



AVENTUS: Assessing the Safety and Efficacy of the treatment for Acute Pulmonary Embolism using the Inquis Medical Aventus Thrombectomy System™

Clinical Investigation Plan

CT-0001

Revision D

Release Date

March 28, 2024

Device Name

Aventus Thrombectomy System™

Sponsor

Inquis Medical, Inc.

127 Independence Drive

Menlo Park, CA, 94063

Telephone: 408-209-8326

DISCLOSURE STATEMENT

This document contains information that is confidential and proprietary to Inquis Medical, Inc. This information is being provided to you solely for the purpose of evaluating or conducting a clinical study for Inquis Medical. You may disclose the contents of this document only to study personnel under your supervision who need to know the contents for this purpose and to your Institutional Review Board (IRB) or Ethics Committee (EC). Otherwise, the contents of this document may not be disclosed without the prior authorization from Inquis Medical. The foregoing shall not apply to disclosure required by governmental regulations or laws. Any supplemental information that may be added to this document also is confidential and proprietary to Inquis Medical and must be kept in confidence in the same manner as the contents of this document.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Investigator Agreement

- I agree to conduct the study in accordance with this agreement, the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation and all device testing involving human subjects.
- I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 (or waiver under 45 CFR 46.116(d)) and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I have read and understand the information in the investigator's brochure and/or protocol, including the device's potential risks and side effects.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records according to 21 CFR 812.140(a) and make those records available for inspection by 21 CFR 812.145.
- I will ensure that an IRB that complies with 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary, to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators, requirements in 21 CFR Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA.
- I agree to provide, or have provided, the Sponsor with a current curriculum vitae and similar statement of my relevant experience, including the dates, location, extent, and type of experience.
- I confirm that I have not been involved in an investigation or other terminated research or have provided the Sponsor with a written explanation of the circumstances that led to termination.
- I agree to provide sufficient accurate financial disclosure information to allow the Sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR Part 54.
- I agree to promptly update this information if any relevant changes occur during the investigation and for one year following completion of the study.
- I understand that I retain the right to publish, in accordance with the Clinical Trial Agreement, the data from the clinical work that I perform. I agree that Inquis Medical will be allowed to review and comment on such a document prior to its publication to ensure that the document does not disclose any trade secrets or other confidential information which may be known to me by virtue of my participation in the clinical study. I will not disclose any information regarding the study without permission from Inquis Medical.

_____, MD

Name of Clinical Investigator (Printed or Typed)

Signature of Clinical Investigator

Date

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Table of Contents

Contents

1. CLINICAL INVESTIGATION SUMMARY	8
2. INTRODUCTION.....	12
2.1. Clinical Background.....	12
2.2. Current Treatments	12
2.2.1. Anticoagulation Therapy	13
2.2.2. Surgical Embolectomy.....	13
2.2.3. Thrombolytic Therapy.....	13
2.2.4. Catheter-directed Thrombolysis	13
2.2.4.1. Standard Catheter-directed Thrombolysis	14
2.2.4.2. Ultrasound-assisted catheter-directed thrombolysis	14
2.2.4.3. Pharmacomechanical Catheter-directed Thrombolysis	14
2.2.5. Catheter Based Mechanical Thrombectomy	14
2.2.6. Current mechanical thrombectomy systems.....	15
2.3. Limitations of Current Treatments.....	15
2.4. Treatment Description	17
Figure 1: Aventus Thrombectomy System™	18
2.5 Principles of Operation	19
3. STUDY OBJECTIVE, DESIGN AND ENDPOINTS.....	19
3.1. Primary Objective.....	19
3.2. Study Design, Enrollment and Follow-up	19
3.3. Primary Efficacy Endpoint.....	19
3.4. Primary Safety Endpoint.....	20
3.5. Observational Endpoints	20



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

4. STUDY POPULATION, SCREENING, RECRUITMENT, AND ENROLLEMNT PROCEDURES.....	20
4.1. Subject Population.....	20
4.2. Inclusion Criteria.....	21
4.3. Exclusion Criteria.....	21
4.4. Screening and Enrollment	22
4.5. Screen Failures	22
4.6. Enrollment Procedure.....	22
5. STUDY PROCEDURE, CLINICAL PROCEDURES, AND LABORATORY EVALUATIONS.....	23
5.1. Study Procedure	23
5.1.1. Preparation	23
5.1.2. Pre-Procedure	23
5.1.3. Baseline Imaging.....	23
5.1.4. Index Procedure	24
5.1.5. Post Procedure.....	24
5.1.7. Post-procedure Clot/Blood Measurement.....	25
5.2. Study Visit Schedule.....	25
5.3. Termination of Subject Participation	27
5.4. Lost to Follow-up.....	27
5.5. Subject Withdrawal	27
6. ADVERSE EVENTS.....	27
6.1. Adverse Event	27
6.2. Serious Adverse Event	28
6.3. Device Deficiency / Device Returns.....	29
6.4. Adverse Device Effect (ADE).....	29
6.5. Assessment of Adverse Events.....	29

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Table 2. Adverse Event Severity Definitions	31
Table 3. Adverse Event Expectedness Definitions	31
Table 4. Adverse Event Relationship to Study Device	31
Table 5. Adverse Event Relationship to Study Procedure.....	32
6.6. Reporting Requirements	32
Table 6. Adverse Event Reporting Timelines.....	32
6.7. Risk/Benefit Assessment	33
6.7.1. Risks.....	33
6.7.2. Risk Mitigation.....	34
6.7.3. Benefits	34
7. STATISTICAL CONSIDERATIONS	35
7.1. Accrual and Follow-up.....	35
7.2. Primary Efficacy Endpoint.....	35
7.3. Primary Safety Endpoint.....	35
7.4. Interim Analysis	36
7.5. Study Success.....	36
7.6. Analysis of Adverse Events	36
7.7. Analysis Populations	36
7.8. Roll-In population.....	37
7.9. Statistical Analyses.....	37
7.10. Handling of Missing Data	37
7.11. Poolability	38
7.12. Subgroup Analyses.....	39
7.13. Sample Size Justification	39
7.14. Overall Study Sample Size	41
8. DATA MANAGEMENT and SECURITY.....	41



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

9. SUBJECT CONSIDERATIONS	42
9.1. Ethics Review	42
9.2. Informed Consent.....	43
9.3. Clinical Trial Termination.....	43
9.4. Subject Data Protection	43
10. ADMINISTRATIVE CONSIDERATIONS	44
10.1 Study Activation	44
10.2 Study Coordination	44
10.3 Study Monitoring	44
10.4 Protocol Compliance	45
10.5 Protocol Deviations.....	45
10.6 Study Audits	45
10.7 Record Keeping	45
10.8 Data Retention	47
10.9 Reports.....	47
10.10 Investigator Reports	48
10.11 Imaging	48
10.12 Device Inventory Requirements	48
10.13 Publication of Information	48
10.14 Insurance	49
11. STUDY OVERSIGHT	49
11.1 Medical Monitor	49
11.2 Clinical Events Committee	49
11.3 Data Safety Monitoring Board (DSMB)	50
11.4 Imaging Core Laboratory	50
11.5 Investigator Responsibilities	50

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

11.6 Sponsor Responsibilities	51
APPENDIX I: Study Abbreviations	52
APPENDIX II: Study Definitions	56
APPENDIX III: References.....	61

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

1. CLINICAL INVESTIGATION SUMMARY

Study Title:	AVENTUS: Assessing the Safety and Efficacy of the treatment for Acute Pulmonary Embolism using the Inquis Medical Aventus Thrombectomy System™
Study Objective:	To evaluate the safety and efficacy of the Aventus Thrombectomy System™ for aspiration thrombectomy in subjects with acute pulmonary embolism (PE).
Study Design:	This is a prospective, multi-center, single-arm, non-blinded clinical trial.
Study Device:	The Aventus Thrombectomy System™ is manufactured by Inquis Medical, Inc. and consists of the Aventus™ Aspiration Catheter and the Aventus™ Clot Management System.
Indications for Use:	The Aventus Thrombectomy System™ is indicated for the non-surgical removal of emboli and thrombi from blood vessels, for the injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel, and for autologous blood transfusion. The Aventus Thrombectomy System™ is intended for use in the peripheral vasculature and for the treatment of pulmonary embolism.
Enrollment and Follow-up:	Up to 120 subjects will be enrolled at up to 35 U.S. investigative sites. Each site can enroll a maximum of 30 subjects, establishing an enrollment cap at 25% of the total sample size. In addition, each site may enroll up to 2 roll-in subjects for a total of up to 50 roll-in subjects. Roll-in subjects will be analyzed separately from the Safety and Efficacy analysis populations. Subjects will be followed for 30-days (± 7 days) and then exited from the clinical trial.
Subject Population:	Subjects presenting with symptoms of acute intermediate risk PE defined as having clinical signs and symptoms for 14 days or less from the index procedure with an RV/LV ratio of ≥ 0.9 and who are indicated for treatment with aspiration thrombectomy will be screened for this clinical trial. Subjects must meet all inclusion criteria and not meet any of the exclusion criteria to be enrolled.
Inclusion Criteria:	1. Age ≥ 18 and ≤ 80 years 2. Subject or legally authorized representative (LAR) is willing and able to provide written informed consent prior to receiving any non-standard of care protocol specific procedures

	3. Subject is willing and able to comply with all protocol required follow-up visits 4. PE symptom(s) duration ≤ 14 days from index procedure 5. PE diagnosis ≤ 48 hours prior to index procedure 6. CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery based on Investigator determination) 7. CTA evidence of dilated RV with an RV/LV ratio of ≥ 0.9 at baseline based on Investigator determination 8. Systolic blood pressure ≥ 90 mmHg without need for vasopressors (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with intravenous fluids prior to index procedure) 9. Stable heart rate < 130 BPM prior to index procedure 10. Subject is deemed medically eligible for interventional procedure(s), per institutional guidelines and clinical judgment
Exclusion Criteria:	1. Prior PE ≤ 180 days from index procedure 2. Current hospitalization for other condition(s) 3. Thrombolytic use ≤ 14 days of baseline CTA 4. Pulmonary hypertension with peak pulmonary artery systolic pressure > 70 mmHg by right heart catheterization 5. FiO₂ requirement $> 40\%$ or > 6 LPM to keep oxygen saturation $> 90\%$ 6. Hematocrit $< 28\%$ within 6 hours of index procedure 7. Platelets $< 100,000/\mu\text{L}$ 8. Serum creatinine > 1.8 mg/dL 9. International normalized ratio (INR) > 3 10. Presence of intracardiac lead in the right ventricle or right atrium placed < 180 days prior to index procedure 11. Cardiovascular or pulmonary surgery ≤ 7 days prior to index procedure 12. Actively progressing cancer treated by chemotherapeutics 13. Known bleeding diathesis or coagulation disorder 14. Left bundle branch block 15. History of severe or chronic pulmonary arterial hypertension 16. History of chronic left heart disease with left ventricular ejection fraction $\leq 30\%$ 17. History of uncompensated heart failure 18. History of underlying lung disease that is oxygen dependent 19. History of chest irradiation



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

	20. History of heparin-induced thrombocytopenia (HIT) 21. Any contraindication to systemic or therapeutic doses of heparin or anticoagulants 22. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated 23. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for aspiration thrombectomy intervention such as the inability to navigate to target location, predominantly chronic clot or non-clot embolus 24. Life expectancy of < 90 days, as determined by Investigator 25. Female who is pregnant or nursing 26. Current participation in another investigational drug or device treatment study that has not reached the primary endpoint or the Investigator feels would impact their ability to participate in this clinical trial 27. Subject has known residual Iliac Deep Vein Thrombosis (DVT), Inferior Vena Cava (IVC) clot or clot in transit (right atrium and/or right ventricular) 28. Subject on extracorporeal membrane oxygenation (ECMO)
Primary Efficacy Endpoint:	Core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (± 8 hours) post-index procedure as measured by CTA
Primary Safety Endpoint:	Composite of device related major adverse events (MAEs) within 48 hours (± 8 hours) of the index procedure, as adjudicated by the Clinical Events Committee (CEC), including: • Death • Major bleed • Clinical deterioration • Pulmonary vascular injury • Cardiac injury

Observational Endpoints:

- Length of stay in the Intensive care unit (ICU) related to index procedure
- Length of stay in the hospital (general ward) related to index procedure
- Core laboratory adjudicated change in Refined Miller Score from baseline to 48 hours (± 8 hours) post-index procedure as assessed by CTA
- Use of thrombolytics within 48 hours (± 8 hours) of the index procedure
- Device related death within 48 hours (± 8 hours) of the index procedure*
- Device related major bleed within 48 hours (± 8 hours) of the index procedure*
- Device related clinical deterioration within 48 hours (± 8 hours) of the index procedure*
- Device related pulmonary vascular injury within 48 hours (± 8 hours) of the index procedure*
- Device related cardiac injury within 48 hours (± 8 hours) of the index procedure*
- Symptomatic PE recurrence within 30 days (± 7 days) of index procedure confirmed by imaging*
- Device related SAEs within 30 days (± 7 days) of the index procedure*
- All cause death within 30 days (± 7 days) of the index procedure
- Change in Six-Minute Walk Test (6MWT) from 48 hours (± 8 hours) to 30 days (± 7 days)
- Change in quality of life through 30 days (± 7 days) as measured by the PEmb-QoL Questionnaire

*CEC adjudicated

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

2. INTRODUCTION

2.1. Clinical Background

Pulmonary Embolism is a major cause of morbidity and mortality. It complicates post operative recovery for cancer subjects, subjects with trauma, and immobilized subjects of all types. The annual incidence of pulmonary embolism (PE) worldwide is approximately 1 in 1000 persons^{1,2}.

PE occurs when venous thrombi are dislodged from peripheral venous sites where they have formed. These thrombi often develop within the leg or pelvic veins, and approximately half of all deep-vein thrombi embolize to the pulmonary vasculature³. Dislodged thrombus migrates to the right heart, and then pumped out to the pulmonary artery vasculature as it arborizes into smaller vessels, obstructing some or all the flow to one or more segments of the lungs. This pulmonary vascular obstruction reduces lung gas exchange and ventilatory capacity and raises the resistance to flow through the lung vasculature. The blockage of circulation in the lungs due to embolized blood clots, strains the right ventricle (RV) and may lead to sudden death due to RV failure³. RV failure due to pressure overload is considered the primary cause of death in severe PE.

Symptoms of PE include acute shortness of breath, chest discomfort, palpitations, dyspnea, dizziness or syncope, extremity pain, or swelling⁴.

2.2. Current Treatments

Initial treatment of pulmonary embolism is guided by risk stratification of the pulmonary embolism as high, intermediate, or low risk based on the subject's clinical presentation. Recommendations concerning the treatment of PE are published by the American College of Chest Physicians (ACCP)⁵, the American Heart Association (AHA)⁶, the European Society of Cardiologists (ESC)⁷, and the Pulmonary Embolism Response Team (PERT) Consortium⁸. Approximately 5% of subjects present with high-risk pulmonary embolism, involving shock, end-organ hypoperfusion, hypotension (systolic blood pressure less than 40 mm Hg that is not caused by sepsis, arrhythmia, or hypovolemia), or cardiac arrest⁹.

Intermediate Risk Subjects with echocardiographic or CT evidence of right heart strain, elevated cardiac biomarkers (such as troponin or brain natriuretic peptide), or both are considered to have intermediate-risk pulmonary embolism⁸. Low Risk Subjects with pulmonary embolism whose conditions are hemodynamically stable and who have no right ventricular strain and normal cardiac biomarkers are considered to have low-risk pulmonary embolism⁹.

Treatment for many years consisted of systemic anticoagulation based upon clinical diagnosis made with limited peripheral imaging and nuclear or invasive angiography. Most cases left significant thrombus burden in place resulting in long term scarring of the

pulmonary vessels and pulmonary hypertension. With the advent of rapid magnetic resonance imaging (MRI) and computed tomography (CT) imaging in the acute setting and thrombolytics for lysis of thrombus, subjects have been diagnosed much earlier and the existing acute coronary Cath lab workflow can be leveraged for rapid definitive therapy.

Currently, the following clinical options are used in the treatment of PE: anticoagulation therapy, surgical embolectomy, thrombolytic therapy, catheter-directed thrombolysis and mechanical thrombectomy.

2.2.1. Anticoagulation Therapy

The benefit of early therapeutic anticoagulation to improve mortality and decrease recurrence in acute PE is well established¹⁰. Anticoagulation should be initiated even prior to the confirmed diagnosis when there is high clinical suspicion of acute PE and the bleeding risk is low, particularly if results of diagnostic tests are expected to be delayed⁷. Even when additional therapeutic modalities are considered, anticoagulation should not be delayed unless contraindicated^{5,7}.

2.2.2. Surgical Embolectomy

Surgical embolectomy has been reserved for subjects with high-risk PE who are either in cardiogenic shock or those cases where less invasive measures (including thrombolysis) have failed or are contraindicated. This treatment option is highly invasive and associated with morbidity and mortality¹¹.

2.2.3. Thrombolytic Therapy

Systemic thrombolysis is given to achieve rapid clot resolution and restoration of pulmonary perfusion thereby improving ventilation/perfusion matching, and importantly relieving RV afterload, reducing pulmonary vascular resistance, and thereby improving hemodynamics^{5,12,13}. Systemic thrombolysis, however, is associated with an increase in hemorrhagic complications including intracranial hemorrhage^{5-7,14,15}. The decision to administer systemic thrombolysis therapy in subjects with PE should be based on the delicate balance between a subject's clinical and hemodynamic status and individualized risks of bleeding⁸.

2.2.4. Catheter-directed Thrombolysis

There are several types of catheter-directed thrombolysis available: standard Catheter Directed Thrombolysis (CDT), Ultrasound facilitated Catheter Directed Thrombolysis (UCDT), and Pharmacomechanical Catheter Directed Thrombolysis.

2.2.4.1. Standard Catheter-directed Thrombolysis

Catheter placement in the pulmonary artery allows for the delivery of thrombolytic agents proximal to or intra-emboli. CDT in the treatment of PE has the potential to offer similar clinical benefits as systemic thrombolytics while resulting in less bleeding by using a lower total drug dose. Studies have suggested that doses of tissue plasminogen activator (tPA) that are less than the FDA-approved dose are safe and effective in both massive and submassive PE subjects¹⁶⁻¹⁷. CDT may be theoretically safer than systemic thrombolysis, but definitive data are not available. Existing studies are not sufficiently powered to definitively make this conclusion¹⁸. The optimal dose and mode of administration for local thrombolytic treatment is still to be determined. The use of tPA for treatment of submassive PE has not been approved by the FDA and remains a widely debated topic; nevertheless, tPA is often used off-label to treat submassive PE^{19,20}.

2.2.4.2. Ultrasound-assisted catheter-directed thrombolysis

Ultrasound-facilitated thrombolysis relies on the principle of enhancing thrombolytic drug delivery into the thrombus using ultrasound energy²¹. The use of UCDT achieves thrombolysis using lower doses of fibrinolytic agents compared to systemic administration of these agents, which often require much higher doses. Due to the lower dose of the fibrinolytic agents, the risk of major or serious bleeding is lower²¹.

2.2.4.3. Pharmacomechanical Catheter-directed Thrombolysis

The pharmacomechanical approach to endovascular treatment of acute pulmonary embolism is based on the principle of delivering even lower doses of a fibrinolytic drug with mechanical thrombus fragmentation, to enhance the delivery of the fibrinolytic agent. The AngioJet catheter (Boston Scientific, Marlborough, MA) can be used to deliver tPA during thrombectomy, but the use of this device was associated with a high rate of complications in a meta-analysis by Kuo and colleagues²². Another currently available catheter is the Bashir Endovascular catheter (BEC, Thrombolex, New Britain, PA) which is based on the principle of pharmacomechanical fragmentation and thrombolysis²³. The recent RESCUE trial, a multicenter prospective study enrolled 109 subjects with intermediate-risk acute PE resulting in a RV/LV diameter ratio decrease of 0.56 (33.3%)²³.

2.2.5. Catheter Based Mechanical Thrombectomy

Catheter based mechanical thrombectomy has emerged as the treatment of choice for subjects presenting with intermediate-risk PE in recent years. Intermediate-risk (submassive) PE is more common compared to high-risk (massive) acute PE, comprising nearly one third of all subjects presenting with acute PE²⁴. In addition to

that, these subjects remain at high risk for severe complications and progression to hemodynamic instability. In these subjects, catheter-based therapies offer a potential clinical benefit without exposing the subjects to the risk of high-dose systemic thrombolytic therapy.

2.2.6. Current mechanical thrombectomy systems

The current thrombectomy systems rely on various size catheters percutaneously placed in the pulmonary vasculature to fragment, macerate, and aspirate the obstructive thrombi with various consistencies from the pulmonary vasculature. The main advantage of mechanical thrombectomy over CDT is potentially the quicker reduction in pulmonary vascular obstruction and the ability to achieve this without using fibrinolytic agents. However, some of these advantages are offset by the need to place large-bore venous access cannulas for some device systems and the risk of distal embolization to normally functioning segments of the pulmonary circulation. Few devices are available in this category.

Two important devices in this category that have received FDA clearance include the FlowTrieve Retrieval/Aspiration system and the Penumbra Indigo aspiration catheter system. The FlowTrieve Retrieval/Aspiration (Inari Medical, Inc., Irvine, California) catheter is available in three sizes 16F, 20F, and 24F. In addition to the aspiration cannula, this system also has three nitinol mesh disks, which can be deployed beyond the thrombus and then retrieved into the aspiration catheter²⁵. The safety and efficacy of this catheter was tested in the FLARE trial, a prospective, single-arm trial, which enrolled 106 subjects with acute intermediate-risk pulmonary embolism and right ventricular strain defined as RV/LV ratio ≥ 0.9 ²⁶. Another thrombectomy device, the Penumbra Indigo (Penumbra, Alameda, CA) aspiration catheter, is a continuous aspiration system, available in two sizes 8F and 12F. The safety and efficacy of this device were evaluated in the EXTRACT PE trial. This trial enrolled 119 subjects with intermediate-risk acute PE and showed a significant reduction of mean RV/LV ratio at 48 h²⁷.

2.3. Limitations of Current Treatments

The goal of a successful interventional pulmonary thrombectomy procedure is reducing elevated pulmonary vascular resistance to improve cardiac output and RV outflow. This critical therapy needs to be done in a rapid and efficient way. The timely and more complete removal of thrombus is essential in interrupting a potentially lethal cascade of increasing RV dilatation and strain leading to hemodynamic collapse with excess morbidity and mortality.



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Current medical guideline for high-risk and intermediate risk PE consists of using anticoagulation as the primary treatment, and the use of thrombolytics is restricted to hemodynamically unstable subjects⁵⁻⁷. Guidelines further suggest that thrombolytics not be routinely used to treat intermediate-risk PE but should instead be considered on a case-by-case basis. The potential benefit of thrombolytics as just described comes at the acute risk of potential fatal or dangerous bleeding into the brain, at vascular access sites, and any other occult gastrointestinal (GI) or vulnerable anatomic locations. Such bleeding requires transfusion of blood cells and clotting factors, with attendant increased morbidity and mortality and cost.

In recent years, percutaneous catheter based mechanical thrombectomy systems have been approved. They offer a non-lytic treatment option for removing thrombus, reducing the risk of lytic therapy associated with major bleeding complications. Existing mechanical thrombectomy systems, while safe and effective in restoring the hemodynamic balance and blood flow^{26,27}, still have several limitations.

Unnecessary and potentially dangerous blood loss: Inability to verify the optimal positioning of the tip of the catheter against the blood clot during the procedure is one of the major shortcomings of the current treatments. This results in unnecessary aspiration of blood or applying unnecessary aspiration force on the vessel wall if the tip of the catheter is against the vessel wall instead of the blood clot.

Procedural complexity, safety and time: Multiple wire exchanges are required to deliver and navigate existing catheter systems through the pulmonary vasculature. These additional steps add procedural risk and time. They are associated with the risk of vessel damage or perforation and increased x-ray exposure to subject and staff.

For the many thousands of subjects with life threatening intermediate and high-risk Pulmonary Embolism, there is an urgent and large unmet need for a safer, more effective aspiration thrombectomy system. Such a system needs to enable the treatment of subjects with improved ease of use, optimized thrombus detection and removal while maintaining hemodynamic stability. Interventional catheter based thrombectomy approaches developed to date to address this need have established a start to addressing this unmet need, but are limited in their efficacy, safety, ease of use and are ineffective at quickly removing thrombus. Thrombus location and consistency are rate limiting and procedures are not user friendly and effective at removing thrombus burden quickly.

The Aventus Thrombectomy System™ has been designed to significantly address the current available product and procedure limitations. The system includes ease of use features for reduced procedure steps, leveraging operators existing standard interventional skills and visualization abilities. It thus enables optimal catheter positioning critical for the safe and efficient aspiration of obstructive thrombus. Its additional features

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

streamline the procedure and enable potential for more complete thrombus detection and removal.

2.4. Treatment Description

The Aventus Thrombectomy System™ (Figure 1) is a catheter-based manual aspiration system designed for minimally invasive removal of emboli and thrombi from the peripheral vasculature and pulmonary arteries. The Aventus Thrombectomy System™ is comprised of the following major components:

- Model Number IM-1001: Aventus™ Aspiration Catheter
- Model Number IM-1002: Aventus™ Clot Management System

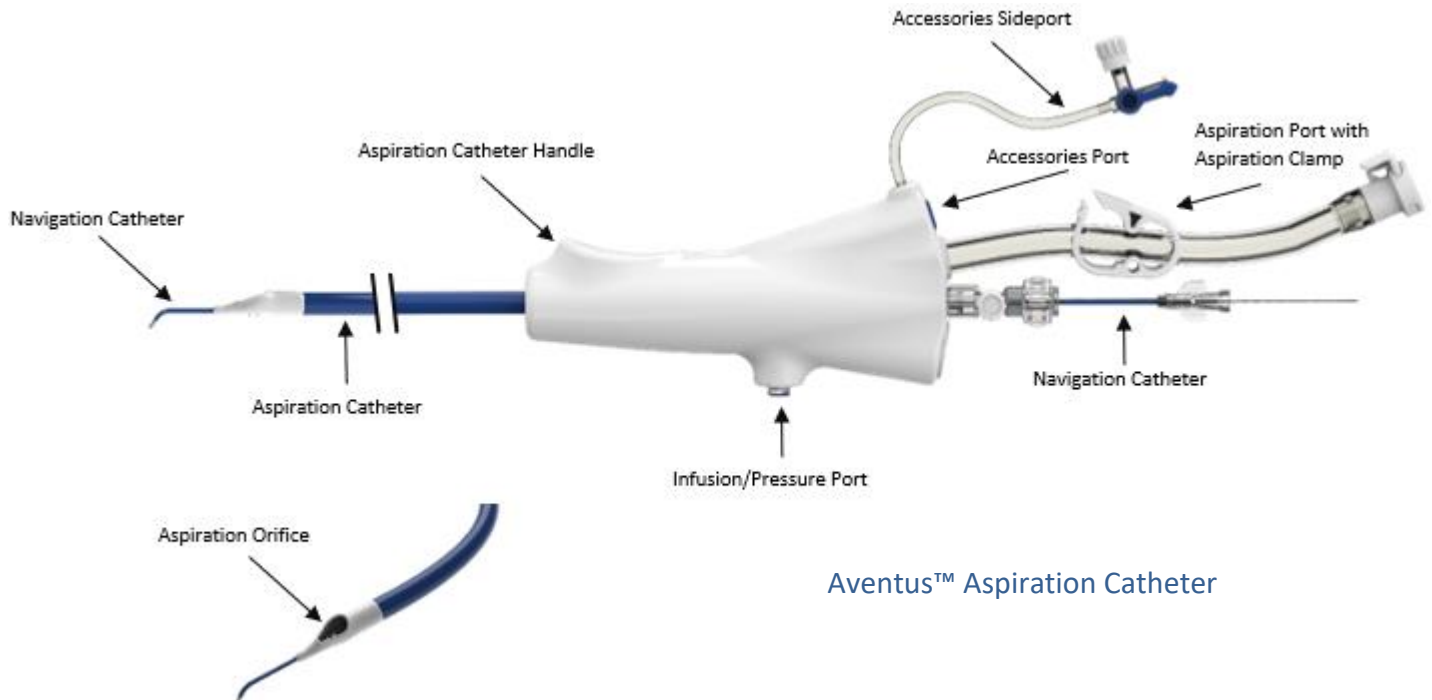
The Aventus Thrombectomy System™ is compatible with a standard 24F introducer sheath and is to be used with 0.035" guidewires. The system is also compatible with blood transfusion filters and standard 135 cm length support catheters. The Aspiration Catheter and Clot Management System are provided sterile and are intended for single use only.

The Aventus Thrombectomy System™ has the following features that enable the system to efficiently remove emboli and thrombus from vasculature:

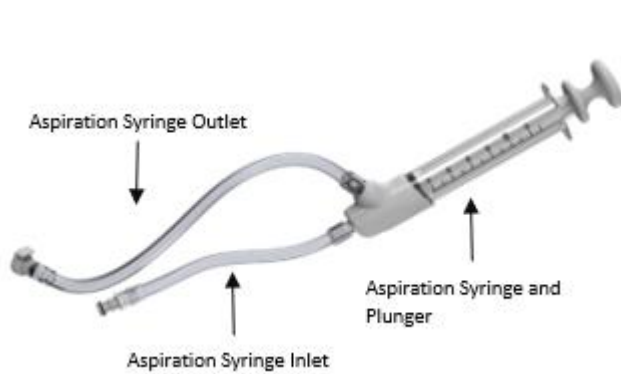
- Angled aspiration orifice for Directional Aspiration
- Navigation lumen for trackability and guidewire management
- Beveled atraumatic catheter tip precluding the need for dilator or obturator insertion during tracking within anatomy
- Clot Canister with filter for streamlined clot management

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

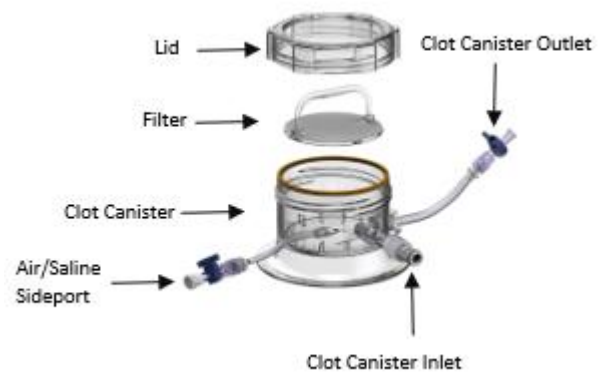
Figure 1: Aventus Thrombectomy System™



Aventus™ Aspiration Catheter



Aventus™ Aspiration Syringe



Aventus™ Clot Canister



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

2.5 Principles of Operation

The Aspiration Catheter is introduced through a commercially available (i.e., not provided by Inquis Medical) 24F compatible vascular introducer sheath into the subject's peripheral vasculature and fluoroscopically guided over a commercially available 0.035" guidewire to the site of the occlusion. Once at the occlusion, the clinician applies suction to the aspiration lumen via the Aspiration Syringe to aspirate the emboli or thrombi from the target vessel. The clinician then navigates the Aspiration Catheter to another occlusion to aspirate additional thrombus.

As desired, the clinician can inject contrast through a dedicated infusion lumen in the Aspiration Catheter that will generate a radiopaque plume around the tip of the catheter within the blood stream enabling visualization using fluoroscopy. This dedicated lumen can also be used to monitor the vessel pressure by connecting the lumen to the Cath lab hemodynamic monitoring system via a standard luer extension line.

The user retracts the Aspiration Syringe plunger to apply suction to the system, thus aspirating blood/clot from the body. When the Aspiration Syringe plunger is advanced, a pair of one-way valves directs the blood/clot from the Aspiration Syringe into the Clot Canister which contains a filter that separates the clot from the removed blood. Filtered blood can then be returned to the patient through a suitable blood transfusion filter into an access or introducer sheath.

3. STUDY OBJECTIVE, DESIGN AND ENDPOINTS

3.1. Primary Objective

The primary objective of this trial is to evaluate the safety and efficacy of the Aventus Thrombectomy System™ for aspiration thrombectomy in subjects with acute pulmonary embolism.

3.2. Study Design, Enrollment and Follow-up

This is a prospective, multicenter, single-arm, non-blinded clinical trial. Up to 120 subjects will be enrolled at up to 35 U.S. investigative sites. Each site can enroll a maximum of 30 subjects, establishing an enrollment cap at 25% of the total sample size. In addition, each site may enroll up to 2 roll-in subjects for a total of up to 50 roll-in subjects. Roll-in subjects will be analyzed separately from the Safety and Efficacy analysis populations. Subjects will be followed for 30-days (± 7 days) and then exited from the clinical trial.

3.3. Primary Efficacy Endpoint

Core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (± 8 hours) post-index procedure as measured by CTA.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

3.4. Primary Safety Endpoint

Composite of device related major adverse events (MAEs) within 48 hours (± 8 hours) of the index procedure, as adjudicated by the Clinical Events Committee (CEC), including:

- Death
- Major bleed
- Clinical deterioration
- Pulmonary vascular injury
- Cardiac injury

3.5. Observational Endpoints

- Length of stay in the Intensive care unit (ICU) related to index procedure
- Length of stay in the hospital (general ward) related to index procedure
- Core laboratory adjudicated change in Refined Miller Score from baseline to 48 hours (± 8 hours) post-procedure as assessed by CTA
- Use of thrombolytics within 48 hours (± 8 hours) of the index procedure
- Device related death within 48 hours (± 8 hours) of the index procedure*
- Device related major bleed within 48 hours (± 8 hours) of the index procedure*
- Device related clinical deterioration within 48 hours (± 8 hours) of the index procedure*
- Device related pulmonary vascular injury within 48 hours (± 8 hours) of the index procedure*
- Symptomatic PE recurrence within 30 days (± 7 days) of index procedure confirmed by imaging*
- Device related SAEs within 30 days (± 7 days) of the index procedure*
- All cause death within 30 days (± 7 days) of the index procedure
- Change in Six-Minute Walk Test (6MWT) from 48 hours (± 8 hours) to 30 days (± 7 days)
- Change in quality of life through 30 days (± 7 days) as measured by the PEmb-QoL Questionnaire

*CEC adjudicated

4. STUDY POPULATION, SCREENING, RECRUITMENT, AND ENROLLEMNT PROCEDURES

4.1. Subject Population

Subjects presenting with symptoms of acute intermediate risk PE defined as having clinical signs and symptoms 14 days or less from the index procedure with an RV/LV ratio



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

of ≥ 0.9 on CT angiography and systolic BP ≥ 90 mmHg and who are indicated for treatment with aspiration thrombectomy will be screened for this clinical trial. Subjects must meet all inclusion criteria and not meet any of the exclusion criteria to be enrolled.

4.2. Inclusion Criteria

1. Age ≥ 18 and ≤ 80 years
2. Subject or legally authorized representative (LAR) is willing and able to provide written informed consent prior to receiving any non-standard of care protocol specific procedures
3. Subject is willing and able to comply with all protocol required follow-up visits
4. PE symptom(s) duration ≤ 14 days from index procedure
5. PE diagnosis ≤ 48 hours prior to index procedure
6. CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery based on Investigator determination)
7. CTA evidence of dilated RV with an RV/LV ratio of ≥ 0.9 at baseline based on Investigator determination
8. Systolic blood pressure ≥ 90 mmHg without need for vasopressors (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90 mmHg with intravenous fluids prior to the index procedure)
9. Stable heart rate < 130 BPM prior to the index procedure
10. Subject is deemed medically eligible for interventional procedure(s), per institutional guidelines and clinical judgment

4.3. Exclusion Criteria

1. Prior PE ≤ 180 days from index procedure
2. Current hospitalization for other condition(s)
3. Thrombolytic use ≤ 14 days of baseline CTA
4. Pulmonary hypertension with peak pulmonary artery systolic pressure > 70 mmHg by right heart catheterization
5. FiO₂ requirement $> 40\%$ or > 6 LPM to keep oxygen saturation $> 90\%$
6. Hematocrit $< 28\%$ within 6 hours of index procedure
7. Platelets $< 100,000/\mu\text{L}$
8. Serum creatinine > 1.8 mg/dL
9. International normalized ratio (INR) > 3
10. Presence of intracardiac lead in the right ventricle or right atrium placed < 180 days prior to the index procedure
11. Cardiovascular or pulmonary surgery ≤ 7 days prior to the index procedure
12. Actively progressing cancer treated by chemotherapeutics
13. Known bleeding diathesis or coagulation disorder



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

14. Left bundle branch block
15. History of severe or chronic pulmonary arterial hypertension
16. History of chronic left heart disease with left ventricular ejection fraction $\leq 30\%$
17. History of uncompensated heart failure
18. History of underlying lung disease that is oxygen dependent
19. History of chest irradiation
20. History of heparin-induced thrombocytopenia (HIT)
21. Any contraindication to systemic or therapeutic doses of heparin or anticoagulants
22. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated
23. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for aspiration thrombectomy intervention such as the inability to navigate to target location, predominantly chronic clot or non-clot embolus
24. Life expectancy of < 90 days, as determined by Investigator
25. Female who is pregnant or nursing
26. Current participation in another investigational drug or device treatment study that has not reached the primary endpoint or the Investigator feels would impact their ability to participate in this clinical trial
27. Subject has known residual Iliac Deep Vein Thrombosis (DVT), Inferior Vena Cava (IVC) clot or clot in transit (right atrium and/or right ventricular)
28. Subject on extracorporeal membrane oxygenation (ECMO)

4.4. Screening and Enrollment

Subjects presenting with signs and symptoms of acute intermediate risk PE will be screened for possible enrollment. Informed consent will be obtained once a subject has satisfied standard of care screening criteria and prior to performing any study-specific assessments or procedures. Sites will be encouraged to evaluate subjects for residual lower extremity DVT prior to treatment.

4.5. Screen Failures

Subjects who meet all Inclusion criteria and none of the Exclusion criteria, have signed the informed consent form, but do not have any component of the Aventus Thrombectomy System™ introduced into the body will be considered a screen failure. The reason for screen failure will be captured and should be entered into the EDC.

4.6. Enrollment Procedure

Consecutive subjects presenting with acute PE will be screened for this trial. A subject is considered enrolled if the informed consent form is signed by either the subject or the subject's LAR and in whom the Aventus Thrombectomy System™ has crossed the introducer sheath.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Any subject that has the Aventus Thrombectomy System™ introduced into their body but no thrombectomy performed will be followed for Adverse Events (AEs) from the start of index procedure through 48 hours (± 8 hours) post procedure or hospital discharge, whichever comes first, and then exited from the study. Any AEs will be documented accordingly.

The first two (2) subjects at each site may be enrolled as roll-in subjects and must be prospectively identified and documented accordingly, including date and time of roll-in designation. Designation of a subject as a roll-in subject is not permitted after the index procedure has been initiated.

5. STUDY PROCEDURE, CLINICAL PROCEDURES, AND LABORATORY EVALUATIONS

5.1. Study Procedure

The thrombectomy procedure should be performed per standard institutional guidelines. The Aventus Thrombectomy System™ should be used per the approved Instructions for Use (IFU).

5.1.1. Preparation

Ensure that the subject or subject's LAR has signed and dated the Informed Consent Form (ICF) and the subject has met all screening and baseline study entrance criteria. Anesthesia or sedation should be administered, as appropriate to assure subject comfort and safety. The type of sedation used will be captured on the electronic case report form (eCRF).

5.1.2. Pre-Procedure

The following pre-procedure assessments should be performed, and details captured on the eCRFs.

- Vital Signs including blood pressure, heart rate, respiratory rate, oxygen saturation
- Concomitant Medications
- Pulmonary Artery Pressure (PAP)
- Hematocrit and Hemoglobin (within 6 hours of the index procedure)

5.1.3. Baseline Imaging

Prior to enrollment, the following CTA imaging assessments must be performed:

- Confirmation of proximal PE indicated by filling defect in at least one main or lobar pulmonary artery based on Investigator determination
- RV/LV Ratio (must have dilated RV with an RV/LV ratio of ≥ 0.9)

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

- Refined Miller Score (calculated by core laboratory)
- Clot Location
- Evidence of reflux into the IVC

5.1.4. Index Procedure

The Aventus Thrombectomy System™ must be the first and primary device used for thrombectomy. Additional adjunctive devices or drugs may be used at the discretion of the Investigator. Any use of adjunctive treatments for the purpose of reducing clot burden in the pulmonary arteries, intra-procedural and up to 48 hours (± 8 hours) post procedure, will be analyzed separately per the Statistical Considerations section of this CIP.

The following Index Procedure assessments should be performed, and details captured on the eCRFs.

- Vascular Access (performed per standard institutional guidelines for thrombectomy)
- Concomitant medications administered
- ACT measurements
- Adverse event assessment
- Adjunctive devices and/or thrombolytics used
- Concomitant procedure
- Procedure times
- Contrast and fluoroscopy details
- Blood loss estimation
- Total number of times the clot canister was cleaned
- Total clot volume removed
- Number of times the Study Device was removed from Subject
- Index procedure and treatment details
- Angiographic imaging (may be collected for the purposes of training and education)

5.1.5. Post Procedure

The following post procedure assessments should be performed, and details captured on the eCRFs.

- Vital Signs including blood pressure, heart rate, respiratory rate, oxygen saturation
- Concomitant Medications
- Adverse Event Assessment
- Pulmonary Artery Pressure

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

- Evidence of Vessel Injury (Perforation/Dissection)
- Review of post procedure imaging for PE status

5.1.6. Post-procedure Clot/Blood Measurement

Future product considerations may include a sensing system to allow the operator to easily differentiate between blood and clot at the tip of the aspiration catheter. For subjects that provide consent, the following parameters may be measured:

- Extracted leftover Blood (blood that won't be returned to the subject)
 - Temperature
 - Magnitude Impedance @ 100kHz
 - Phase Angle @ 100 kHz
- Clot
 - Temperature
 - Weight
 - Classification of Clot (optional photo)
 - Magnitude Impedance @ 100kHz
 - Phase Angle @ 100 kHz

Tissue and blood will not be collected by the sponsor and will get disposed at the end of the testing according to hospital procedures. This data will not be collected on the eCRFs.

5.2. Study Visit Schedule

All scheduled exams listed in Table 1 must be performed at the designated time point and the results documented. The following table details the clinical and laboratory procedures required from Screening through the 30-day (± 7 days) follow-up visit. Most of these tests and procedures are considered standard of care for all subjects under treatment of clinically significant PE.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Table 1. Lists the data to be captured at the various time points in the trial.

Assessment/Method	Screening	Procedure			48 ± 8 Hours (or discharge if earlier)	Follow-Up 30 ± 7 days ^h
		Pre-Procedure	Index Procedure	Post-Procedure		
ICF & Demographics	X					
Medical History	X					
Vital Signs ^a	X	X		X	X	X
DVT Assessment ^b	X					
6 MWT					X	X
Echocardiogram ^c	X				X	X
Lab Tests ^d	X				X	
CTA ^e	X				X	
Concomitant Medications ^f	X	X	X	X	X	X
Pregnancy Test	X					
Pulmonary Artery Pressure		X		X		
Index Procedure ^g			X			
PEmb-QOL	X					X
Adverse Events			X	X	X	X
PE Recurrence					X	X

- Vital signs include Blood pressure, Heart Rate, Respiratory Rate, and Oxygen Saturation.
- Sites should be encouraged to scan for residual lower extremity DVT prior to treatment at screening.
- Echocardiogram results should be collected only if performed as standard of care, and should include: right ventricular dilation, right ventricular hypokinesis, septal flattening, right ventricular systolic pressure, TAPSE score, clot visualized in heart, and left ventricular ejection fraction
- Lab Tests include: FiO₂, Hematocrit (within 6 hours of the procedure), Hemoglobin (within 6 hours of the procedure), Serum Creatinine, INR, D-dimer, Troponin, N-terminal pro BNP and Lactate. Repeat Hematocrit and Hemoglobin pre-procedure if Screening occurred > 6 hours prior to the pre-procedure timepoint.
- CTA assessment includes Refined Miller Score (calculated by core lab), RV/LV ratio, clot location, and Evidence of reflux into the IVC
- Concomitant medications include anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study
- Index procedure includes Blood loss estimation, # of times clot canister cleaned, # of times the investigational device was removed from the body during the procedure, Adjunctive Thrombectomy Devices (include catheter-directed thrombolysis), Clot location and treatment, Total clot volume removed, Total Procedure time, Total time aspiration catheter in the body, Total contrast and Fluoroscopy used
- If Subject refuses or is unable to complete the 30-day follow-up visit in person, all attempts should be made to capture any data possible remotely

5.3. Termination of Subject Participation

All subjects have the right to terminate their participation at any point during the study. In addition, Principal Investigators also can terminate subject participation in the study. Reasons for termination include completion of study, subject withdrawal, physician-directed subject withdrawal, lost-to-follow-up, and death. A description of the reason for their termination will be documented in the subject's medical file and on the appropriate eCRF.

5.4. Lost to Follow-up

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the Principal Investigator must be sent to the subject's last known address. Both telephone and letter contact efforts to obtain follow-up must be documented in both the subject's medical records and on the eCRFs.

5.5. Subject Withdrawal

All study subjects have the right to withdraw their consent at any time during the study. Whenever possible, the site staff should obtain written documentation from the subject that wishes to withdraw his/her consent for future follow-up visits and contact. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the subject and clear documentation of the subject's withdrawal will be in the subject's source documents.

Withdrawal of a subject from the study can occur at the direction of the Principal Investigator or the Sponsor. Reasons for physician-directed subject withdrawal include but are not exclusive to the subject being enrolled in another study that conflicts with the evaluation of the primary endpoints, or if the physician deems it in the best interest for the safety or welfare of the subject.

6. ADVERSE EVENTS

6.1. Adverse Event

Any undesirable clinical event occurring in a subject during a clinical trial, whether or not it is considered related to the investigational product (device). This includes a change in a subject's condition or laboratory results that has or could have a deleterious effect on the subject's health or well-being.

For purposes of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions do not need to be reported as an AE or Serious Adverse Event (SAE) unless there is an increase in severity or frequency during the study. If an intervention is planned prior to enrollment and it has been documented in the medical chart, then this will not be reported as an AE or SAE.

6.2. Serious Adverse Event

An adverse event is serious if the subject outcome was:

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

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

drug dependence or drug abuse would also be examples of important medical events.

6.3. Device Deficiency / Device Returns

A device deficiency means the failure of a device to meet its performance specifications or otherwise perform as intended during the study procedure. Performance specifications include all claims made in the labeling for the device. All device deficiencies must be reported to the Sponsor via the eCRF.

If a device deficiency results in an AE for the subject, then the AE must be reported on the AE eCRF. Device deficiencies that do not result in an adverse event for the subject do not need to be recorded as an AE, as they are not considered an AE.

In the event the device is suspected of a deficiency, every effort should be made to return the device to Inquis Medical.

6.4. Adverse Device Effect (ADE)

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or any malfunction of the device. This definition includes any event resulting from use error or from intentional misuse of the investigational device.

A serious adverse device effect (SADE) is an ADE that that resulted in any of the consequences characteristic of a SAE.

An unanticipated serious adverse device effect (USADE) is a SADE which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, investigator brochure, or Investigational IFU.

Unanticipated adverse device effect also includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.5. Assessment of Adverse Events

Safety will be assessed by collecting AE data on each subject and will be captured on the eCRFs. AE reporting begins with the start of the Inquis Medical procedure (venous puncture) and continues through 30-day (± 7 days) follow-up or study exit.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

All AEs must be recorded on the eCRFs and must be carefully monitored during the entire study. At each evaluation, the Investigator or designee will determine whether any AEs have occurred. In addition, subjects should be instructed to contact the Investigator, and/or study coordinator if any significant AEs occur between study evaluation visits.

AEs should be followed up to resolution or stabilization. AEs that are present at the end of a subject's participation in the study should be marked as unresolved at time of study exit on the eCRF and the subject should receive post-treatment follow-up as appropriate and standard of care at the institution.

The following information should be obtained for each AE:

- A description of the event including diagnosis based on signs, symptoms, and other supporting data
- Date of onset
- Date of Site awareness
- Action taken including treatment
- Outcome including date of resolution
- Severity (see Table 2)
- Seriousness
- Expectedness (see Table 3)
- Relationship to the device or procedure (see Table 4 and 5)

Additional documentation may be requested by the Sponsor or designee including an event narrative detailing the clinical course of the event, correspondence with the Institutional Review Board (IRB), and hospital records.

The Investigator will report any serious adverse event or adverse device effect to the Sponsor as soon as possible from awareness of the event. All serious adverse events or serious device effects must be entered into the database on the Adverse Events form along with an explanation of any medical treatment administered.

In case of subject death, additional information should be collected if allowed by local law including date of death, cause of death, death certificate, and autopsy report. If a subject death occurs at a remote center, it is the site's responsibility to request information about the death from the remote center.

The IRB must be informed by the Investigator about serious adverse events or device effects associated with the use of the product, as requested by their local guidelines.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Table 2. Adverse Event Severity Definitions

Mild	Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae
Moderate	Interferes with the subject's usual activity and/or requires symptomatic treatment
Severe	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment

Table 3. Adverse Event Expectedness Definitions

Unanticipated	Nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, instructions for use, or Investigator Brochure.
Anticipated	Event is known to be associated with the intervention or condition under study. Anticipated AEs include but are not limited to those listed in section 6.7

Table 4. Adverse Event Relationship to Study Device

Unrelated	The event is definitely not associated with device application. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Possible	The temporal sequence between device application and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant, or the event abates upon device application completion/removal or the event cannot be reasonably explained by the subject's condition.
Definite	The temporal sequence is relevant, and the event abates upon device application completion/removal.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Table 5. Adverse Event Relationship to Study Procedure

Unrelated	The event is definitely not associated with the study procedure. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Possible	The temporal sequence between the study procedure and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant, or the event abates upon study procedure completion or the event cannot be reasonably explained by the subject's condition.
Definite	The temporal sequence is relevant, and the event abates upon study procedure completion.

6.6. Reporting Requirements

The investigator is responsible for reporting AEs according to the timelines in Table 6 and in accordance with local/regional laws and regulations. AEs are reported to the Sponsor using an Adverse Event CRF.

Table 6. Adverse Event Reporting Timelines

Type of Event	Reporting Requirements
- SAE - SADE - Device Deficiency that could have led to a SADE	Report to the Sponsor immediately upon awareness and no later than 72 hours after site awareness of the event. New or supporting information must be provided to the Sponsor in a timely manner as it becomes available. Submit to IRB and regulatory authority according to local reporting requirements.
- UADE - USADE	Report to the Sponsor immediately upon awareness and no later than 72 hours after site awareness of the event. UADEs must be



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Type of Event	Reporting Requirements
	reported to the IRB as soon as possible but in no event later than 10 working days after the investigator first learns of the effect. Submit to IRB and regulatory authority according to local reporting requirements
• Other Reportable AEs	Report to the Sponsor in a timely manner, no later than 14 days after site awareness of the event.

6.7. Risk/Benefit Assessment

6.7.1 Risks

The risks of intra-arterial thrombectomy/embolectomy are similar to those associated with existing intra-arterial methods of recanalization. These risks include:

Access site hematoma	Myocardial infarction
Adverse reaction to contrast, thrombolytics, or anticoagulants	Nausea / vomiting
Angina	Neurological deficit
Arteriovenous fistula	Organ impairment
Bradycardia	Perforation of pulmonary arteries
Cardiac arrhythmias	Pericardial effusion
Cardiac tamponade	Peripheral nerve damage
Cardiac perforation	Pneumothorax
Cardiogenic shock	Pseudoaneurysm
Death	Pulmonary infarction
Embolism	Renal failure

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Fever	Respiratory failure
Foreign body embolism	Retroperitoneal hemorrhage
Fistulation	Right bundle branch block
General discomfort, tenderness or pain	Stroke / transient ischemic attack
Hemoglobinuria	Tachycardia
Hemoptysis	Valvular disruption / injury
Hypotension or hypertension	Vascular spasm
Hypoxemia	Vasovagal reaction
Infection	Ventricular rupture
Inflammatory response	Vessel dissection / perforation
Major blood loss	Vessel stenosis
Pulmonary edema	

6.7.2 Risk Mitigation

Awareness of the potential for serious complications is essential to the safe use of the Aventus Thrombectomy System™. Additional risk mitigations include:

- Use of study sites that have sufficient expertise and resources to manage adverse events and provide appropriate additional therapies if needed
- Specialized/Experienced Investigators with appropriate training
- Careful subject selection based on study inclusion/exclusion criteria
- Informed consent process
- Timely reporting of adverse events
- Independent Clinical Events Committee/ Data and Safety Monitoring Board

6.7.3 Benefits

There are no guaranteed benefits from participation in this study. In general, endovascular interventions (e.g., catheterization) are well-established in medical

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

practice and are substantiated to minimize the risks to subjects of: anesthesia complications, wound healing, bleeding, and infection.

The tissue and other bodily trauma associated with open surgical procedures are much greater compared to minimally invasive techniques. As more tissue is exposed to air in an open surgical procedure, the risk of infection is greatly increased. As such, the medical option of an open surgical procedure is far inferior to the safer, less traumatic, endovascular procedure. The reduced tissue trauma may benefit the Subject by reducing pain as well as faster recovery time. By minimizing tissue manipulation, the Aventus Thrombectomy System™ may also benefit medical practice by reducing the operative time offering potential cost savings. Systemic administration of thrombolytic agents carries significant risk of bleeding, especially when predisposing conditions or comorbidities exist. The Aventus™ system has an immediate impact on the vascular obstruction. The Aventus™ system is not reliant on the use of thrombolytics and therefore the AVENTUS study does not exclude subjects with recent surgeries nor those at a high risk of catastrophic bleeding. Information gained from the conduct of this Study may be of benefit to other people with the same medical condition.

7. STATISTICAL CONSIDERATIONS

7.1. Accrual and Follow-up

The trial is anticipated to last two years, and each subject will be in the trial for approximately 30 days.

7.2. Primary Efficacy Endpoint

The primary efficacy endpoint is core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (±8 hours) post-procedure as measured by CTA.

That is:

Change from Baseline in RV/LV Ratio = Baseline RV/LV Ratio - 48-hour Post-Treatment Visit RV/LV Ratio such that a positive value indicates a decrease in the RV/LV Ratio, while a negative value indicates an increase.

The paired t-test will be used to compare the average Change from Baseline in RV/LV Ratio 48 hours (±8 hours) after treatment to a minimum efficacy threshold value of 0.20.

7.3. Primary Safety Endpoint

Composite of all MAEs within 48 hours (±8 hours) of the index procedure, as adjudicated by the CEC, including device related:

- Death

- Major bleed
- Clinical deterioration
- Pulmonary vascular injury
- Cardiac injury

The one-sample exact binomial test will be used to compare the percent of subjects with a composite MAE within 48 hours (± 8 hours) after treatment to a maximum safety threshold value of 0.25.

7.4. Interim Analysis

No interim analysis is planned for this study.

7.5. Study Success

The study is considered a success when the test for the primary efficacy endpoint and the test for the primary safety endpoint are both statistically significant.

No formal hypothesis tests are planned for observational endpoints.

7.6. Analysis of Adverse Events

Adverse events will be categorized as serious and non-serious, device-related and non-device-related, and anticipated and unanticipated. All AEs will be followed through to study exit. The subject will be referred to his or her primary care physician for any ongoing medical issues or AEs continuing beyond study exit.

Adverse events judged as probably or definitely related to the Aventus Thrombectomy System™ will be analyzed as device related. Adverse events judged as probably or definitely related to the procedure will be analyzed as procedure related.

The frequency of each event will be summarized by seriousness, severity, and relationship to the device. Since some subjects may report the same event several times (e.g., headache), the first occurrence of the worst reported case of the event will be used for the purpose of these analyses.

7.7. Analysis Populations

The following analysis populations will be used:

Safety/Intention-to-Treat (ITT) analysis population: All subjects in whom the Aventus Thrombectomy System™ has been introduced into their body. The data from this population would be analyzed even if the subject did not follow the protocol until completion. Analyses for all safety related endpoints will be performed using the Safety/ITT Cohort.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Modified ITT analysis population: A subset of the ITT analysis sample which excludes subjects that received adjunctive treatments for the purpose of reducing clot burden in the pulmonary arteries (intra-procedure and up to 48 hours (± 8 hours) post procedure) or had received any thrombolytics during the procedure and up to 48-hours (± 8 hours) post-procedure. This population will be the primary population for all efficacy related endpoints.

Thrombolytic & Treatment population: A subset of the ITT analysis sample which includes subjects that received adjunctive treatments and/or thrombolytics during the procedure and up to 48-hours (± 8 hours) post-procedure. Subjects in this Cohort will be analyzed separately from the primary efficacy cohort with descriptive statistics.

7.8. Roll-In population

To ensure that investigators have adequate training with the investigational device, sites will be permitted to use the investigational device in up to two (2) Roll-In subjects per site. Subjects in the Roll-In Cohort will be analyzed separately from the safety and efficacy cohorts.

7.9. Statistical Analyses

All subjects' data will be summarized by follow-up visit, where applicable. Change and percentage change from baseline to post-procedure follow-up timepoints will be calculated. Mean, median, standard deviation, minimum and maximum will generally be reported for continuous variables. Frequencies and proportions will be reported for categorical variables.

Within-subject changes in a continuous endpoint (Change-from-Baseline) will be analyzed parametrically using the Paired t-test if the differences are normally distributed, or non-parametrically using the Signed-Rank Test if the differences are not normally distributed. Normality will be assessed with a Shapiro-Wilk test; a p-value of <0.05 for this test will be taken as evidence of non-normality.

Exact binomial confidence intervals, 95% Newcombe Corrected Confidence Interval, will be generated for estimates of proportions. Asymptotic confidence intervals based on the t-distribution will be generated for estimates of means. Except where otherwise noted, the p-values of all tests will be reported without any correction for the multiplicity of tests performed.

The SAS version 9.4 or higher will be used to perform all analyses.

7.10. Handling of Missing Data

Every attempt will be made to prevent missing data. However, if missing data occurs, multiple imputation methods will be used in the analysis of the primary endpoints. This will be done separately for the primary efficacy and primary safety endpoints based on a fully

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

conditional specification regression approach. A total of 100 imputed data sets will be generated and combined for inference (via SAS PROC MIANZLYZE), based on the following covariates for the imputation model:

- Gender
- Age (< 65 versus ≥ 65)
- Race
- Ethnicity
- Baseline RV/LV Ratio
- Baseline N-terminal pro BNP
- Baseline sPESI score (calculated from baseline vital signs and medical history)
- Baseline PAP
- Baseline Refined Miller Score
- Subjects Receiving Thrombolytic Agents

A tipping point sensitivity analysis will be used to assess the effect of missing data on the primary endpoints and further detailed in the Statistical Analysis Plan (SAP).

All other endpoints will be analyzed “as-is” without any special data imputation methods used to replace missing data.

7.11. Poolability

Data will be pooled from multiple study sites for this analysis. The justification for pooling is made on a clinical basis²⁸. The basis for pooling comes from three critical factors: the study sites must implement one common protocol; the Sponsor must provide monitoring of study site compliance; the study sites must use common data collection procedures.

A test for site effect will be based on a regression approach for each of the primary endpoints. A p-value of 0.15 will be taken as potential evidence of site heterogeneity for an endpoint and exploratory analyses would then be performed to examine and quantify such heterogeneity.

Poolability across study sites will be assessed by presenting results across study centers. Differences in results between sites, if deemed to be only quantitative in nature as opposed to qualitative (i.e., if only due to a difference in magnitude of treatment effect across sites as opposed to a difference in direction of treatment effect across sites), will not necessarily disqualify study sites from being pooled. Site differences of a quantitative nature, (i.e., all sites show the treatment to be beneficial, but perhaps to a different degree by study site) will not be an impediment to pooling. Site differences of a qualitative nature (i.e., most sites show the treatment to be beneficial, but one or more sites show the treatment to be detrimental), will require extensive evaluation of the sites with contrary results to attempt to determine what factors at those sites led to the result.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

7.12. Subgroup Analyses

Analyses of all endpoints may be repeated for the following subgroups:

- Gender
- Age (< 65 versus ≥ 65)
- Race
- Ethnicity
- Baseline RV/LV Ratio
- Baseline N-terminal pro BNP
- Baseline sPESI score
- Baseline PAP
- Baseline Refined Miller Score
- Subjects Receiving Thrombolytic agents

These analyses are exploratory in nature, and the results may be used when generating hypotheses for future studies. Summary statistics will be generated for each of the subgroups without any hypothesis tests being performed. Confidence intervals may be generated to aid in the interpretation of the results.

7.13. Sample Size Justification

Sample size calculations were done using PASS 2019.

Primary Efficacy Endpoint

A performance goal of 0.20 has been chosen, consistent with the EXTRACT-PE study (PG=0.20, Penumbra Indigo Aspiration System²⁷) and exceeding the performance goal for the FLARE study (0.12, Inari FlowTrieve²⁶). Based on publications of mechanical and vacuum thrombectomy devices of similar design^{26,27}, it is estimated that the Aventus Thrombectomy System™ will demonstrate an RV/LV change of at least 0.30 with a standard deviation no greater than 0.35.

Statistical Hypothesis:

$$H_0: \mu_{\text{Inquis}} \leq \mu_{\text{Minimum}} \text{ versus } H_1: \mu_{\text{Inquis}} > \mu_{\text{Minimum}}$$

where μ_{Inquis} is the average Change from Baseline in the RV/LV Ratio 48 hours after treatment, and μ_{Minimum} is the minimum efficacy threshold for the average Change from Baseline in the RV/LV Ratio 48 hours after treatment.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Statistical Methodology: paired t-test

μ_{Inquis} : 0.30
 μ_{Minimum} : 0.20
Standard Deviation: 0.35
Significance Level: One-sided 2.5%
Statistical Power: 0.80
Minimum Sample Size: 99 subjects

Primary Safety Endpoint

The Performance Goal for the statistical testing of the primary safety endpoint is an MAE rate of 25%. This Performance Goal is consistent with, or more stringent than, other similar catheter-based PE devices such as the Inari FlowTrievers (25%)²⁶ or the Penumbras Indigo aspiration system (40%)²⁷. Based on publications of mechanical and vacuum thrombectomy devices of similar design^{26,27}, it is estimated that the Aventus Thrombectomy System™ will demonstrate an MAE rate of 13.8% or less.

Statistical Hypothesis: $H_0: \pi_{\text{Inquis}} \geq \pi_{\text{Maximum}}$ versus $H_1: \pi_{\text{Inquis}} < \pi_{\text{Maximum}}$

where π_{Inquis} is the percent of treated subjects with a composite MAE within 48 hours (± 8 hours) after treatment, and π_{Maximum} is the maximum safety threshold for the percent of treated subjects with a composite MAE within 48 hours (± 8 hours) after treatment

Statistical Methodology: one-sample exact binomial test

π_{Inquis} : 0.1348
 π_{Maximum} : 0.25
Significance Level: One-sided 2.5%
Statistical Power: 0.80
Minimum Sample Size: 108 subjects

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

7.14. Overall Study Sample Size

The statistical tests for both endpoints need to be statistically significant for the study to be considered success.

Assuming roughly a 10% attrition rate, including patients that were lost to follow-up, withdrawn, received thrombolytic agents within 48 hours (± 8 hours) of the procedure, or if a primary endpoint assessment is missing, i.e., CTA at 48 hours (± 8 hours) post procedure, up to 120 subjects will be enrolled to ensure at least 108 subjects are evaluable for the primary safety and efficacy endpoints.

8. DATA MANAGEMENT and SECURITY

All study data will be entered into an electronic data capture (EDC) system provided by a vendor. Standardized eCRFs will be provided for use at all investigational sites. The subjects will be identified in the eCRFs with a unique subject identifier. Study personnel will have individual login and password to access the clinical study information based upon each individual's roles and responsibilities. The application provides hierarchical user permission data entry, viewing, and reporting options. All data entry and data update information, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system. This application is designed to support compliance with the appropriate regulations and guidance for industry.

Data entry will be performed at the investigational sites. Investigators are responsible for completion and timely submission of the data. Every reasonable effort should be made to complete data entry within (seven) 7 days of data collection. The EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Inquis Medical clinical personnel access project information and study data centrally via a Web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of entered data and data listings by qualified data managers will be used to identify data discrepancies or inconsistencies. The study site will be queried for clarification concerning eCRF discrepancies or inconsistencies identified. If eCRF corrections are necessary, they will be made by the Investigator or an authorized member of the Investigator's staff that is delegated to CRF/EDC Data Entry.

Questions or problems with submitted data will be addressed to the Principal Investigator and/or study staff under his/her direction via an electronic querying system, or through direct contact. The Investigator will review the eCRFs for completeness and accuracy and provide his/her electronic signature and date to eCRFs as evidence thereof. Any data items that have been changed will require reapplication of the electronic signature.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

All hard copy forms and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, subject report forms, supporting medical records, study worksheet, and informed consent forms. The source documents will be used during the regular monitoring visits to verify information submitted on the eCRFs.

For each enrolled subject, CTA images will be appropriately de-identified, and submitted to the Core Lab for evaluation. The Core Lab and CEC reviews will also be entered into the EDC system. Queries may be issued to the Core Lab or CEC for clarification concerning possible EDC discrepancies or inconsistencies. If angiographic images are collected, they will be appropriately de-identified, and submitted to the Sponsor for training and educational purposes.

9. SUBJECT CONSIDERATIONS

9.1. Ethics Review

This investigation will be conducted in compliance with this clinical investigation plan, the signed clinical study agreement, the ethical principles stated in the latest version of the Declaration of Helsinki, 21 CFR Parts 11, 50, 54, 56, and 812, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and applicable local regulations in order to provide the greatest protection for the subject. Any deviations from this investigation plan that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the IRB per each site's guidelines. Additional requirements imposed by the local IRB or regulatory authority will be followed where appropriate.

Investigator will submit this protocol, site-specific informed consent form, and other requested documents for review and approval to a properly constituted independent IRB responsible for oversight of the research conducted at the study site.

After initial review and approval, the responsible local IRBs will review the protocol at least annually and prior to study termination or completion. Annual progress reports accompanying the protocol provided for each IRB's annual review will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes to research activity, and all unanticipated problems involving risks to subjects or others.

All protocol amendments must be submitted to and approved by the relevant IRBs prior to implementing the amendment.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

9.2. Informed Consent

The nature of the planned treatment and objectives of the Inquis study will be thoroughly explained to the subject, or the subject's legally authorized representative. Details of the Study should include, but are not limited to, the following items:

- Purpose of the study
- Alternative treatments
- Potential risks/benefits for participation
- Participation is voluntary and there is no penalty for withdrawal
- Need to return to clinic for follow-up visit
- Contact information to ask questions or voice concerns

It is the responsibility of the Investigator to give each subject full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent and authorization for use of the subject's protected health information from all subjects prior to enrollment in the study. Such informed consent and authorization will be obtained in accordance with US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25(a,b), CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), and local regulations. In the event a subject is unable to sign the IRB approved informed consent form, a legally authorized representative (LAR) can sign on behalf of the subject. The original, signed consent and authorization are retained at the site with the site's subject study records, and a copy is provided to the subject.

9.3. Clinical Trial Termination

Inquis Medical may decide to interrupt or terminate this clinical study if they believe that this is necessary. Regulators will be informed of the study completion.

9.4. Subject Data Protection

Information about subjects will be kept confidential and managed according to the requirements of HIPAA. The subjects will be identified in the CRFs with a subject number. All subject study records will be kept securely at the site to prevent unauthorized disclosure of subject information.

The subject must be informed that the data will be stored and analyzed by computer, that local and national regulations for handling of computerized data will be followed, and that only the Investigator and the Sponsor or designee will have access to individual subject data. Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the hospital records by the Sponsor or appropriate regulatory agency.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Activation

All Investigators must complete the site qualification process and participate in a site initiation visit. A fully executed Clinical Trial Agreement is required to be in place before a site can be activated to participate in the study.

In addition, the following documents are required from all Investigators (including Sub-Investigators):

- Signed and dated current curriculum vitae
- Signed Investigator Agreement
- Signed Financial Disclosure
- Medical License (for Nurse Practitioners or Physician's Assistance designated as Sub-Investigators or delegated to perform medical assessments, a current license will need to be provided to the Sponsor for filing).

Pending successful submission of all required documents, Inquis Medical staff will 'activate' the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

10.2 Study Coordination

Study implementation will be directed by this protocol as well as all study related plans. The protocol team will monitor closely and communicate with the study site on a regular basis regarding: rates of accrual, adherence, follow-up and AE incidences.

10.3 Study Monitoring

On-site and/or remote monitoring will be performed in accordance with the study specific monitoring plan. The Sponsor or its representatives will visit sites to:

- Verify compliance with human subjects requirements and other research regulations and guidelines;
- Assess adherence to the study protocol;
- Confirm the quality and accuracy of information collected at the study site and entered in the study database.

Site Investigators will allow the Sponsor or its representatives to inspect study facilities and documentation (e.g., informed consent forms, clinical and laboratory records, source documents) as well as observe performance of study procedures.

Investigators also will allow inspection of all study-related documentation by authorized representatives of Inquis Medical, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval of the Sponsor.

10.5 Protocol Deviations

A protocol deviation occurs when, without significant consequence, the activities on a study diverge from the IRB-approved protocol. Any protocol-required test, assessment, or procedure that is not done or is done out of window is considered a protocol deviation. For example, a subject missing a protocol-required visit due to being away on vacation would be considered a protocol deviation. All protocol deviations must be documented in EDC and reported to the Sponsor by the PI or designee upon first knowledge of the deviation and to the IRB per IRB reporting requirements.

10.6 Study Audits

Audits of the study may be conducted by the Sponsor, regulatory agencies, or a third party designated by the Sponsor to evaluate compliance with the protocol, Investigator Agreement, and written procedures. These audits may cover all involved parties, systems, and facilities supporting the conduct of the study and are independent of, and separate from, routine monitoring functions.

In the event that an Investigator is contacted by a regulatory agency regarding this study, the Investigator will notify the Sponsor or its designee immediately. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The Investigator must provide the Sponsor or designee with copies of all correspondence that may affect review of the current study. The Sponsor may provide needed assistance in responding to regulatory audits.

10.7 Record Keeping

Records to be maintained by the investigator include:

- Clinical investigation plan and amendments
- Signed clinical study agreement
- IRB approval letters including informed consent form
- IRB membership roster



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

- Curriculum vitae for each investigator, lab director (if applicable), and all staff listed on the Delegation of Authority (DOA) log
- Investigator's medical license and medical licenses of all MDs or other individuals delegated to perform medical assessments
- Current GCP certificates for all staff listed on the DOA log
- Study logs including:
 - o Study personnel/delegation log
 - o Training log
 - o Screening log
 - o Enrollment log
 - o Site visit/monitoring log
 - o Device accountability log
- Subject records including:
 - o Informed consent
 - o eCRFs (stored electronically)
 - o Source documentation to support eCRFs
 - o Procedure reports, procedure nursing notes, and results of interventional procedures while enrolled in the study
 - o Record of any complications, AES, and device problems/malfunctions, with supporting documentation
 - o Records pertaining to subject deaths throughout the course of the study (including death records, death certificate, and autopsy report, if performed)
- Lab certification and lab test normal ranges
- Study correspondence
- Site training records
- Protocol deviations (if applicable)
- Financial disclosure forms for all Investigators



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

- Study reports including final report and periodic reports required by the IRB
- Copy of all IRB approved subject-related materials and/or study advertising materials
- Investigator Brochure, if required by local regulations
- Insurance certificate, if required by local regulations

The Sponsor reserves the right to secure additional medical documentation as needed for data clarification regarding subjects enrolled in the study.

10.8 Data Retention

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives, and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by subject identification number. Complete subject identification will be kept at the study site.

Essential records that support the data collected in the study must be retained in compliance with GCP guidelines and local regulations. All site study records will be retained at the site for at least 2 years (or longer as required by local regulations) after the records are no longer required for purposes of supporting a regulatory submission or until 2 years following the date of study closure as determined by the Sponsor. These documents may be retained for a longer period by agreement with the Sponsor or in compliance with local regulations. No records may be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to notify the investigator when records no longer need to be retained. The Investigator will take measures to ensure that these records are not accidentally damaged or destroyed.

If the investigator moves from the current investigational site, the Sponsor must be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored.

10.9 Reports

The Sponsor will prepare progress reports and a final study report in accordance with requirements established by local regulatory authorities. The sponsor will submit progress reports at least yearly to the central IRB of record and to all participating study sites for submission to their IRBs per IRB reporting requirements. The final study report will be submitted within six (6) months of closing the database at the end of the study.



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

10.10 Investigator Reports

The investigator will prepare a final report as well as periodic reports as required by the reviewing IRB. Investigators must submit progress reports to the Sponsor and the IRB no less often than yearly.

The investigator shall provide the IRB and the Sponsor with an accurate final report within 3 months after completion, termination, or discontinuation of the study or the investigator's part of the study. The final report may not precede final data submission which has not been monitored.

10.11 Imaging

Sites will be required to submit images for sponsor, CEC and Core Lab review. These images should be submitted within 7 days of procedure. Sites will be provided with instructions for how images should be collected and submitted to the sponsor. If the site is unable to provide the images within this timeframe, the appropriate Sponsor contact should be notified. Study staff shall ensure that no images contain PHI as defined by the Health Insurance Portability and Accountability Act of 1996 (Pub.L. 104–191, 110 Stat. 1936, enacted August 21, 1996).

10.12 Device Inventory Requirements

The Investigator shall maintain records pertaining to device inventory. Devices are labeled for clinical investigation and will be managed by the Sponsor as clinical study lots.

The use of each device including device lot number and the date of device use shall be captured in the corresponding subject CRFs and study documents. Each component of the product opened and/or used during the procedure will be recorded in the CRFs.

The Investigator will ensure that, for the purpose of this investigation, only trained physicians who are Sub-Investigators in this study will use the Aventus Thrombectomy System™.

10.13 Publication of Information

The study will be registered on Clinicaltrials.gov in compliance with 42 CFR Part 11.

Results of the study, including an unanticipated early termination of the trial, will be posted to the Clinicaltrials.gov database at the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis.

At the conclusion of the trial, an abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

center experience within the trial is not allowed until the aggregate study results have been published unless there is written consent from the study Sponsor.

The Investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy. All information not previously published concerning the device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Inquis Medical. The Investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

All information and data generated in association with this study will be held in strict confidence until the study is completed. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from Sponsor.

10.14 Insurance

The Sponsor will provide proof of appropriate insurance coverage for this clinical investigation as required by applicable local laws.

11. STUDY OVERSIGHT

11.1 Medical Monitor

The Sponsor will be responsible for identifying a Medical Monitor who possess the appropriate expertise and medical knowledge to provide safety oversight and guidance. The Medical Monitor responsibilities may include but not limited to:

- Review of selected safety events to determine the need for additional information and/or supporting documentation to facilitate safety review
- Provide answers to sites, IRBs, and or Sponsor to questions requiring medical expertise pertaining to this protocol
- Identify potential need for protocol amendments

11.2 Clinical Events Committee

The CEC is made up of independent physicians specialized in areas such as Interventional Radiology or Interventional Cardiology who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study, which are based on the protocol.

At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed to classify a clinical event. The CEC will review regularly and adjudicate appropriate safety events for causality and attribution.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

The CEC will have final adjudication to determine whether each safety event satisfied the definition of the primary safety endpoint for the primary safety analysis.

The CEC data superseded the investigator-reported data in all analyses of safety events.

11.3 Data Safety Monitoring Board (DSMB)

A DSMB will be comprised of 3 members not participating in the trial and will include one statistician and 2 physicians specialized in areas such as Interventional Radiology or Interventional Cardiology.

The DSMB will exercise review of the overall safety of the trial using safety data. The DSMB will make recommendations to adjustments in the study protocol, should any be considered necessary for safety or other related reasons. Additional details will be specified in the DSMB charter.

11.4 Imaging Core Laboratory

The independent imaging core laboratory will review images from baseline to 48 hours (± 8 hours) post procedure to determine the change in RV/LV ratio, the Refined Miller Score, clot location, CT Obstruction Index and Evidence of reflux into the IVC. Other data collection may be performed by the core laboratory to support safety review and/or additional analysis as required.

11.5 Investigator Responsibilities

The clinical investigators will be responsible for:

- Obtaining approval (and renewals as appropriate) from the IRB for the institution at which procedures will be performed
- Providing the Sponsor with the following prior to enrollment:
 - IRB approval letters
 - Informed consent form approved by the IRB
 - Signed clinical study agreement
 - Signed financial disclosure form
 - Curriculum vitae for each investigator
- Maintaining accurate and complete logs including study personnel/delegation and training, subject screening and enrollment, and site visit/monitoring
- Completing Sponsor-required training prior to conducting any study-related tasks and complying with the Sponsor's requirements for training of study personnel
- Supervising research personnel
- Assuring that all subjects enrolled in the study conform to the subject selection criteria

- Obtaining informed consent (including HIPAA language as appropriate) from all subjects before enrollment
- Maintaining accurate records of receipt, use, and return of investigational devices
- Performing the study procedures according to this investigation plan
- Completing eCRFs accurately, and reviewing and signing eCRFs
- Maintaining sufficient source data to support eCRFs
- Making every effort to maintain contact with all enrolled subjects
- Retaining study records as described in this protocol
- Preparing a final report and periodic reports required by the IRB

11.6 Sponsor Responsibilities

The Sponsor will be responsible for:

- Ensuring adherence to Sponsor responsibilities under 21 CFR and ISO 14155:2011.
- Preparing study documents including the clinical investigation plan, eCRFs, study logs, and a draft informed consent form
- Obtaining Investigational Device Exemption (IDE) approval from FDA and communicating with FDA
- Preparing and obtaining approval for IDE supplements as necessary
- Informing investigators of their responsibilities
- Informing investigators of any new information about the study that may affect the health, safety, or welfare of subjects or may influence their decision to participate in the study
- Site initiation assessments and approvals
- Training of investigators and site research personnel
- Providing investigational devices to the site
- Data monitoring
- Data management
- Providing resources for statistical analysis and study report writing necessary to complete reporting of study results

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

APPENDIX I: Study Abbreviations

Acronyms	Definition
ACCP	American College of Chest Physicians
ACT	Activated Clotting Time
AE	Adverse Event
AHA	American Heart Association
ASADE	Anticipated Serious Adverse Device Effect
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
BPM	Beats Per Minute
CDT	Catheter Directed Therapy
CEC	Clinical Events Committee
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECLS	Extracorporeal Life Support



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Acronyms	Definition
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESC	European Society of Cardiologists
FDA	Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practices
GI	Gastrointestinal
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIT	Heparin-induced Thrombocytopenia
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISS	Injury Severity Score
ITT	Intent to Treat



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Acronyms	Definition
IVC	Inferior Vena Cava
LAR	Legally Authorized Representative
LPM	Liters Per Minute
LV	Left Ventricle
MAE	Major Adverse Event
mmHg	Millimeters of Mercury
MRI	Magnetic Resonance Imaging
PA	Pulmonary Artery
PAP	Pulmonary Artery Pressure
PE	Pulmonary Embolism
PERT	Pulmonary Embolism Response Team
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
sPESI	Simplified Pulmonary Embolism Severity Index



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Acronyms	Definition
tPA	Tissue Plasminogen Activator
UADE	Unanticipated Adverse Device Effect
UCDT	Ultrasound-assisted Catheter-direct Thrombolysis
USADE	Unanticipated Serious Adverse Device Effect

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

APPENDIX II: Study Definitions

Term	Definition
Adjunctive Treatment	Additional treatment with devices or drugs for the purpose of reducing clot burden following initial thrombectomy and up to 48 hours (± 8 hours) post-procedure. For other procedures performed during the index procedure for purposes other than reducing clot burden, see ‘Concomitant Procedure’
Adverse Device Effect (ADE)	An adverse device effect is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or any malfunction of the device. This definition includes any event resulting from use error or from intentional misuse of the investigational device.
Adverse Event (AE)	Any undesirable clinical event occurring in a subject during a clinical trial, whether or not it is considered related to the investigational product (device). This includes a change in a subject ‘s condition or laboratory results that has or could have a deleterious effect on the subject ‘s health or well-being.
Bleeding	Defined as loss of blood from the vascular system. Bleeding was classified by the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding criteria: Major bleeding includes GUSTO Severe/life threatening and Moderate categories: GUSTO Severe: • Intracranial Hemorrhage • Fatal/life threatening bleeding • Resulting in substantial hemodynamic compromise requiring intervention GUSTO Moderate: • Requiring blood transfusion but did not result in hemodynamic compromise



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Term	Definition
	Minor bleeding includes GUSTO Mild bleeding: GUSTO Mild bleeding that does not meet above criteria
Clinical Deterioration	Also referred to hemodynamic collapse, is defined as having one of the following: - need for cardiopulmonary resuscitation, intubation, vasopressors, ECMO/ECLS; or systolic blood pressure (SBP) <90 mm Hg for at least 15 minutes, or drop of SBP by at least 40 mm Hg for at least 15 minutes with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL/h or altered mental status); or - need for catecholamine administration to maintain adequate organ perfusion and a SBP >90 mm Hg (including dopamine at the rate of >5 micrograms/kg per minute).
Cardiac Injury	The following events are examples of possible cardiac injury: - Acute heart failure - Acute myocardial infarction - Arrhythmia requiring intervention - Cardiac hematoma - Tricuspid or Pulmonic valve damage
Concomitant Procedure	Procedure(s) performed during the Index Procedure for purposes other than reducing clot burden in the pulmonary arteries. For treatment performed to reduce clot burden, see definition for 'Adjunctive Treatment'.
Device Deficiency	A device deficiency means the failure of a device to meet its performance specifications or otherwise perform as intended during the study procedure. Performance specifications include all claims made in the labeling for the device



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Term	Definition
Device-related Death	Device related death is defined as any death directly related to the device not performing as expected. Device related death would include death from: • Vascular or cardiovascular injury • Device malfunction • Device-induced cardiac arrhythmia • Worsening pulmonary or right heart function (exclusive of worsening from recurrent PE)
Index Procedure	The interventional procedure during which the study device is introduced into the body.
Intent-to-treat (ITT) subjects	Consists of all subjects in whom the Inquis Medical System has been introduced into their body.
Modified ITT analysis (mITT) population	A subset of the ITT analysis sample which includes subjects that received adjunctive treatments for the purpose of reducing clot burden in the pulmonary arteries (intra-procedure and up to 48 hours (± 8 hours) post procedure) or had received any thrombolytics during the procedure and up to 48-hours (± 8 hours) post-procedure would be excluded.
Primary Efficacy Endpoint	Core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (± 8 hours) post-procedure as measured by CTA
Primary Safety Endpoint	Composite of device related major adverse events (MAEs) within 48 hours (± 8 hours) of the index procedure, as adjudicated by the Clinical Events Committee (CEC), including: • Death • Major bleed • Clinical deterioration • Pulmonary vascular injury • Cardiac injury
Pulmonary Vascular Injury	Pulmonary vascular injury may include the following events occurring in the pulmonary vasculature:



Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™

CT-0001

Revision: D

Term	Definition
	• Arterial Venous Fistula • Dissection • Hemorrhage • Intimal flap • Perforation • Rupture • Thromboembolic occlusion resulting in permanent damage i.e., infarction
Recurrent Pulmonary Embolism (PE)	Symptomatic PE objectively confirmed on contrast-enhanced chest CT, ventilation-perfusion lung scan, or invasive contrast pulmonary angiography.
Serious Adverse Device Event (SADE)	A serious adverse device effect (SADE) is defined as an adverse device effect (ADE) that results in any of the consequences characteristics of a serious adverse event (SAE).
Serious Adverse Event (SAE)	An adverse event if the subject outcome was: • Death • Life-threatening • Hospitalization (initial or prolonged) • Disability or Permanent Discharge • Required Intervention to Prevent Permanent Impairment or Damage (Devices) • Other Serious (Important Medical Events)
Thrombolytic & Treatment population	A subset of the ITT analysis sample which includes subjects that received thrombolytics during the procedure and up to 48 hours (± 8 hours) post-procedure.
Unanticipated Adverse Device Event (UADE)	A UADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

Term	Definition
	supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

	Treatment of Acute Pulmonary Embolism with the Aventus Thrombectomy System™	
	CT-0001	Revision: D

APPENDIX III: References

1. Lehnert P, Lange T, Møller CH, Olsen PS, Carlsen J. Acute pulmonary embolism in a national Danish cohort: increasing incidence and decreasing mortality. *Thromb Haemost* 2018;118:539-46.
2. Payne JG, Tagalakakis V, Wu C, LazoLangner A. Current estimates of the incidence of acute venous thromboembolic disease in Canada: a meta-analysis. *Thromb Res* 2021;197:8-12.
3. Jiménez D, Aujesky D, Díaz G, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med* 2010;181:983- 91.
4. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol*. 2011;57(6):700-706.
5. Konstantinides S, Torbicki A, Agnelli G, et al; Authors/Task Force Members. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC), Endorsed by the European Respiratory Society (ERS). *Eur Heart J*. doi: 10.1093/eurheartj/ehu283. PubMed PMID: 25173341.
6. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012 Feb; 141(2 Suppl):e419S-94S.
7. Jaff MR, McMurtry MS, Archer SL, et al. on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011; 123:1788-1830
8. Rivera-Lebron B, McDaniel M, Ahrar K, Alrifai A, Dudzinski DM, Fanola C, Blais D, Janicke D, Melamed R, Mohrien K, Rozycki E, Ross CB, Klein AJ, Rali P, Teman NR, Yarboro L, Ichinose E, Sharma AM, Bartos JA, Elder M, Keeling B, Palevsky H, Naydenov S, Sen P, Amoroso N, Rodriguez-Lopez JM, Davis GA, Rosovsky R, Rosenfield K, Kabrhel C, Horowitz J, Giri JS, Tapon V, Channick R; PERT Consortium. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. *Clin Appl Thromb Hemost*. 2019 Jan-Dec;25:1076029619853037. doi: 10.1177/1076029619853037. PMID: 31185730; PMCID: PMC6714903.

9. Kahn SR, de Wit K. Pulmonary Embolism. *N Engl J Med*. 2022 Jul 7;387(1):45-57. doi: 10.1056/NEJMcp2116489. PMID: 35793208.
10. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest*. 2010;137(6):1382–1390.
11. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a populationbased study. *J Thromb Haemost*. 2007; 5(4):692-699.
12. Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. *Am J Cardiol*. 1998;82(8):966–970.
13. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341(8844):507–511.
14. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110(6):744–749.
15. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402–1411.
16. Wang C, Zhai Z, Yang Y, et al; China Venous Thromboembolism (VTE) study group. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary embolism: a randomized, multicenter, controlled trial. *Chest*. 2010; 137(2):254-262.
17. PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED Investigators. *Chest*. 1990; 97:528-533.
18. Sista AK. Submassive pulmonary embolism: opportunity emerging from a challenging disease. *Endovascular Today*. Jul 2015: 53-58.
19. Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. *Circulation*. 2010; 122: 1124- 1129.
20. Rehman A, Yousef S, Chugh A. Thrombolysis in submassive pulmonary embolism, prudent or puerile? *BMJ Case Reports*. 2013;2013:bcr2012007549. doi:10.1136/bcr-2012-007549
21. EkoSonic™ Endovascular System - Boston Scientific [Internet]. Available from: <https://www.bostonscientific.com/content/gwc/en-US/products/thrombectomy-systems/ekosonic-endovascular-system.html>
22. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann L V. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol*. Elsevier; 2009;20:1431–40.

23. Bashir R, Foster M, Iskander A, Darki A, Jaber W, Rali PM, Lakhter V, Gandhi R, Klein A, Bhatheja R, Ross C, Natarajan K, Nanjundappa A, Angle JF, Ouriel K, Amoroso NE, Firth BG, Comerota AJ, Piazza G, Rosenfield K, Sista AK. Pharmacomechanical Catheter-Directed Thrombolysis With the Bashir Endovascular Catheter for Acute Pulmonary Embolism: The RESCUE Study. *JACC Cardiovasc Interv.* 2022 Dec 12;15(23):2427-2436. doi: 10.1016/j.jcin.2022.09.011. Epub 2022 Sep 17. PMID: 36121244.
24. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol.* 2008 Mar;28(3):370-2. doi: 10.1161/ATVBAHA.108.162545. PMID: 18296591; PMCID: PMC2873781.
25. Chauhan CA, Scolieri SK, Toma C. Percutaneous pulmonary embolectomy using the FlowTrieve Retrieval/Aspiration System. *J Vasc Interv Radiol Elsevier Inc.*; 2017. p. 621–3.
26. Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, et al. A Prospective, Single-Arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv* [Internet]. Elsevier Inc.; 2019 [cited 2020 Sep 19];12:859–69.
27. Akhilesh K. Sista, MD,^a James M. Horowitz, MD,^a Victor F. Tapson, MD,^b et al. Indigo Aspiration System for Treatment of Pulmonary Embolism. *JACC Cardiovasc Interv.* 2021, 14:319-329.
28. Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis.* Oxford University Press, New York.