and feasibility of the Bashir™ Endovascular Catheter for the administration of low dose thrombolytic for acute submassive pulmonary embolism.
SAMPLE SIZE	Up to ten (10) subjects will be enrolled and treated.
SITES	Up to five (5) sites will be qualified to participate in this study.
PRIMARY ENDPOINTS	1. Safety: Major bleeding, as defined by International Society of Thrombosis and Hemostasis (ISTH), within 72 hours of initiation of r-tPA administration. Bleeding criteria are as follows: Major Bleeding in Non-Surgical Patients 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 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells. 2. Feasibility: Device success defined as the ability to use the Bashir™ Endovascular Catheter as described in this protocol.
SECONDARY ENDPOINTS	1. All-cause mortality at hospital discharge through 30-day follow-up. 2. SAEs through 30-day follow-up. 3. Anticipated (non-serious) adverse events (AEs) through 30-day follow-up. 4. Recurrent PE through 30-day follow-up. 5. 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. 6. Technical procedural complications. 7. RV/LV end diastolic diameter ratio at 24 hours after completion of r-tPA infusion compared to baseline, by echocardiogram. 8. RV/LV diameter ratio at 48 hours after completion of r-tPA infusion, by contrast-enhanced chest CTA compared to baseline. *Continued on next page*

1.0 PROTOCOL SYNOPSIS (CONTINUED)

SECONDARY ENDPOINTS (CONTINUED)	9. Modified Miller Index at 48 hours post completion of the r-tPA infusion as compared to baseline by contrast-enhanced chest CTA. 10. Systolic PA pressure measured at completion of infusion and compared to baseline. 11. Cardiac output (CO by modified Fick calculation) and cardiac index (CI) following completion of infusion, upon return to the IR suite/Cath lab compared to baseline.
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Willing and able to provide informed consent; 2. 18 years of age and less than 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 contrast enhanced chest CT; 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. Cerebrovascular Accident (CVA) or transient ischemic attack (TIA) within one (1) year; 2. Head trauma, or other active intracranial, or intraspinal disease within one (1) year; 3. Recent (within one month) or active bleeding from a major organ; 4. Intracranial condition(s) that may increase the risk of bleeding (e.g., neoplasms, arteriovenous malformations, or aneurysms); 5. Patients with bleeding diathesis; 6. Hematocrit < 30%; 7. Platelets < 100,000/μL; 8. INR > 1.5; 9. aPTT > 50 seconds in the absence of anticoagulants; 10. Major surgery within fourteen (14) days; 11. Serum creatinine > 2.0 mg/dL; 12. Clinician deems high-risk for catastrophic bleeding; 13. History of heparin-induced thrombocytopenia (HIT); 14. Pregnancy; 15. Systolic blood pressure < 90 mmHg for > 15 minutes; 16. Any vasopressor support; 17. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR); 18. Evidence of irreversible neurological compromise; 19. Life expectancy < one (1) year; 20. Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to inclusion in the study; *Continued on next page*

1.0 PROTOCOL SYNOPSIS (CONTINUED)

ELIGIBILITY CRITERIA (CONTINUED)	21. Use of non-vitamin K oral anti-coagulants (NOACs), such as rivaroxaban, apixaban, dabigatran, edoxaban within 48 hours prior to inclusion in the study; 22. Use of enoxaparin sodium injection (Lovenox®) within 12 hours of procedure start time; 23. Profound bradycardia requiring a temporary pacemaker and/or inotropic support; 24. Previous enrollment in this study; 25. Morbidly obese (BMI >45 kg/m^2) patient who by the judgement of the investigator is high risk for bleeding; 26. Absolute contraindication to anticoagulation; 27. Uncontrolled hypertension; 28. Currently participating in another study; 29. 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 eleven (11) months.
DATA SAFETY MONITOR	Gregory Piazza MD, MS Brigham and Women's Hospital Boston, MA
STUDY MANAGEMENT	Eminence Clinical Research, Inc. 13521 Northgate Estates Drive Suite 150 Colorado Springs, CO 80921
DATA MONITORING	
EDC	
CTA / ECHO INDEPENDENT CORE LAB	Medical Metrics, Inc. 2121 Sage Road Suite 300 Houston, TX 77056

2.0 STUDY CONTACTS

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3.0 TERMS AND DEFINITIONS

TERM	DEFINITION
AE	Adverse Event - An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)).
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 to diagnose heart failure quickly.
BSA	Body Surface Area - Du Bois formula**:** $BSA = 0.007184 \times W^{0.425} \times H^{0.725}$ Du Bois D, Du Bois EF (Jun 1916). A formula to estimate the approximate surface area if height and weight are known.[21] This formula is not required if sites have ability to calculate BSA per other standard method.
CBC	Complete Blood Count
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
CMP	Complete Metabolic Panel
CTA	Computerized Tomography Angiogram
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.
DSM	Data Safety Monitor: Physician experienced in the treatment of PE with mechanical thrombolysis will adjudicate all adverse events in this study.
GTT	Drip
Modified Fick Calculation	$CO = \frac{O_2 \text{ Consumption } (VO_2) \text{ ml/min}}{(CaO_2 - CvO_2) \times 10} = L/min$ $VO_2 = 125 \times BSA$ $CaO_2 = (1.36 \times Hgb \times SaO_2)$ $CvO_2 = (1.36 \times Hgb \times SvO_2)$ ***This Modified Fick calculation is required in this protocol.***

3.0 TERMS AND DEFINITIONS (CONTINUED)

HIT	Heparin Induced Thrombocytopenia
Hrs	Hours
IJ	Internal Jugular
INR	International Normalized Ratio
LCFV	Left Common Femoral Vein
Modified Miller Index (MMI)	To define the CT obstruction index, the arterial tree of each lung is regarded as having 10 segmental arteries (3 to the upper lobes, 2 to the middle lobe and the lingula, and 5 to the lower lobes). The presence of embolus in a segmental artery is scored 1 point, and emboli in the most proximal arterial level are scored a value equal to the number of segmental arteries arising distally. To provide additional information about the residual perfusion distal to the embolus, a weighting factor is assigned to each value, depending on the degree of vascular obstruction. This factor is equal to zero, when no thrombus is observed; 1, when partially occlusive thrombus is observed; or 2, with total occlusion. Thus, the maximal CT obstruction index is 40 per patient.[22]
PAD	Pulmonary Artery Diastolic Pressure
PaO_2	Partial Pressure of Arterial Oxygen
PAP	Pulmonary Artery Pressure
PAS	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.
RV/LV	Right Ventricular / Left Ventricular
SAEs	Serious Adverse Event - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1. Death 2. Life-threatening adverse events *Continued on next page*

3.0 TERMS AND DEFINITIONS (CONTINUED)

SAEs (Continued)	3. Inpatient Hospitalization or Prolongation of existing hospitalization 4. A Persistent or Significant Incapacity or a substantial disruption in the ability to conduct normal life functions, or 5. Congenital Anomaly or Birth Defect. 6. Important medical events that may not result in death, be life-threatening or require hospitalization, may be considered serious when based upon appropriate medical judgement they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
SaO_2	Arterial oxygen saturation
SpO_2	Arterial oxygen saturation measured by pulse oximetry
Submassive PE	A normotensive patient with PE and evidence of RV dysfunction.
SvO_2	Venous oxygen saturation
Troponin I	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 cTnI levels support the diagnosis of severe 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, patients 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 work-ups 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/hour over 12 hours (bilateral PE). This treatment methodology achieved an absolute reduction in RV:LV ratio of 0.42 (±0.36), the mean baseline was 1.55 (±0.39) and at 48 hours 1.13 (±0.2).[15,17]

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 first-in-man study will utilize the Bashir™ Endovascular Catheter to administer catheter directed thrombolysis in patients with submassive PE who have consented and meet all eligibility criteria. The Bashir™ catheter represents 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).[16] 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.[17] The design of the Bashir Endovascular Catheter with the multiple infusion limbs creating a basket-like formation when expanded, provides 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, presented at ISET, February 6, 2018, 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. 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.[18]

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.[17] We therefore propose to utilize the following regimen: r-tPA 2mg in 20 cc administered in 1mg and 10cc increments x 2 into the PA for a total of 2 pulse sprays into the infusion basket via its infusion port on the handle, using a syringe, followed by a 10mg infusion at 1.27mg per hour until complete for unilateral PE, and 5mg infusion into each pulmonary artery for bilateral PE, at 0.65mg/hour until complete for a total dose of 1.3mg/hour for bilateral PE. This is a total of 12 mg over approximately 8 hours (pulse spray 1mg x 2 sprays = 2mg plus infusion at 1.27mg/hour x 7.87 hours (approximately 8 hours = 12mg) for unilateral PE. For bilateral PE, we propose to administer the same pulse spray and one-half of the infusion dose into each PA to total the unilateral infusion dose, for a total of 14mg administered including the pulse sprays and the infusions. 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. Additionally, an efficacy study stopping rule has been established for this study based on the reduction in RV:LV diameter ratio observed in the SEATTLE II study (0.42-0.36). The minimal reduction of 0.06 in SEATTLE II formed the basis for the efficacy study stopping rule for this study. If a reduction is less than 0.06 (refer to Section 18.3) in the first three patients, the study will be paused to re-evaluate the r-tPA dosage and administration.

5.0 INVESTIGATIONAL DEVICE

The Bashir™ Endovascular Catheter is a device 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 and retractable radial array of conduits with multiple 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.[19]

Figure 1. Bashir Endovascular Catheter

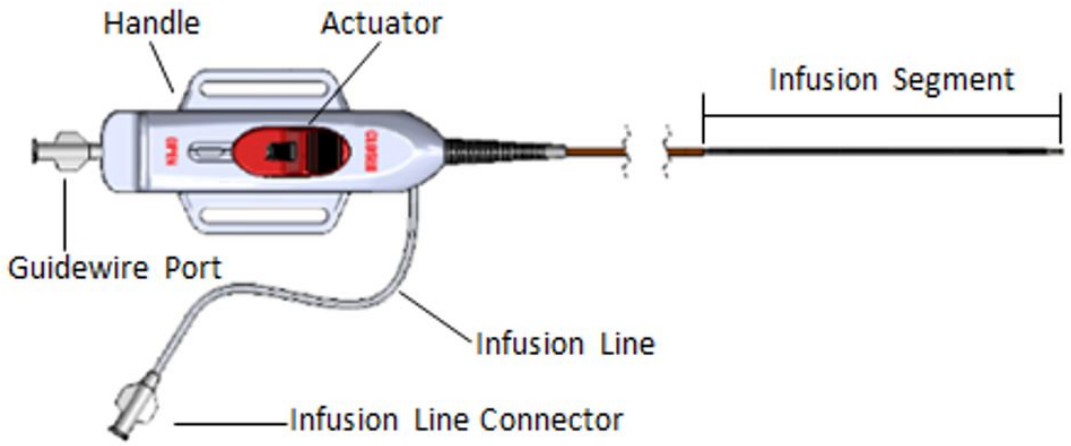

Figure 2. Bashir Endovascular Catheter with Basket Expanded

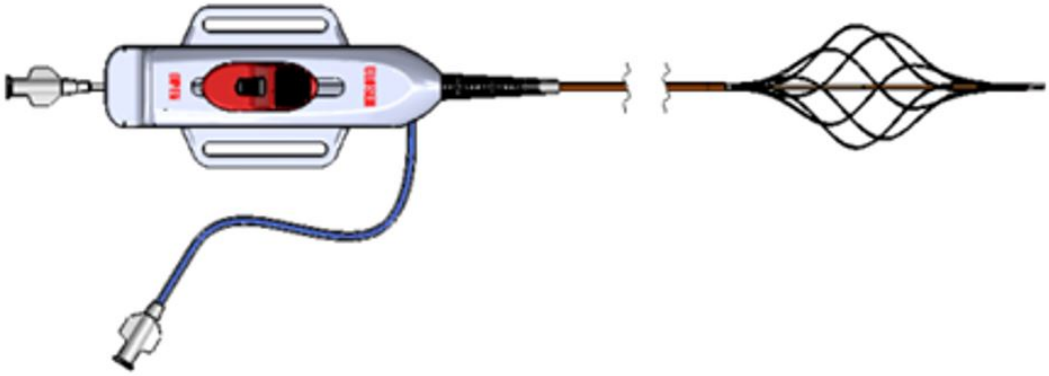

Table 1. Bashir™ Endovascular Catheter Dimensions

French Size	7 F (2.3 mm)
Effective Length	92.5 cm (35.44 in)
Infusion Segment Length	12.50 cm (4.92 in)

6.0 STUDY DESIGN

6.1 Study Objective

Assess the safety and feasibility of the Bashir™ Endovascular Catheter for the administration of low dose thrombolysis for acute submassive pulmonary embolism.

6.2 Primary and Secondary Endpoints

The primary endpoints below are appropriate for a first-in-man study. The secondary endpoints are for the purpose of additional safety assessments, additional procedure data related to any device issues (if any), and initial efficacy parameters.

6.2.1 Primary Endpoints

1. Safety: Major bleeding, as defined by International Society of Thrombosis and Hemostasis (ISTH), within 72 hours of initiation of r-tPA administration. Bleeding criteria are as follows: Major Bleeding in Non-Surgical Patients.
   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 2g/dL (1.24mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.[23]
2. Feasibility: Device success defined as the ability to use the Bashir™ Endovascular Catheter as per this protocol.

6.2.2 Secondary Endpoints

1. All-cause mortality at hospital discharge through 30-day follow-up.
2. SAEs through 30-day follow-up.
3. Anticipated (non-serious) adverse events (AEs) through 30-day follow-up.
4. Recurrent PE through 30-day follow-up.
5. 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.
6. Technical procedural complications.
7. RV/LV end diastolic diameter ratio at 24 hours after completion of r-tPA infusion compared to baseline, by echocardiogram.

8. RV/LV diameter ratio at 48 hours after completion of r-tPA infusion, by contrast enhanced chest CTA compared to baseline.
9. Modified Miller Index at 48 hours post r-tPA infusion as compared to baseline by contrast enhanced chest CTA.
10. Systolic PA pressure measured at completion of infusion 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.

6.3 Eligibility Criteria

The population to be enrolled in this study includes patients who present to the hospital with a submassive pulmonary embolism with symptom onset within 14 days. Patients 18 years of age and older will be evaluated for this study and must meet all inclusion criteria and will have none of the exclusion criteria.

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. 18 years of age and less than 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 contrast enhanced chest CT Scan (CTA);
5. RV/LV diameter ratio ≥ 0.9 by contrast enhanced chest CT scan (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. Cerebrovascular Accident (CVA) or transient ischemic attack (TIA) within one (1) year;
2. Head trauma, or other active intracranial or intraspinal disease within one (1) year;
3. Recent (within one month) or active bleeding from a major organ;
4. Intracranial condition(s) that may increase the risk of bleeding (e.g., neoplasms, arteriovenous malformations, or aneurysms);
5. Patients with bleeding diathesis;
6. Hematocrit < 30%;
7. Platelets < 100,000/μL;
8. INR > 1.5;
9. aPTT > 50 seconds in the absence of anticoagulants;
10. Major surgery within fourteen (14) days;

11. Serum creatinine > 2.0 mg/dL;
12. Clinician deems high-risk for catastrophic bleeding;
13. History of heparin-induced thrombocytopenia (HIT);
14. Pregnancy;
15. Systolic blood pressure < 90 mmHg for greater than 15 minutes;
16. Vasopressor support;
17. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR);
18. Evidence of irreversible neurological compromise;
19. Life expectancy < one (1) year;
20. Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to inclusion in the study;
21. Use of non-vitamin K oral anti-coagulants (NOACs), such as rivaroxaban, apixaban, dabigatran, edoxaban within 48 hours prior to inclusion in the study;
22. Use of enoxaparin sodium injection (Lovenox®) within 12 hours of procedure start time;
23. Profound bradycardia requiring a temporary pacemaker and/or inotropic support;
24. Previous enrollment in this study;
25. Morbidly obese (BMI >45 kg/m^2) patient who by the judgement of the investigator is high risk for bleeding;
26. Absolute contraindication to anticoagulation;
27. Uncontrolled hypertension;
28. Currently participating in another study;
29. 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 five (5) sites will enroll a total of ten (10) subjects over nine (9) months.

6.4.2 Follow-up

The follow-up for each subject will be completed at one (1) month post-discharge.

6.4.3 Complete Study Period

It is estimated that this study will require eleven (11) months to complete enrollment and follow-up.

6.4.4 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 I and BNP** – These tests will be drawn within 48 hours pre-procedure.
2. **aPTT** – Drawn within 48 hours pre-procedure. Unfractionated heparin will be infused to prolong the aPTT (suggested range is 60-80 seconds) prior to the administration of r-tPA. The institution is to follow the standard of care for the administration of heparin through the completion of the r-tPA infusion and the monitoring of aPTT in addition to the aPTTs measured at certain time points required by this protocol.
3. **International Normalized Ratio (INR)** – INR will be drawn within 48 hours pre-procedure for patients who are on Coumadin and must be ≤ 1.5 to be eligible for enrollment. Patients who are on Coumadin and have an INR ≤ 1.5 who are in the study the coumadin will be discontinued during the heparin infusion and the r-tPA infusion and can be restarted prior to discharge.
4. **Fibrinogen** – Fibrinogen levels are required to be checked within 48 hours prior to the procedure. *The assay method must be recorded (e.g. Clauss, PT-derived fibrinogen assay, immunological, gravimetric, other)*

7.1.2 Imaging

1. **Contrast Enhanced CTA of Chest** – A contrast enhanced CTA of chest will be performed within 48 hours pre-procedure. The contrast enhanced chest CTA is used to determine the pre-procedure Modified Miller Index Score within 48 hours prior to the procedure. *CT will be sent to the core lab for analysis.*
2. **Lower Extremity Venous DUS** – A duplex ultrasound is required 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 access may also be used if that is the operator's preference.
3. **Echocardiogram** – The echocardiogram will be done to determine the pre-procedure RV/LV end-diastolic diameter ratio. A core lab protocol will be followed for data acquisition. *The echocardiogram will be sent to the core lab for analyses.*

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 contrast enhanced chest CTA to ensure the subject meets the eligibility criteria of an axial RV/LV ratio ≥ 0.9. RV/LV ratio is required to be assessed by contrast enhanced chest CTA to determine eligibility. The site determines eligibility, and an independent core lab protocol will be followed for data acquisition. *Both the* contrast enhanced chest *CTA and echocardiogram will be sent to the core lab for analysis.*
3. **12-Lead Electrocardiogram (ECG)** – A 12-lead ECG will be performed prior to the procedure.

7.1.4 Anticoagulation

Unfractionated heparin is required to be used for anticoagulation and is to be started pre-procedure by intravenous administration to prolong the aPTT (suggested range is 60-80 seconds) unless the patient has received Lovenox.

The institution is to follow the standard of care for the administration of heparin and the monitoring of aPTT in addition to the aPTTs measured at certain time points required by this protocol. Stop the heparin administration at the completion of the r-tPA infusion. The final aPTT should be measured according to standard of care.

7.1.5 Patients Receiving Lovenox for Treatment of Pulmonary Embolism

Lovenox: Use of Lovenox is permitted pre-procedure for the treatment of PE if it is the standard of care. If Lovenox is administered to a potential study subject, then catheter directed thrombolysis procedure is to start no sooner than 12 hours from the last Lovenox dose.

During the CDT procedure in the IR suite/Cath lab ACTs will be checked and heparin bolus given to achieve ACT ≥ 200 seconds.

After completion of the CDT procedure, a heparin drip will be started prior to leaving the IR suite/Cath lab to maintain therapeutic dose through completion of the r-tPA infusion.

7.1.6 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.

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 medications will be recorded within 48 hours pre-procedure, at baseline.
5. **Modified Miller Index (MMI)** – Modified Miller Index (MMI) will be calculated by the core lab at baseline. The contrast enhanced chest CTA will be sent to the core lab and the MMI will be calculated by the core lab for each contrast enhanced CTA of the chest done in this study.[21]

8.0 IR SUITE/CATH LAB STUDY PROCEDURES

Should the patients 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 of the BEC to expose the infusion basket. A 70 cm length sheath Flexor® Raabe Guiding Sheath (Cook Medical, Inc.) or equivalent for femoral access is recommended for most patients. A shorter sheath may be utilized for IJ access.
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. guide wire lumen (Arrow® or equivalent) or an angled pigtail catheter.
6. 3-way stopcock – with Luer-lock connectors.
7. Infusion pump and IV tubing for r-tPA infusion.
8. Heparinized saline for flushing.
9. 0.9% NaCl intravenous (IV) infusion bag 250cc for r-tPA pulse spray mixture.
10. IV infusion pump and tubing.
11. Sterile water for injection, USP (Do not use bacteriostatic water, USP for injection) - for 2mg vial Cathflo Alteplase (r-tPA) mixture (Genentech, Inc., South San Francisco, CA).
12. Pulse Spray r-tPA vials:
    i. Unilateral PE:
        1. One (1) 2.2mg vial of Cathflo Alteplase (r-tPA) for pulse spray use.
        2. Two (2) 10cc syringes for injecting the pulse sprays.
    ii. Bilateral PE:

1. Two (2) 2.2mg vials of Cathflo Alteplase (r-tPA) for pulse spray use.
2. Four (4) 10cc syringes for injecting the pulse sprays.

13. r-tPA Infusion:
    i. **Unilateral PE**: Obtain five (5) 2.2mg vials of Cathflo Alteplase (r-tPA) for continuous infusion to be started in the IR suite/Cath lab at the end of the procedure for a total of 10 mg for one infusion. *Mixture requirements are in section 9.3.*
    ii. **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 at the end of the procedure for a total of 5 mg for each infusion for two infusions. *Mixture requirements are in section 9.3.*

8.1.2 Procedure Supplies Provided by the Sponsor

1. Bashir™ Endovascular Catheter

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). Print out the initial baseline readings for the PA pressures and retain with the source documentation in the subject binder. Indicate where on the tracing the PAS, PAD and PA Mean are interpreted.

1. PA Pressures measured using a Swan-Ganz catheter or angled pigtail: PAS / PAD / PA Mean
2. SpO_2 – Arterial Oxygen Saturation (pulse oximeter O_2 saturation)
3. SvO_2 - Mixed Venous Oxygen Saturations (from tip of a pigtail catheter or Swan-Ganz Catheter PA port)
4. CO – Modified Fick Calculation (see terms and definitions for formula)
5. CI – Calculation

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™ Endovascular Catheter (BEC).

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, with BP < 180/110 mmHg prior to PMCDT.
2. Discontinue the peripheral IV heparin drip infusions.
3. Obtain venous access using ultrasound guidance and Micropuncture needle. Ultrasound guidance and use of Micropuncture needle is mandatory for both CFV and IJ access.
4. Place 7F sheath(s) or larger in the RCFV or access point of choice (LCFV or IJ).
5. Check ACT - If ACT < 200 seconds, administer additional heparin bolus until ACT is documented to be ≥ 200 seconds.
6. Using a .035in. exchange length wire, insert the wire into a sheath and advance it up to the right atrium.

7. Insert the Swan-Ganz or angled pigtail catheter over the wire and advance it up to the right atrium.
8. Remove the guide wire.
9. Float the Swan-Ganz catheter or angled pigtail, and record baseline hemodynamic data in section 8.2.
10. Insert the exchange length STORQ™ (Cordis) guide wire, or equivalent, into the Swan-Ganz or angled pigtail catheter. Remove the Swan-Ganz or angled pigtail catheter.
11. Exchange the Swan-Ganz Catheter, or angled pigtail, for a long 7F sheath (or larger) which is placed into the PA where the thrombus is located.
12. Remove the guidewire and the dilator carefully from the PA making sure that the sheath does not jump forward.

9.2 Bashir Endovascular Catheter Use – Procedure Steps

1. Prepare all r-tPA solutions and IV infusion mixtures in Section 9.3 prior to opening the Bashir Endovascular Catheter (BEC).
2. Prepare the BEC 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 guide wire, such as Hi-torque Steelcore Peripheral Guide Wire (Abbott Vascular), introduce the wire into the lumen of the long sheath(s) and advance up into the target pulmonary artery.
4. Backload the BEC onto the 0.018" 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 port 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.
8. Do NOT aspirate back from the basket infusion port to back bleed. Only maintain forward flow by infusing the r-tPA at the prescribed rate 95cc/hour for unilateral PE and 65cc/hour for bilateral PE, as stated in Table 2.
9. Keeping the wire in the central wire lumen expand the infusion basket of the BEC.

9.3 r-tPA Administration

9.3.1 Part 1 – r-tPA Pulse Spray - In the IR suite/Cath lab through the BEC

1. Reconstitution of r-tPA Pulse Spray Mixture

a. Obtain a 2.2mg vial of r-tPA (1mg/ml) provided by study site.

b. Mix the lyophilized powdered r-tPA with 2.2ml sterile water for injection provided by study site (as stated in the r-tPA information sheet) to obtain 1mg/ml. Do not use bacteriostatic sterile water for injection.
c. Aspirate exactly 1mg (1ml) into a 3cc syringe (for accuracy)
d. Inject 1mg (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.
e. Repeat (c) and (d) above x 1.
f. This equals two (2) 10cc pulse spray doses (1mg/10cc in one 10cc syringes per pulse spray) with 1mg r-tPA per dose -Total of 2 mgs of r-tPA for unilateral PE).
g. If treating bilateral PE, repeat steps (c) through (f) above.

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

	Pulse Sprays					Infusion		
	No. of 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**	**Number of 2mg Cathflo™ r-tPA Vials Required**	**Amount of Diluent Required 0.9% NaCl**	**Infusion Rate**
Unilateral PE	1	2.2 ml per vial to have 1mg/ml	Total of 20cc including r-tPA	2 mg in 20 cc divided into 2 10cc syringes	2 pulse sprays in two 10cc syringes = two 10cc syringes	5 (10mg x 1 infusion)	750cc total including r-tPA mixture x 1 bag	95cc/hr= 1.27mg/hr x 1 infusion until complete 10mg total
Bilateral PE	2	4.4 ml in 2 vials for 1mg/ml	Total of 40cc including r-tPA	2 mg in 20cc x 2, divided into four 10cc syringes	2 pulse sprays in two 10cc syringes = four 10cc syringes	5 (5mg x 2 infusions)	500cc total including r-tPA mixture x 2 bags	65cc/hr= .65mg/hr per infusion x 2 infusions until complete 10mg total

2. Reconstitution of r-tPA IV Infusion Mixture

a. Unilateral PE
   i. Obtain a 1,000cc bag of 0.9% NaCl for infusion.
   ii. Aspirate 250cc of 0.9% NaCl from the 1,000cc IV bag to have a total diluent of 750cc.
   iii. Mix five (5) vials (2.2 ml injected into 2.2 mg vials) of r-tPA with sterile water for injection until the lyophilized powder is dissolved, for a total of 10 mg of r-tPA.
   iv. Aspirate 10ml (10mg) into a syringe.
   v. Verify 10ml are aspirated in the syringe.

vi. With a new syringe aspirate the amount of fluid from the IV bag that is equal in amount to the r-tPA solution in the r-tPA syringe, 10ml, so the total volume in the bag with the r-tPA will be 750cc.
vii. Inject the 10 mg solution of r-tPA into the IV bag for infusion. You should have a total of 10mg of r-tPA in a total of 750cc of diluent.
viii. Set aside for use at the end of the pulse spray procedure(s).

b. Bilateral PE
i. Obtain two (2) 500cc bags of 0.9% NaCl for infusion.
ii. Mix five (5) 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).
iii. Aspirate 10ml (10mg) dose into a syringe.
iv. Verify 10ml are aspirated into the syringe.
v. Determine the total number of mls in the syringe and note 5ml is one-half of the volume of the solution for one-half of the dose.
vi. With a new syringe aspirate the amount of fluid from the IV bag that is equal in amount to one-half of the r-tPA solution in the r-tPA syringe, 5ml, so the total volume in the bag with the r-tPA will be 500cc once the 5mg of r-tPA is added to the IV bag. Repeat for second IV bag.
vii. Inject 5mg (5ml) solution of r-tPA into one (1) IV bag for infusion. Inject the second 5mg solution of r-tPA into the second IV bag for infusion. You should have a total of 5mg of r-tPA in a total of 500cc of diluent in each IV bag for bilateral PE, a total of 10mg split among the two IV bags.
viii. Set aside for use at the end of the pulse spray procedure(s).

3. Pulse Spray of r-tPA for Unilateral and Bilateral PE

a. **Unilateral PE**: With the catheter in the target PA, and after verification the basket portion of the catheter has exited the sheath under fluoroscopy, and 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. Attach the pulse spray syringe to the unused port of the stopcock attached to the basket infusion port. Pause the infusion pump of the r-tPA infusion. Turn the stopcock so that it is closed to the infusion pump line and open to the syringe and to the basket infusion port.
c. Administer 10cc (1mg 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.
d. Under fluoroscopy, and guidewire in place, collapse the basket and re-expand the basket.
e. Repeat this with the second 10cc syringe (1mg r-tPA in 10ml) over 10-15 seconds.

f. As soon as the pulse sprays are administered, immediately re-start the r-tPA infusion via the basket infusion port of the BEC.
g. **Bilateral PE**: Repeat steps a-f in contralateral pulmonary artery for bilateral PE.
h. Once pulse sprays are complete, the basket(s) should remain expanded.
i. As soon as the pulse sprays are administered, immediately re-start the r-tPA infusion via the basket infusion port of the BEC in accordance with Table 2. Refer to Section 9.3.2 and Table 2 for r-tPA infusion instructions.
j. Remove the guidewire(s) from the wire lumen(s).
k. Ensure the BEC(s) are adequately flushed. Attach the flushed pressure transducer tubing to the wire lumen of the BEC(s). Measure the systolic PA, diastolic PA, and mean PA pressures in each PA with a pulmonary embolism from the tip of the BEC through the guidewire lumen at the back of the BEC handle. Print the PA waveform tracings and mark the tracings where the systolic PA, diastolic PA, and mean PA pressures are interpreted and documented.
l. If the waveform is dampened, adequately flush the wire lumen. If the waveform is still dampened after it is flushed, print the dampened waveform on paper, and retain the waveform with the source documentation for this study. Measure the systolic PA, diastolic PA, and mean PA pressures in each PA with a pulmonary embolism on the tracing. If the waveform becomes phasic prior to leaving the lab, print the waveform, mark on the waveform where the systolic PA, diastolic PA, and mean PA pressures are interpreted and the time the waveform became phasic. Retain the printout with the source documentation for this study.

9.3.2 Part 2 – r-tPA Infusion and Anticoagulation – Prior to Departing the IR suite/Cath lab r-tPA Infusion

Upon completion of the Pulse Sprays, with the basket re-expanded and catheter securely in place, begin r-tPA solution infusion(s), as soon as possible (immediately following the pulse sprays).

1. **For unilateral PE:** The total r-tPA is 10mg at 1.27mg/hr. Using an IV pump at 95cc/hour, infuse the 750cc of 0.9% NaCl with the 10mg r-tPA at 1.27mg/hr until infusion is complete (approximately 8 hours).
2. **For bilateral PE:** The total r-tPA dose is 10mg at 1.30mg/hr. Using two (2) IV pumps at 65cc/hour, infuse the 500cc of 0.9% NaCl x 2 simultaneously with the 5mg r-tPA at 0.65mg/hr for each PE for a total of 1.3mg/hour until complete (approximately 8 hours).
3. **Anticoagulation:** Re-start low dose heparin infusion into each sheath to prolong the aPTT (suggested range 40 to 60 seconds) prior to leaving the

IR suite/Cath lab to maintain therapeutic dose through completion of the 48-hour CT scan.

The institution is to follow the standard of care for the administration of heparin and the monitoring of aPTT in addition to the aPTTs measured at certain time points required by this protocol.

4. **Maintaining Patency Through the Central Lumen of the BEC(s):** Remove the wire from the central lumen of the BEC and attach a 3-way stopcock and flush with heparinized saline to maintain patency in the central lumen of the BEC (both BECs if bilateral PEs) when transferring to ICU.

   If it is standard of care in the IR suite/Cath lab to attach pressure tubing prior to transfer to the ICU for continuous PA pressure monitoring in the ICU, that may be done in lieu of heparinized flush in a syringe to maintain patency when transferring from the IR suite/Cath lab to the ICU. The central lumen of the BEC will be used for continuous monitoring of the PA pressures in the ICU. Hospital standard protocol will be used to maintain patency of the central lumen and to perform continuous pressure monitoring through the BEC in the ICU.

   For example, heparinized saline to a pressure bag and pressure monitor tubing connected to the bedside monitor to transduce pressure from the central lumen of the BEC may be performed; if there are two BECs in place for bilateral PEs, the central lumen of both BECs require pressure tubing for continuous pressure monitoring and kept open with standard pressure tubing transduced to the bedside monitor using heparinized saline in a pressure bag to keep the line patent and for continuous PA pressure monitoring and SvO_2 draws.

9.4 Intra-procedure Data Collection Requirements

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

9.5 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. Attach a 3-way stopcock and tubing to maintain patency and for continuous monitoring of the PA pressures in the ICU and an IV to keep open (TKO)

the central lumen (wire lumen) of the catheter per hospital standard protocol for each BEC.

4. Securing the device(s):
   a. For CFV Access: tape device to thigh. Then follow step "e" below.
   b. For 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.
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.

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 eight (8) 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.
   a. **Unilateral PE:** Infusion rate is to be maintained at 95cc/hour through the BEC, for a total of 1.27mg/hour infusing into the patient over approximately eight (8) hours. (95cc/hr= 1.27mg/hour x 1 infusion x approximately 8 hours = 10mg total). Infuse the r-tPA mixture until the infusion is complete.
   b. **Bilateral PE:** Infusion rate is to be maintained at 0.65mg/hour through each catheter, for a total of 1.3mg/hour infusing into the patient (0.65mg/hour through each BEC). This is a rate of 65cc/hour per infusion for a total of 130cc/hour total infusing through two catheters into the patient. Infuse the r-tPA mixture until the infusion is complete
2. **Laboratory Tests**: Four (4) hours (±1 hour) after initiation of heparin infusion started in the IR suite/Cath lab measure:
   a. CBC
   b. aPTT
3. **Hemodynamic Readings**: Record the following pressures in the ICU beginning with the 1st reading two (2) hours (±30 minutes) after the initiation of the r-tPA infusion and then every thirty (30) minutes (±15 minutes) thereafter through the central lumen of the BEC. If a waveform, or both waveforms (if bilateral) appear dampened, verify each BEC pressure transducer is set up properly when study subject arrives in ICU. If the waveform continues to be dampened, document the date and time when the waveform becomes phasic and print the waveform from the monitor. Mark on the waveform where the systolic PA, diastolic PA, and mean PA pressures are read and retain with the source documentation for this study. Please note that when the waveform becomes phasic, it must be documented even if it outside of the "every 30 minutes" scheduled readings. This is so the length of time from the 1st pulse spray (in the Cath/IR lab) to when the

clot dissolves in each PA with a pulmonary embolism will be known. Please note that printouts are not required for every reading, only when the dampened waveform becomes phasic, if dampened when subject arrives in the ICU. These readings are required through the completion of r-tPA infusion:

a. PAS / PAD / PA Mean Pressures
b. SpO_2 – Arterial Oxygen Saturation (pulse oximeter O_2 saturation)

4. **Mixed Venous Oxygen Saturation (SvO_2):** Record every two (2) hours (±30 minutes) in the ICU starting after the initiation of the r-tPA infusion. These readings are required through the completion of r-tPA infusion:
    a. SvO_2 – Mixed Venous Oxygen Saturations (Sample is from tip of the BEC, drawn from the central lumen of the BEC at the end of the handle. If bilateral, either BEC is acceptable for drawing the SvO_2.)
5. **Anticoagulation – Intensive Care Unit During r-tPA Infusion:** Heparin drip should be administered until the r-tPA infusion is complete (approximately 8 hours).
6. **Anti-coagulation Immediately Post-rtPA Infusion:** Once the r-tPA infusion is complete, turn off the heparin gtt. Starting 45 minutes (±15 minutes) after the r-tPA completion, administer Lovenox 1mg/kg sub-Q every 12 hours (±30 minutes) through the completion of the 48-hour CTA.
7. **Physical Exam:** A physical exam is required to be performed at the completion of the r-tPA infusion.
8. **Stopping r-tPA Infusion in ICU at the End of 8 Hours:** Upon completion of r-tPA infusion, maintain patency through the BEC by replacing r-tPA with heparinized saline using the infusion pump, at TKO, and transport to IR suite/Cath lab to remove BEC. Heparinized saline should infuse via infusion pump through the basket infusion port until subject arrives at the IR suite/Cath lab for catheter removal.

10.2 Return to The IR suite/Cath lab at The Completion of Infusion

At the end of the infusion the patient returns to the IR suite/Cath lab within eight (8) hours (+8 hours) of the completion of the r-tPA infusion for removal of the BEC(s) and final hemodynamic measurements.

1. Under fluoroscopy, collapse the basket(s) of the BEC.
2. Remove the BEC by pulling the catheter(s) carefully into the sheath(s) and then removing them from the body.
3. Back bleed or aspirate the sheath(s) and flush with heparinized saline to prevent clot formation.
4. **Catheter for Hemodynamic Readings and Blood Draws:** Insert a Swan-Ganz or angled pigtail catheter through the sheath and record the following.

    a. Hemodynamic Readings
        i. SvO_2 – Mixed Venous Oxygen Saturations
        ii. SpO_2 – Arterial Oxygen Saturation (pulse oximeter)
        iii. PA Pressures: PAS / PAD / PA Mean

iv. CO – Modified Fick calculation (Refer to Terms and Definitions for required calculation)
v. CI – Calculation

b. Fibrinogen – To be drawn at the time of the device removal in the IR suite/Cath lab. *The assay method must be recorded (e.g. Clauss, PT-derived fibrinogen assay, immunological, gravimetric, other)*

10.3 Tests Required at End of Infusion(s) and 24 Hours After r-tPA Infusion

10.3.1 Laboratory Tests and Other Tests

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

2. **aPTT** – To be drawn once heparin gtt is stopped according to standard of care and ONLY IF it is standard of care to check aPTT after heparin gtt is discontinued.

10.3.2 Imaging

1. **Echocardiogram** – The echocardiogram will be done to determine the RV/LV end-diastolic diameter ratio at 24 hours (±8 hours) from the completion of the r-tPA infusion. A core lab protocol will be followed for data acquisition. *The echocardiogram will be sent to the core lab for analyses.*

10.3.3 Assessments

1. **Physical Examination** – The physician will perform a physical examination at the end of the infusion and 24 hours (±8 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.

10.3.4 Data Collection

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

1. **Medications** – All medications 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.
3. **RV/LV End Diastolic Diameter Ratio** – This will be measured and calculated by echocardiogram at 24 hours (±8 hours) following completion of the r-tPA infusion. The imaging will be sent to the independent core lab for analysis.

10.4 Tests Required 48 Hours Following End of r-tPA Infusion

10.4.1 Imaging

1. **Contrast Enhanced CTA of the Chest –** A contrast enhanced chest CTA will be performed at 48 hours (±6 hours) after completion of the r-tPA infusion. The contrast enhanced chest CTA is used to determine the post-procedure RV/LV diameter ratio and Modified Miller Index Score. Please note that subject must be on Lovenox 1mg/kg every 12 hours through the completion of the 48-hour CTA. *The CT will be sent to the core lab for analyses.*

10.4.2 Assessments

1. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through 48 hours.

10.4.3 Data Collection

1. **Medications** – All medications will be recorded that are administered within 48 hours following the infusion completion.
2. **RV/LV End Diastolic Diameter Ratio** – This will be measured and calculated by CTA at 48 hours (±6 hours) following completion of the r-tPA infusion. The imaging will be sent to the independent core lab for analysis.
3. **Modified Miller Index Score** – This will be documented by the core lab after the contrast-enhanced chest CTA is performed. This will also be performed by the independent core lab.

10.5 Anticoagulation and Sheath Removal

10.5.1 Lovenox Administration

The subject must continue Lovenox 1mg/kg administered sub-Q every 12 hours (±30 minutes) through the completion of the 48-hour CTA.

10.5.2 FDA Approved Anticoagulation Regimen

At the time of r-tPA infusion completion and through the completion of the 48-hour CTA, administer Lovenox 1mg/kg subcutaneously. Study subjects may be prescribed any FDA approved regimen of anticoagulation after the 48-hour CTA scan is complete. The long-term anticoagulation administration is according to the physician's discretion.

10.5.3 Sheath Removal

The sheath removal date and time will be determined by the treating investigator and the study subject's condition and coagulation status. The sheath(s) shall be removed as soon as possible after removal of the BEC. Before removal, the sheath should be carefully aspirated then flushed to eliminate any clots.

10.6 Tests Required 72 Hours (+12 hours) Following Start of r-tPA Administration

10.6.1 Assessments

1. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through discharge. *Bleeding complications will be assessed through 72 hours (-4 / +12 Hours) following initial administration of the first r-tPA dose that was administered in the IR suite/Cath lab.*

10.6.2 Data Collection

1. **Medications** – All medications will be recorded that are administered within 72 hours following the infusion.

10.7 Tests Required Just Prior to Hospital Discharge

10.7.1 Assessments

1. **Physical Examination** – The physician will perform a physical examination within eight (8) hours (-8 Hours) of discharge.
2. **AE/SAEs** – Adverse events will be monitored and reported on the CRF post-procedure through discharge.
3. **12-Lead Electrocardiogram** – To be done prior to and no greater than within eight (8) hours (-8 Hours) prior to discharge.

11.0 30-DAY FOLLOW-UP VISIT POST PROCEDURE

11.1 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.

11.2 Data Collection

1. **Medications –** All medications since discharge will be recorded at 30-day follow-up.

12.0 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 associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)).

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. A suspected adverse reaction is an adverse event where there is a reasonable possibility the drug caused the adverse event. The sponsor is responsible for making the causality.

12.1 Bashir Endovascular Catheter Anticipated Adverse Events

Table 3. Anticipated Adverse Events Related to the Investigational Device[18]

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

12.2 r-tPA Anticipated Adverse Events

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

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 blood vessel
Thromboembolism	Obstruction of a blood vessel by a clot that has become dislodged

12.3 Anticipated Adverse Events Related to the Procedure

Table 5. Anticipated Adverse Events Related to the Procedure[20]

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

13.0 ADVERSE EVENT REPORTING

13.1 Serious Adverse Events and Serious Suspected Adverse Reactions

Serious adverse events (SAE) or serious suspected adverse reaction (SUSAR) must be reported to the study manager within 24 hours of knowledge of the event.

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Death;
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect;

5. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following event definitions, as defined in 21 CFR 312.32(a) will be reported as serious adverse events and the reporting requirements above must be followed.

Life-threatening adverse event (or life-threatening suspected adverse reaction): An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

13.2 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

The following event definitions, as defined in 21 CFR 312.32(a) will be reported as serious adverse events and the reporting requirements above must be followed.

An Adverse Event or Suspected Adverse Reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

It is anticipated that no unexpected adverse reactions will occur as r-tPA is FDA approved for the treatment of pulmonary embolism. The currently approved labeling requires 100mg of r-tPA to be administered intravenously over two (2) hours. This is 86mg more than the maximum dose required in this protocol administered over two (2) hours, not over approximately eight (8) hours as in this protocol.

13.3 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.

13.4 Adverse Event Relatedness

Table 6. Adverse Event Categories of Device Relatedness

Relatedness Term	Relatedness Definition

Related	The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
Possibly Related	An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
Not Related	The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

13.5 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 patients' 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. Patients 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.

14.0 REGULATORY REQUIREMENTS

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

14.1 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 CFR part 50. [21 CFR 312 Subpart D]. 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 subpart G.
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. The r-tPA, sterile water, and 0.9% NaCl for infusion will be provided by the site. Detailed documentation of the dosage and administration of the drug will be performed by the site for each study subject. Disposition of each study device will be documented by the site.
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. Form 1572 will be completed and signed by the investigator prior to commencement of the study.
7. 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.
8. 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.

9. 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.
10. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
11. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
12. 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
13. 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 and Echocardiograms:

    Medical Metrics, Inc.
    2121 Sage Road
    Suite 300
    Houston, TX 77056

14. 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).

14.2 Sponsor Responsibilities

1. General Duties
   a. Submitting the IND 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 312, 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. Investigator Brochure
   c. Case Report Form
   d. Informed Consent
   e. FDA Letter to Commence the Study

4. Refer to Section for Section 18 for Safety Reporting Requirements

14.3 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.

15.0 DEVICE AND DRUG ACCOUNTABILITY

15.1 Bashir™ Endovascular Catheter Packaging for the IR suite/Cath lab

The Bashir™ Cather is 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.

15.2 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.

15.3 Drug Accountability

The sites shall provide Cathflo® Activase (Alteplase) (r-tPA) and sterile water from their respective pharmacy for use in this study. The site will document each vial and drug disposition on the drug accountability log provided to the site.

16.0 STATISTICAL CONSIDERATIONS

16.1 Sample Size Justification

The sample size selected (10) is considered to be a number sufficient to gather essential early information on the safety and performance of the device. The essential information is identified in the primary and secondary endpoints defined. The sample size will also assist in identifying additional meaningful data points, refine study endpoints, and improve study procedures before proceeding to a larger statistically powered pivotal trial.

16.2 Data Analysis

Data collected will be summarized using descriptive statistics. The study is not statistically powered for the analysis of primary endpoints. Concomitant medications will be coded using the World Health Organization (WHO)-drug dictionary and AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA).

16.3 Data Entry

Data will be entered into a 21 CFR 11 compliant database, electronic data capture (EDC) for this study. The site staff shall be responsible for data entry.

17.0 DATA SAFETY MONITOR

A data safety monitor will be selected to review the study conduct, feasibility data, and safety data and will adjudicate all types of adverse events reported in this study. The independent DSM shall have the final adjudication for the events. A data safety charter will be established and will be approved by the data safety monitor. Qualifications for the DSM, at a minimum, shall include current experience with catheter directed thrombolysis for the treatment of massive and 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 DSM meetings in addition to following the charter.

18.0 STUDY STOPPING CRITERIA

This first-in-man study is to demonstrate safety and device success defined as the ability to use the Bashir™ Endovascular Catheter as intended for the treatment of pulmonary embolism. The treatment for pulmonary embolism in this study utilizes the Bashir™ Endovascular Catheter for the delivery of r-tPA into the pulmonary artery. The dose of r-tPA in this study is much less than the FDA approved prescribed dose (FDA approved dosing 100mg infused intravenously over two hours for massive PE versus this study dose of approximately 12mg [for unilateral PE] to approximately 14mg [for bilateral PEs] over approximately 8 hours into the PA). The study stopping criteria will be based on criteria related to bleeding, device use, and early efficacy.

18.1 General Study Stopping Rules

18.1.1 The Sponsor, DSM, 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.

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

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

18.2 Safety Study Stopping Rule

If two (2) patients undergoing the investigational procedure die or experience an unprovoked intracranial hemorrhage, confirmed by independent DSM 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.

18.3 Efficacy Study Stopping Rule

Should the treatment not achieve a reduction in RV:LV ratio as measured by CT at 48 hours by at least 0.06 compared to baseline, in three of the first three patients, the study shall be paused for re-evaluation.

18.4 Device Study Stopping Rules

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

18.4.2 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 three (3) patients from being treated in this study, the study shall be paused for re-evaluation. 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.

18.5 Study Safety Reporting Requirements

The following reporting requirements are the responsibility of the sponsor and are transferred to Eminence Clinical research, Inc. to meet these reporting obligations. For investigations of marketed drugs under an IND, such as in this study requiring the administration of FDA approved r-tPA, Eminence Clinical Research, Inc. shall submit IND safety reports for suspected adverse reactions that are observed in the clinical study at study sites (21 CFR 312.32).

Diane Horwitz, PhD
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Principal Regulatory Consultant
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19.0 VERSION CONTROL

Add to table below for each protocol amendment

PROTOCOL THRO-CLIN-2018-01		
VERSION	**SUMMARY OF THE CHANGE**	**RATIONALE**
0.0	Original for FDA Review	N/A
1.0	Efficacy study stopping rule added	Response to FDA Clinical Hold Letter
2.0	Efficacy study stopping rule wording clarified; Core Lab Contact Updated; Supplier of CathFlo® Activase changed from Sponsor to Site; Typographical errors corrected	Respond to FDA request; make additional corrections
3.0	r-tPA Infusion calculation correction; elimination of "end diastolic" referenced with CTA; Modify anticoagulation protocol for patients on Lovenox	Additional corrections and clarifications
4.0	Change BMI exclusion to >45; clarify heparin infusion duration; specify use of 7Fr sheath of appropriate length; add instruction to maintain patency of BEC with infusion pump after r-tPA infusion; re-order procedure steps for heparin bolus after obtaining access; Change 24 and 48 hour assessments start point from "start of r-tPA administration" to "end of r-tPA infusion"	Additional corrections and clarifications
5.0	Remove heparin infusion following completion of r-tPA infusion; administer Lovenox for anti-coagulation at completion of r-tPA through the completion of the 48-hour CTA. Continue anti-coagulation according to standard of care after the CTA is complete.	Edit protocol with recommendations from the sponsor's Scientific Advisory Board
6.0	Change time of commencing r-tPA infusion in the IR Suite / Cath Lab and specify the window of time permitted for Lovenox to be started and then administered every 12 hours.	Prevent blood from clotting in the infusion limbs of the basket. Window added for clarification.

20.0 REFERENCES

1. Raskob GE, Angchaisuksiri P, Blanco AN et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;24:2363-2371.
2. Konstantinides S, Barco S, Lankeit M et al. Management of pulmonary embolism. Journal of the *Amer Col of Cardiol* 2016;67:976-90.
3. Heit J. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol*. 2008;28(3):370-72.
4. Heit J, Cohen A, Anderson Jr F. Estimated annual number of incident and recurrent non-fatal and fatal venous thromboembolism (VTE) events. *US. Blood Journal*; 2005;106:910.
5. Beckman M, Hooper C, Critchley S et al. Venous thromboembolism: a public health concern. *Amer J of Preventive Med* 2010;38(4S)S495-S501
6. https://www.cdc.gov/ncbddd/dvt/data.html accessed online January 21, 2018
7. Aggarwal V, Nicolais C, Lee A, Bashir R. et al. Acute management of pulmonary embolism. *J of the Amer Col of Cardiol* 2017:1-24
8. Zarghouni M, Charles H, Maldonado T et al. Catheter-directed interventions for pulmonary embolism. *Cardiovasc Diagn Ther* 2016;6(6):651-61.
9. Dudzinksi DM, Giri J, and Rosenfield K. Interventional treatment of pulmonary embolism. *Circ Cardiovasc Interv*. 2017;10:e004345:1-10.
10. Jaff M, McMurtry S, Archer S et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. *Circulation*. 2012;126:e104.
11. Daley MJ, Murthy MS, and Peterson EJ. Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem. *Therapeutic Advances in Drug Safety*; 2015;6(2):57-66.
12. Jarrett H, Bashir R. Interventional management of venous thromboembolism: state of the art. *Amer J of Roentgenol* 2017; 208(4):1-8
13. Enden T, Wik H, Kvam A et al. Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes fo the randomized, non-blinded, parallel-group CaVenT study. *Brit Med J* Open 2013:3:1-8
14. Søgaard K, Schmidt M, Pedersen L et al. 30-year mortality after venous thromboembolism: a populated-based cohort study. Circulation. 2014;130:829-36.
15. Ferrigno L, Bloch R, Threlkeld et al. Management of pulmonary embolism with rheolytic thrombectomy. *Can Respir J*, Vol 18(4):e52-e58
16. Activase_prescribing package, 2017 Revision.
17. Piazza G, Hohlfelder B, Jaff M et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism-SEATTLE II Study. *J Am Coll Cardiol Interv.* 2015;8:1382–92.

18. Sterling KM. Late-breaking Trial Results: Long-term Results of the OPTALYSE PE Trial. Oral Presentation: *International Society of Endovascular Therapy*, January 2018.

19. Bashir™ Endovascular Catheter Instructions for Use, 2017 Thrombolex, Inc.

20. Evans DC, Doraiswamy VA, Prosciak MP et al. Complications of pulmonary artery catheters: A comprehensive critical review.2009;98:199-208.

21. http://www.calculator.net/body-surface-area-calculator.html accessed online January 28, 2018. *Archives of Internal Medicine* 17 (6): 863-71.

22. Qanaldi SD, Hajjam ME, Vieillard-Baron A et al. New CT Index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. American J of Radiol, 2001;176:1415-20.

23. Schulman S, Angeras U, Bergqvist D et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. Journal of Thrombosis and Haemostasis, 2009;8:202-04.

21.0 APPENDICES

APPENDIX 21.1 REQUIRED STUDY PROCEDURES

Test	Pre-Procedure	Procedure	Post-Procedure	End of Infusion	24 Hrs Post-r-tPA Completion	48 Hrs Post-r-tPA Completion	72 Hrs Post- r-tPA Initiated	Before Dis-charge	30-day Follow-up
Visit Window	≤ 48 Hrs of procedure			+8 Hrs	±8 Hrs	±6 Hrs	-4 / +12 Hrs	-8 Hrs	±7 Days
Informed Consent	X								
Demographics and Medical History	X								
Physical Examination	X			X	X			X	X
12 Lead ECG	X							X	
CBC, INR[1]	X		X[2]		X				
aPTT	X[2]		X	X					
Fibrinogen[3]	X			X					
CMP	X								
BMP					X				
Cardiac Biomarkers: Troponin I, 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			
Echocardiogram	X				X				
RV/LV Diameter Ratio with each Echocardiogram	X				X				
Eligibility Criteria	X	X							
Anticoagulation[3] (Heparin, Lovenox)	X	X	X	X	X	X			
IR / Cath Lab: Invasive Hemodynamic Data / ACT[4]		X		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 q 30 Min via BEC			X	X					
ICU: Mixed venous SvO_2 q2 Hours via BEC			X	X					
r-tPA Infusion		X	X						
Medications	X	X	X	X	X	X	X	X	X
AEs / SAEs		X	X	X	X	X	X	X	X
Contrast Enhanced CTs to Core Lab	X					X			
Echocardiograms to Core Lab	X				X				

[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.

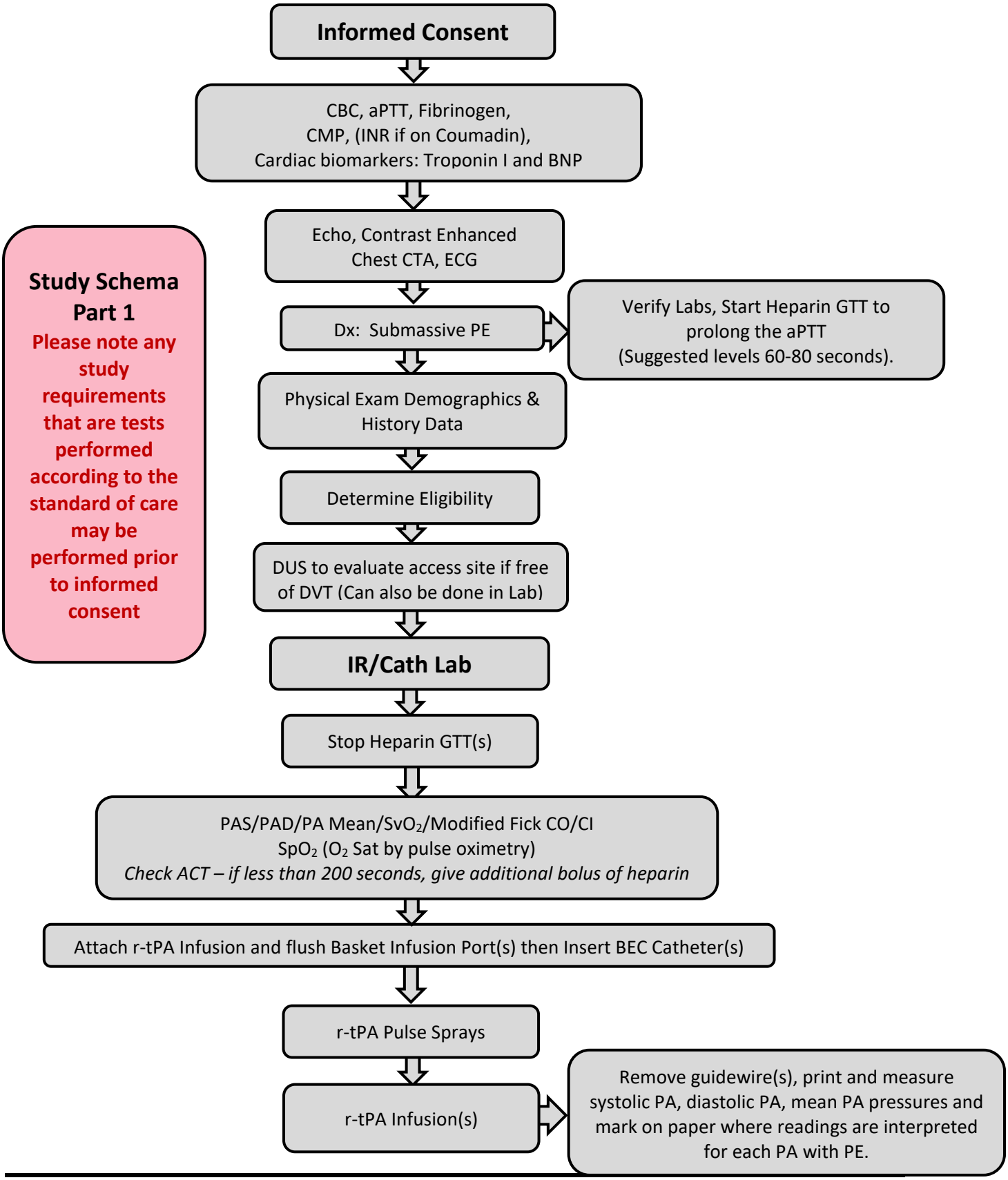
[2] Pre-procedure suggested aPTT 60-80s. Suggested aPTT during r-tPA administration is 40-60s. Check aPTT and CBC 4 hr (±1 hr) after heparin is restarted in the IR suite/Cath lab (suggested range 60-80s).

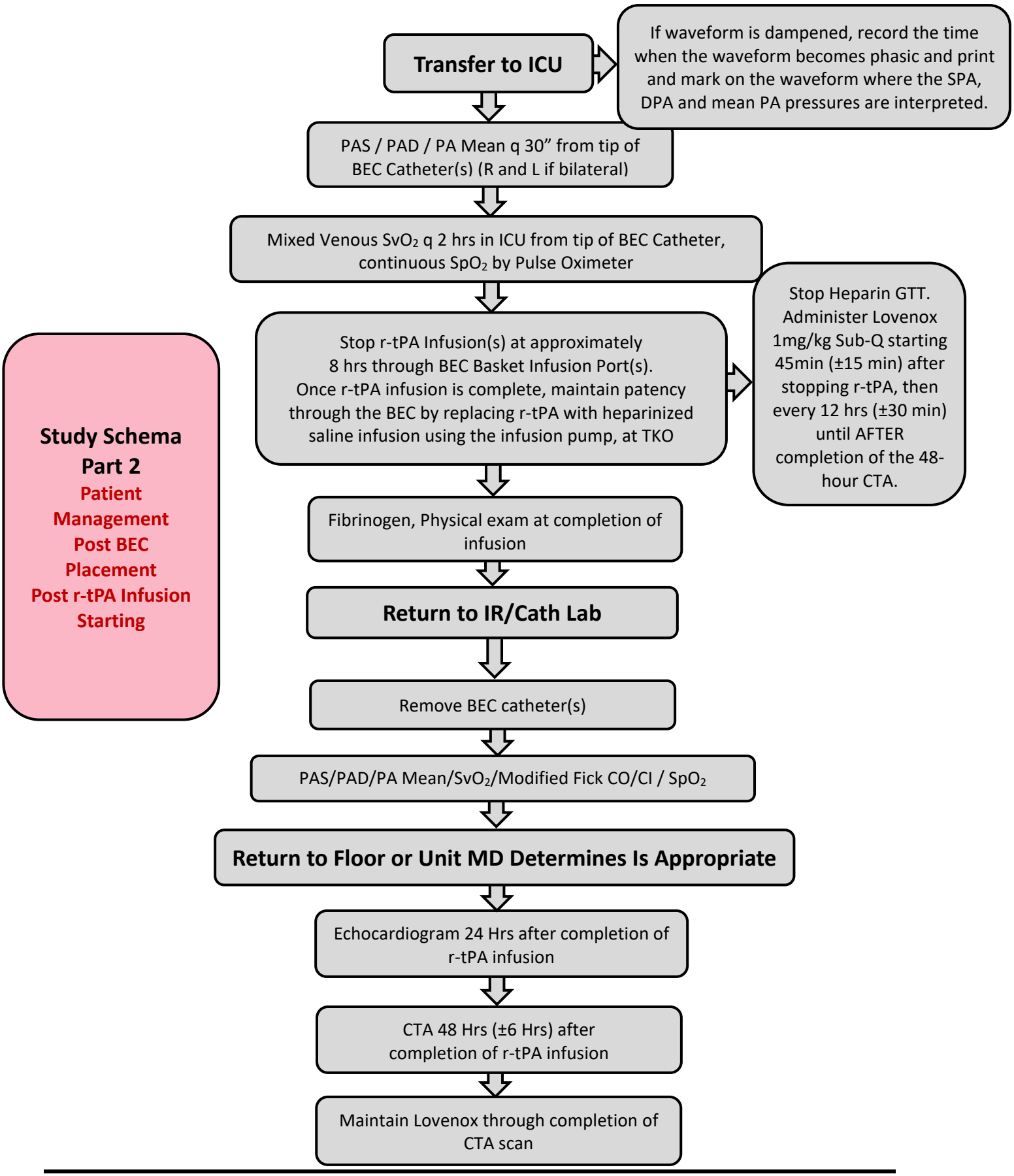
[3] Unfractionated Heparin will be infused IV pre-procedure or Lovenox. Stop Heparin prior to start of procedure. Restart Heparin post procedure with r-tPA infusion. Fibrinogen to be drawn at time of BEC removal in IR suite/Cath lab. Heparin infusion will continue until the completion of the r-tPA infusion. Lovenox 1mg/kg Sub-Q will be started 45 minutes (±15 minutes) from the completion of the r-tPA infusion and given q12hrs (±30 min).

[4] Required: PAS, PAD, PA Mean, CO, CI, SpO_2, SvO_2 / ACT - in IR/Cath lab at baseline (print waveforms) and post-infusion in the IR suite/Cath Lab. Swan-Ganz or angled pigtail may be used. CO= Modified Fick calculation. ACT will be done to achieve (and document) an ACT ≥ 200 seconds.

[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 at the rate prescribed in this protocol, which is a duration of approximately 8 hours. Once the r-tPA infusion is complete, heparinized saline must infuse TKO using the infusion pump until BEC removal.

APPENDIX 21.2 STUDY SCHEMA





APPENDIX 21.3 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 21.4 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 21.5 CORE LAB PROTOCOLS

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

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