Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) $F18^{85}$ PE for Treatment of Acute Pulmonary Embolism

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SPONSOR CONTACT PERSON: LIZ MANNING, DIRECTOR, CLINICAL AFFAIRS

APPROVAL SIGNATURES

CLINICAL INVESTIGATION PLAN NUMBER: **2021-EVT-01**

CLINICAL INVESTIGATION PLAN TITLE:

Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE for Treatment of Acute Pulmonary Embolism

I, the undersigned, have read this clinical investigation plan and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Juan Carlos Serna Sr VP, Scientific and Clinical Affairs AngioDynamics, Inc. DocuSigned by: 2AED37B3A7DF46C...	Date 7/24/2023
Venkat Shankarraman Manager, Medical Science Liaison AngioDynamics, Inc. DocuSigned by: Venkat Shankarraman C3BF7F0CEC6F476...	Date 7/24/2023

SUMMARY OF CHANGES

Date	Version	Changes since last version
July 18, 2023	5.1	1. Administrative update to specify that IDE progress reports will be submitted to FDA at 6-month intervals
June 13, 2023	5.0	1. Minor formatting updates throughout 2. Updated number of sites to 30 3. Updated the 30-day follow-up visit to include the option of a virtual visit in the entire document 4. Removed references to device accountability 5. Added a Per Protocol analysis population 6. Updated Primary Efficacy Endpoint to specify that all CTA data will be read centrally by the core lab.
August 15, 2022	4.0	1. Updated version number from 3.0 to version 4.0 in the entire document 2. Included Pericardial Effusion, Cardiac arrest, Pulmonary Artery Injury/Wire Perforation, and Hemothorax as an adverse event in section 10.11 and Appendix I 3. Updated index procedure to Day 1 from Day 0 in section 8.2 (Study Visits)
February 22, 2022	3.0	1. Updated version number from 2.0 to version 3.0 in the entire document 2. Updated the definition of the 'As Treated' population to include patients in whom the device was introduced in the entire document 3. Table 5 in section 10.1 (Adverse Events) was revised to include grade 5 in the adverse event severity scale 4. Corrected cannula description to include 18F in section 5.2F.2 5. Section 10.5 now provides and option of emailing the sponsor 6. Added 'Important medical event' as one of the SAEs in section 10.1.1 7. Information on handling missing data in section 11.7 was updated to include efforts that would be made to minimize missed visits and drop-outs along with a discussion on expected percentage of missing data 8. Updated section 11.4.2 on the null hypothesis and alternative hypothesis for the primary safety endpoint, to change the directionality of the hypotheses (i.e., H_0: MAE < 0.25 changed to H_0: MAE > 0.25 and H_1: MAE ≥ 0.25 changed to H_1: MAE ≤ 0.25) 9. Added section 11.8 and section 11.9 to provide additional information on sensitivity analysis and poolability of data 10. Formatting edits were made throughout the document (font, numbering, alignment)
September 3, 2021	2.0	1. Updated version number from 1.0 to version 2.0 in the entire document 2. Updated product name from AlphaVac MMA System to AlphaVac Multipurpose Mechanical Aspiration (MMA) $F18^{85}$ PE in the entire document 3. Updated sample size of the study to enroll 122 patients in (Section 7: Study Design and Section 11: Statistical considerations) 4. Updated Section 2 to include an enrollment CAP of 24 patients per site 5. Added a secondary endpoint that will evaluate the change in modified

		miller index between baseline and 48 hours post procedure by CTA (Section 2: Protocol Summary and Section 6.4) 6. Added an Exploratory endpoint to access the health-related social needs during the patient's baseline visit (Section 2: Protocol Summary and Section 6.4 and Section 11.4.5) 7. Included section 14.8.1: Impact on Medicare Beneficiaries 8. Revised the ITT and MITT terms to "as treated" and "Modified as treated populations" for the primary analysis, respectively in the entire document 9. Updated "as treated" and "modifies as treated" definitions (Section 2: Primary Analysis Summary) and Section 11.3 (Analysis Population) 10. Minor update to Section 10.11 (Risk Benefit analysis) 11. Updated Section 11 (statistical analysis) to include the SAS code 12. Added Hemoptysis, Intrapulmonary or intrapleural hemorrhage under pulmonary vascular injury (Appendix I: Study Definitions) 13. Minor formatting edits throughout the document 14. Updated the list of abbreviations 15. Updated References

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
AHC HRSN	Accountable Health Communities Health-Related Social needs Screening Tool
BL	Baseline
BPM	Beats Per Minute
CDT	Catheter Directed Therapy
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CRF	Case Report Form
CI	Confidence Interval
CIP	Clinical Investigational Plan
CT Scan	Computed Tomography Scan
CTA	Computed Tomography Angiography

CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
d	Day
DEI	Data Element Identifier
DMC	Data Monitoring Committee
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
EA	Efficacy Analysis
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
FDA	U.S. Food and Drug Administration
FU	Follow up
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of1996
HIT	Heparin Induced thrombocytopenia
ICF	Informed Consent Form
ICH	International Committee on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
IRE	Irreversible Electroporation
ISO	International Organization for Standardization
ISS	Injury Severity Score
LOS	Length of Hospital Stay
LPM	Liters per minute
LTFU	Lost to follow up
LV	Left Ventricle
m	Month
MAE	Major Adverse Events

MMA	Manual Mechanical Aspiration
MRI	Magnetic Resonance Imaging
PAP	Pulmonary Artery Pressure
PE	Pulmonary Embolism
PI	Principal Investigator
PMT	Percutaneous Mechanical thrombectomy
PPMAE	Peri-Procedural Major Adverse Events
QC	Quality Control
RCT	Randomized Clinical Trial
RV	Right Ventricle
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDV	Source Data Verification
SIV	Site Initiation Visit
SN	Serial number
SOC	Standard of Care
SOP	Standard Operating Procedure
tPA	Tissue-plasminogen activator
w	Week
y	Year

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1 STATEMENT OF COMPLIANCE

The study will be conducted in compliance with the US FDA Title 21 CFR Part 50 – Protection of Human Patients and Part 56 – Institutional Review Boards and Part 812 – Investigational Device Exemption; the International Council for Harmonisation for Pharmaceuticals for Human Use (ICH) GCP guidelines E6R2 ; the Belmont Report; US Title 45 CFR Part 164 Subpart E – Privacy of Individually Identifiable Health Information and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule; and any applicable national guidelines.

The protocol, informed consent form(s), recruitment materials, and all participant's materials will be submitted to the Food and Drug Administration (FDA), Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before a participating site may enroll participants. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

2 PROTOCOL SUMMARY

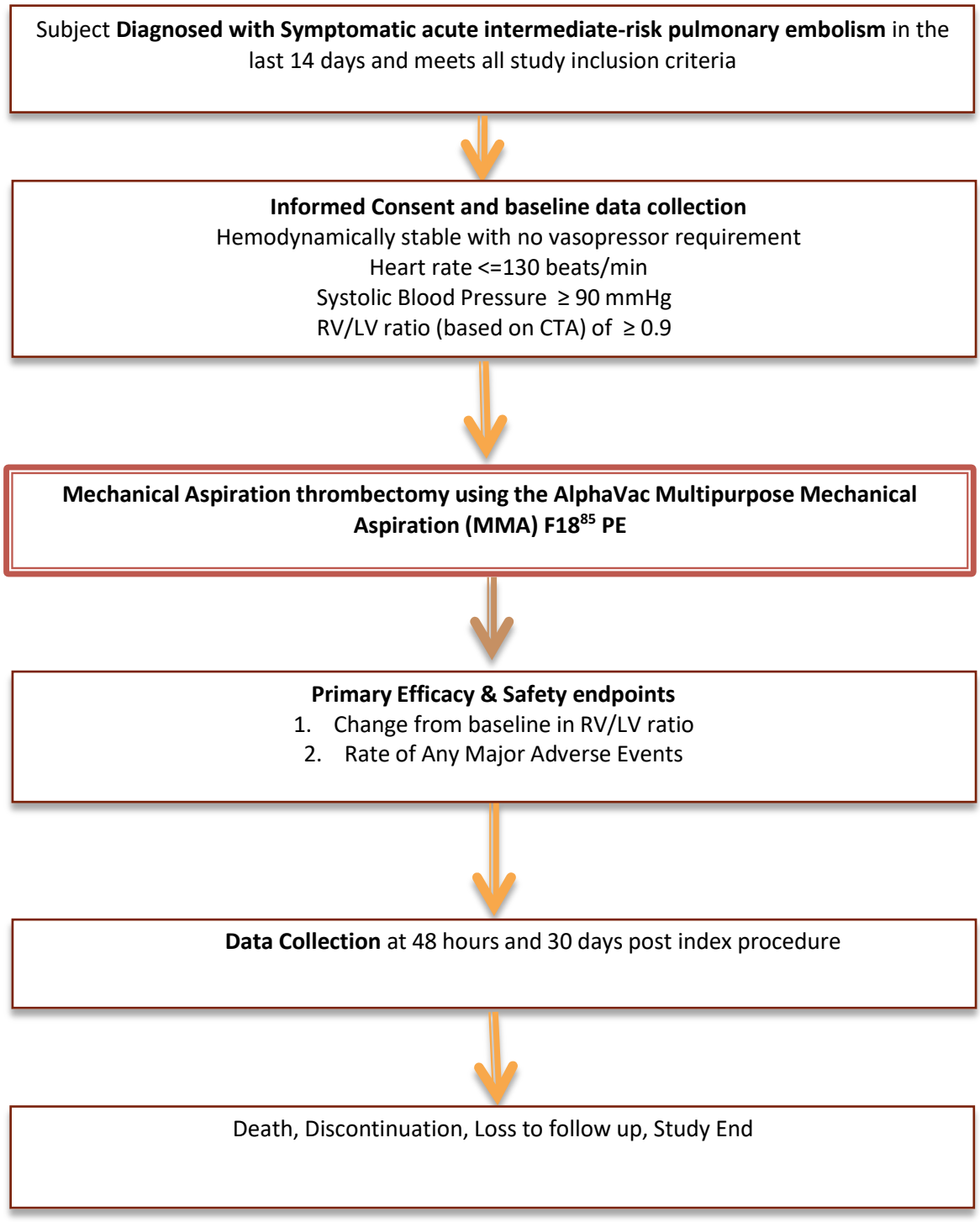
STUDY TITLE:	**Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE for Treatment of Acute Pulmonary Embolism**
DEVICE NAME:	AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE
DEVICE DESCRIPTION:	The AngioDynamics' AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE has five main components, a flexible cannula (F18^{85}), sheath, tapered obturator, aspirator handle, and waste bag. The AlphaVac MMA F18^{85} PE is a mechanical aspiration thrombectomy device with a nitinol basket reinforced, self-expandable funnel shaped distal tip, that is collapsed using an over-sheath that is advanced though a 22 Fr sheath and over a guidewire into the venous system percutaneously.
INDICATION FOR USE:	The Cannula is indicated for • The non-surgical removal of thrombi or emboli from vasculature • Aspiration of contrast media and other fluids into or from vasculature The Cannula is intended for use in the venous system and for the treatment of pulmonary embolism. The Aspirator Handle is indicated as a vacuum source for the AlphaVac MMASystem.
MANUFACTURER:	AngioDynamics, Inc.
SPONSOR:	AngioDynamics, Inc.
REGULATORY STATUS:	Proposed Investigational Device Use
STUDY PURPOSE:	To evaluate the safety and effectiveness of percutaneous mechanical aspiration thrombectomy using the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE in a prospective trial of patients with acute intermediate-risk pulmonary embolism (PE).
STUDY DESCRIPTION:	AngioDynamics' prospective, single-arm, multicenter Investigational Device Exemption (IDE) study.

ENDPOINTS:	**Primary Endpoints:** • Primary efficacy endpoint o Reduction in RV/LV ratio between baseline and 48 hours post procedure assessed by CTA. All CTA data will be read centrally by the core lab. • Primary safety endpoint o The rate of Major Adverse Events (MAEs) within the first 48 hours after the index procedure. The MAEs include: ▪ Device-related death ▪ Major bleeding ▪ Device-related SAEs which includes: • Clinical Deterioration • Pulmonary Vascular Injury • Cardiac Injury **Secondary endpoints:** • Secondary efficacy endpoints: o Use of thrombolytics within 48 hours of the procedure. o Length of stay in the Intensive care unit (ICU)/Hospital within 30 days post-procedure. o Change in Modified Miller Index between baseline and 48 hours post procedure assessed by CTA. • Secondary safety endpoints: o Rate of device related complications including clinical deterioration, cardiac injury, pulmonary vascular injury, major bleeding, and device-related death within 48 hours of the index procedure. o Rate of device-related Serious Adverse Events (SAEs) and death for any-cause within 30 days post procedure. o Symptomatic PE recurrence within 30 days. Refer Appendix I for study definitions. **EXPLORATORY ENDPOINT:** This study will collect baseline data to identify unmet social needs such as housing instability, violence, financial strain, etc. Exploratory analysis may be conducted to evaluate unmet healthcare needs with study enrollments and outcomes.
STUDY POPULATION:	Patients with acute intermediate-risk Pulmonary Embolism. <u>Inclusion Criteria</u> A potential subject will be included in the study if he/she meets all the following inclusion criteria: 1. Provision of signed and dated informed consent form. 2. Subject is 18 years of age and older. 3. Subject presents clinical signs and symptoms consistent with acute intermediate-risk pulmonary embolism for less than or equal to 14 days. 4. Subject has a diagnosis of pulmonary embolism detected from computed tomography angiography (CTA). 5. Subject has a RV/LV ratio of 0.9 or higher.

	6. Subject has a systolic blood pressure (SBP) of 90mmHg or higher 7. Subject has a heart rate of 130 beats per minute (BPM) or less prior to the procedure. 8. Subject is deemed medically eligible for interventional procedure(s) per institutional guidelines and/or clinical judgment. <u>Exclusion Criteria</u> A potential subject will be excluded from the study if he/she meets any of the following exclusion criteria: 1. Subjects who are or may be pregnant as determined by a positive pregnancy test or who are breastfeeding. 2. Subjects who have any contraindication to systemic or therapeutic doses of heparin or anticoagulants. 3. Subjects who have used thrombolytics (tPA) in the past 30 days of baseline CTA. 4. Subjects who have pulmonary hypertension with peak pulmonary artery pressure (PAP) > 70 mmHg. 5. FiO2 requirement >40% or >6 LPM to keep oxygen saturations >90% 6. Subjects with hematocrit <28% within 6 hours of index procedure. 7. Subjects with platelets count < 100,000/µL. 8. Subjects with serum creatinine >1.8 mg/dL. 9. Subjects with International Normalized Ratio (INR) > 3 10. Subjects who have undergone a major trauma within the past 14 days of the index procedure and have Injury Severity Score (ISS) > 15. 11. Subjects with the presence of cancer requiring active chemotherapy. 12. Subjects with known bleeding diathesis or coagulation disorder. 13. Subjects who have had a cardiovascular or pulmonary surgery within the past 7 daysof index procedure. 14. Subjects with a history of severe or chronic pulmonary hypertension, uncompensated heart failure, chest irradiation, underlying lung disease that is oxygen dependent, Heparin- induced thrombocytopenia (HIT) and/or chronic left heart disease with left ventricular ejection fraction ≤ 30%. 15. Subjects with known anaphylactic reaction to radiographic contrast agents that cannot be pretreated. 16. Subject requires Vasopressor after fluids to keep pressure ≥ 90mmHg. 17. Subjects with left bundle branch block. 18. Subjects who have intracardiac lead in the right ventricle or atrium. 19. Evidence such as imaging or other that suggest the subject is not appropriate for this procedure. 20. Subjects that have life expectancy < 90 days. 21. Subjects dependent on extracorporeal life support such as extracorporealmembrane oxygenation (ECMO). 22. Participation in another investigational study
STUDY CENTERS & LOCATION:	The clinical study is to be conducted at up to 30 investigative sites in the United States. The investigative sites will consist of hospitals. To reduce bias by sites, each site may enroll up to 24 eligible subjects who have successfully completed their index procedure with the AlphaVac MMA $F18^{85}$ PE.

DESCRIPTION OF STUDY INTERVENTION:	The AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE has five main components, a flexible cannula (F18^{85}), sheath, tapered obturator, aspirator, and waste bag. The AlphaVac MMA F18^{85} PE is a mechanical aspiration thrombectomydevice with a nitinol basket reinforced, self-expandable funnel shaped distal tip, that is collapsed using an over-sheath that is advanced though a 22 Fr sheath and over a guidewire into the venous system percutaneously. During use the cannula is placed within the jugular or one of the common femoral veins and connected to the aspirator handle. Once access is gained, the cannula is advanced under image guidance towards the undesirable intravascular (i.e., thrombus or emboli) until it is engaged, the aspirator is then pulled back creating suction pulling the material into the cannula, removing it from the vasculature. The aspirated material is then moved from the aspiration handle into the waste bag for disposal.
STUDY DURATION:	Individual study participation: Subjects will be followed for 30 days post index procedure. Overall study duration: Accrual is estimated to require 18 months to complete, and the study will be complete 30 days after the enrollment of the last subject.
SAMPLE SIZE STATISTICS:	For the purposes of assessing safety and effectiveness, a minimum of 122 subjects will be enrolled in the clinical study. This accounts for a 15% possible drop-out rate for subjects who will be lost to follow-up.
PRIMARY ANALYSIS SUMMARY:	Analysis Cohorts: • As Treated population: This population includes all subjects who met the inclusion/exclusion criteria and in whom the F18^{85} cannula is placed within the jugular or one of the common femoral veins. • Modified As Treated population: This population includes all subjects in the As Treated population who did not receive thrombolytics during the index procedure. • Per Protocol population: This population includes all subjects in the Modified As Treated population who had no major protocol deviations. Analysis of all efficacy endpoints will be performed on the As Treated, Modified As Treated, and Per Protocol populations, with the Modified Ts Treated population serving as the primary analysis cohort. Analysis of all safety endpoints will be performed on the As Treated population.
CORE LABORATORY:	An independent Core Lab will review imaging scans in analysis of RV/LV diameter.

3 STUDY SCHEMA



4 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Events for Screening, Baseline and Early Follow-up Visits

Study assessment	**Screening**	**Baseline/Procedure [a] (At 0 hours)**	**48 -hours (±6 Hour) Post-procedure**	**Hospital Discharge**	**30- days (± 7 days)[b] Post-procedure**
Medical history and Demographics	X				
ACH- HRSN Screening Tool [f]		X			
Vital Signs	X	X	X	X	X[g]
Hematocrit/FiO_2/ Creatinine/ Platelets/ INR/ Troponin	X		X		
CTA (RV/LV Ratio)	X		X		
Pulmonary Artery Pressure (mmHg)		X[d]			
Concomitant Medications [e]	X	X	X	X	X
Time of Procedure		X			
Major/ Minor Bleeding		X	X	X	
Pregnancy Test [c]	X				
Hospital Stay				X	
Adverse Events		X	X	X	X
Symptomatic PE Recurrence					X

a) Procedure is defined as day zero
b) 30 day follow up begins from procedure. This visit can optionally be completed virtually. However, if during the virtual visit, the site determines the patient should be seen in person, the subject will be asked to come in for evaluation.
c) Pregnancy test can be from urine or blood test
d) Pulmonary pressures will be obtained pre- and post-procedure
e) Concomitant medications include anticoagulants, vasopressors, thrombolytics used, and all other medications given for AEs and SAEs during the study
f) The Accountable Health Communities (ACH) Health-Related Social Needs (HRSN) Screening Tool[1]
g) Vital Signs will be obtained if the patient completes the 30-day follow up visit in person or if deemed necessary after the virtual visit.

5 INTRODUCTION TO THE CLINICAL STUDY

5.1 BACKGROUND

Pulmonary Embolism (PE) represents the third leading cause of cardiovascular mortality.[2] PE is thrombus that traveled and became lodged within the pulmonary arteries. Pulmonary emboli usually arise from thrombi that originate in the deep venous system of the lower extremities; however, they also originate in the pelvic, renal, upper extremity veins, or the right heart chambers, though rarely. PE is commonly broken into three main categories: massive or high risk, submassive or intermediate risk, and low risk. The focus of this study is submassive or intermediate risk PE. Patients with intermediate risk PE typically have RV strain (RV/LV ratio ≥0.9) without hypertension, confirmed via imaging (computed tomography pulmonary angiography) and increased cardiac biomarkers (i.e., troponins or brain natriuretic hormone).[2] Patients with submassive or intermediate-risk PE account for 35% to 55% of hospitalized patients with PE with a mortality rate of 5-24%.[2,4] For such patients, therapies aim to avert possible hemodynamic collapse and death resulting from progressive right-sided heart failure and to expedite symptom resolution.[2]

The current standard of care treatment PE is therapeutic anticoagulation. Specific to patients with intermediate-risk PE the American Heart Association (AHA) discourages the routine administration of thrombolytic therapy (either systemic or catheter directed) and recommends that patients should be promptly anticoagulated, receive supportive measures and be closely monitored.[2] However, adverse outcomes, despite anticoagulation, in patients with intermediate-risk PE has prompted physicians to consider therapeutic escalation through systemic thrombolysis, catheter-directed therapies, or surgical embolectomy.[2]

AHA states that catheter-based embolectomy is an option for patients that remain hemodynamically stable and have had an assessment completed to consider factors that elevated risk of decompensation with an elevated bleeding risk, with the caveat that concerns for procedural hemodynamic or respiratory decompensation.[2]

5.1.1 JUSTIFICATION FOR THE CLINICAL INVESTIGATION

A catheter directed therapy (CDT) that is gaining interest by physicians is percutaneous mechanical thrombectomy (PMT). PMT has been designed to clear large arteries and veins by removing the thrombus from the vasculature. Mechanical aspiration thrombectomy, a subset of PMT, utilizes a large lumen aspiration catheter that utilizes manual suction to remove the thrombus.

While there is limited data available for large-bore thrombectomy devices, instances of acute hemodynamic respiratory collapse as well as right-sided heart and PA injury have been reported.[2] However, PMT has been found to be effective and safe for debulking of centrally located fresh thrombus, lowering PAP and improving hemodynamics and blood oxygenation, all of which permits a rapid reversal of right ventricle overload with a decrease in the mortality rate, in patents contraindication or unsuccessful pharmacological fibrinolysis.[5]

While further comparative studies comparing currently recommended catheter-directed and pharmacological approached are still required, PMT appears to be promising in the treatment of acute Pulmonary Embolism (PE).[2]

At present, it is unknown if the catheter aspiration thrombectomy with AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE can safely and effectively improve patient outcomes for patients with acute PE. This prospective, multicenter analysis will provide outcomes, which will serve as preliminary data to plan to evaluate the use of AlphaVac MMA F18[85] PE in future studies.

5.2 DESCRIPTION OF THE DEVICE

5.2.1 GENERAL DEVICE DESCRIPTION

The device under clinical investigation is AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE which consist of five sterile single use main components: a flexible aspiration cannula (F18[85]), sheath, obturator, aspirator, and a waste bag. All components are packed together as sterile single use device by AngioDynamics located in Latham, NY 12110, United States (US).

The AlphaVac MMA F18[85] PE design allows for the undesirable intravascular material to compress into the cannula's inner lumen and be aspirated from the vasculature and captured in the waste bag.

5.2.2 CANNULA DESCRIPTION

The cannula large bore design (18F) and funnel shaped tip are intended to facilitate the removal of thrombus, embolus and clot during minimally invasive percutaneous procedures.

The stainless-steel wire mid-wall reinforced cannula shaft ensures appropriate stiffness to resist kinking, collapse and deformation that may compromise the lumen and inhibit flow. Additionally, it is flexible enough to allow the cannula to be manipulated through the vasculature utilizing standard percutaneous insertion techniques. The cannula is provided in an 85° angled distal end configuration with a working length of 44.4 inches and a nominal diameter of 18F.

5.2.3 SHEATH DESCRIPTION

The sheath is used place the catheter within the target location, actuate the distal cannula funnel and alter the cannula angle to improve clot engagement.

The sheath is a stainless-steel wire mid-wall reinforced sheath appropriate stiffness and flexibility so that it can be manipulated through the vasculature utilizing standard percutaneous insertion techniques without kinking, collapse and deformation that may compromise the lumen and inhibit compatibility with the catheter.

The sheath is provided in a straight configuration with a working length of 33.5 inches and a nominal diameter of 22F.

5.2.4 OBTURATOR DESCRIPTION

The obturator is used to support the sheath during insertion and re-positioning. The obturator is assembled from a Pebax female luer adaptor with a radiopaque (barium sulfate) doped Pebax shaft/Everglide extrusion that creates a low friction sliding surface during placement. The obturator is provided in a straight configuration with tapered tip at a length of 38.7 inches and a diameter of 17F.

5.2.5 ASPIRATOR HANDLE DESCRIPTION

The Aspirator Handle is a syringe-like aspiration handle intended to be used with the aspiration cannula described above. The aspirator handle utilizes a dual check valve to control flow; the upper port allows inflow, while the lower port enables outflow directed to the waste bag.

5.2.6 WASTE BAG DESCRIPTION

The waste bag for the AlphaVac MMA F18^{85} PE is 250mL and intended to capture and contain the material aspirated during a procedure for disposal. Each AlphaVac MMA F18^{85} PE is packaged with four waste bags.

5.3 MECHANISM OF ACTION FOR THE ALPHAVAC MMA F18^{85} PE

The utilization of AlphaVac MMA F18^{85} PE allows for avoidance of complex, high-risk surgical procedure by providing a percutaneous treatment option for endo-mechanical removal of emboli/thrombus.

Prior to the AlphaVac MMA F18^{85} PE procedure, the patient is prepared and draped in a typical sterile manner for percutaneous/surgical vascular procedures. Using percutaneous vascular access techniques (i.e., Seldinger techniques) and standard off-the-shelf guidewires, and introducer sheaths an appropriate venous blood vessel is accessed, by either internal jugular or one of the common femoral veins.

Once assess is gained, a guidewire is advanced into the vasculature and positioned at or just beyond the desired cannula tip location. The obturator and sheath are then placed over the guidewire and advanced under fluoroscopy into the desired position within the vasculature. Once at the target location the obturator and guidewire are removed.

The cannula is attached to the aspiration handle and waste bag, the system primed, and advanced though the sheath. As the cannula is advanced out of the sheath at the target location the nitinol basket automatically expands into a funnel shape. The self-expanding nitinolbasket reinforced funnel aids in guidance and removal of undesirable intravascular material (i.e. thrombus or emboli).

Once thromboemboli is engaged, the aspiration handle is then pulled back creating suction and pulling the material into the cannula, removing it from the vasculature. The aspirated material is captured and contained within the waste bag for disposal. At the end of the procedure the entire AlphaVac MMA F18^{85} PE System is removed from the patient.

6 CLINICAL STUDY PURPOSE AND ENDPOINT

6.1 OBJECTIVE

The objective of this clinical study is to determine the safety and effectiveness of mechanical aspiration thrombectomy using the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE in a prospective trial of patients with acute intermediate-risk pulmonary embolism (PE).

6.2 PRIMARY SAFETY AND EFFICACY

Table 2. Primary Endpoints

	Outcome
Primary Efficacy:	Reduction in the RV/LV ratio at 48 hours post-procedure assessed by CTA. The primary efficacy analysis will be the difference between the baseline and the 48-hour RV/LV diameter ratio. All CTA data will be read centrally by the core lab.
Primary Safety:	Rate of major adverse events post-procedure within 48 hours after the index procedure. MAEs include: • Device-related death • Major bleeding • Device-related SAEs, which includes:o Clinical deterioration o Pulmonary vascular injury o Cardiac injury Some examples of major bleeding, clinical deterioration, pulmonary vascular injury,and cardiac injury are defined in the study definitions of Appendix I.

6.3 SECONDARY ENDPOINTS

Table 3. Secondary Endpoints

	Outcome
Secondary Efficacy:	• Length of stay in ICU/Hospital setting within 30 days • Use of thrombolytics within 48 hours • Change in Modified Miller Index at 48 hours post-procedure assessed by CTA

Secondary Safety:	• Device-related death within 48 hours • Major bleeding within 48 hours • Clinical deterioration within 48 hours • Pulmonary vascular injury within 48 hours • Cardiac injury within 48 hours • Any-cause mortality within 30 days • Device-related SAEs within 30 days • Symptomatic PE recurrence within 30 days Refer to Appendix I for definitions.

6.4 EXPLORATORY ENDPOINT

This study will collect baseline data to identify unmet social related needs such as housing instability, violence, financial strain, etc. Exploratory analysis may be conducted to evaluate healthcare disparities, unmet healthcare needs with study enrollments and outcomes.

The accountable health communities (AHC) health- related social needs screening tool (HRSN)[1] will be completed by all enrolled patients at their baseline visit.

7 STUDY DESIGN

7.1 STUDY DESCRIPTION

This is a prospective, multicenter, single arm study. This study will include up to 122 patients at up to 30 centers in the United States. Each subject will be in the trial for approximately 30 days.

7.2 STUDY POPULATION

This study will collect data on symptomatic patients with acute intermediate-risk PE. The enrolled patients will be treated with aspiration thrombectomy by the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE.

7.2.1 INCLUSION CRITERIA

All the following criteria must be met in order to be enrolled and continue participation in the study:

1. Provision of signed and dated informed consent form.
2. Subject is 18 years of age and older.
3. Subject presents clinical signs and symptoms consistent with acute intermediate-risk pulmonary embolism for less than or equal to 14 days.
4. Subject has a diagnosis of pulmonary embolism detected from computed tomography angiography (CTA).
5. Subject has a RV/LV ratio of 0.9 or higher.
6. Subject has a systolic blood pressure (SBP) of 90mmHg or higher
7. Subject has a heart rate of 130 beats per minute (BPM) or less prior to the procedure.
8. Subject is deemed medically eligible for interventional procedure(s) per institutional guidelines and/or clinical judgement.

7.2.2 EXCLUSION CRITERIA

A potential subject will be excluded from the study if he/she meets any of the following exclusion criteria:

Exclusion Criteria

A potential subject will be excluded from the study if he/she meets any of the following exclusion criteria:

1. Subjects who are or may be pregnant as determined by a positive pregnancy test or who are breastfeeding.
2. Subjects who have any contraindication to systemic or therapeutic doses of heparin or anticoagulants.
3. Subjects who have used thrombolytics (tPA) in the past 30 days of baseline CTA.
4. Subjects who have pulmonary hypertension with peak pulmonary artery pressure (PAP) > 70 mmHg.
5. FiO2 requirement >40% or >6 LPM to keep oxygen saturations >90%
6. Subjects with hematocrit <28% within 6 hours of index procedure.
7. Subjects with platelets count < 100,000/µL.
8. Subjects with serum creatinine >1.8 mg/dL.
9. Subjects with International Normalized Ratio (INR) > 3.
10. Subjects who have undergone a major trauma within the past 14 days of the index procedure and have Injury Severity Score (ISS) > 15.
11. Subjects with the presence of cancer requiring active chemotherapy.
12. Subjects with known bleeding diathesis or coagulation disorder.
13. Subjects who have had a cardiovascular or pulmonary surgery within the past 7 days of index procedure.
14. Subjects with a history of severe or chronic pulmonary hypertension, uncompensated heart failure, chest irradiation, underlying lung disease that is oxygen dependent, Heparin- induced thrombocytopenia (HIT) and/or chronic left heart disease with left ventricular ejection fraction ≤ 30%.
15. Subjects with known anaphylactic reaction to radiographic contrast agents that cannot be pretreated.
16. Subject requires Vasopressor after fluids to keep pressure ≥ 90mmHg.
17. Subjects with left bundle branch block.
18. Subjects who have intracardiac lead in the right ventricle or atrium.
19. Evidence such as imaging or other that suggest the subject is not appropriate for this procedure.
20. Subjects that have life expectancy < 90 days.
21. Subjects dependent on extracorporeal life support such as extracorporeal membrane oxygenation (ECMO).
22. Participation in another investigational study.

7.3 STUDY ENROLLMENT

Patients presenting with signs and symptoms of acute intermediate risk PE will be screened for possible enrollment as a patient into the trial based on Inclusion/Exclusion Criteria.

7.3.1 ENROLLMENT PROCEDURE

Consecutive patients presenting with acute intermediate-risk PE will be screened for this trial. Those who do not meet the study's Inclusion/Exclusion Criteria will not be enrolled with the reason recorded.

A patient is considered enrolled once the patient informed consent form and HIPAA Authorization are signed by the patient, and in whom the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE has been introduced into their body.

Any patient enrolled into the trial, but in whom the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE is not able to access a pulmonary embolus is considered an as treated patient and will be monitored per protocol until the end of required follow-up period of 30days. Any patient that experiences an adverse event after venous puncture but in whom the Cannula is not inserted will be monitored through discharge for safety.

Refer to Warnings, Precautions, and Potential Adverse Events in the Instructions for Use prior to use.

8 STUDY PROCEDURES

8.1 STUDY PROCEDURES

All data elements for all subjects will be collected using electronic case report forms (eCRFs). Source data originally captured in electronic format may be used to populate eCRF data fields where possible to reduce unnecessary duplication of data and to reduce the possibility of transcription errors. Data will be entered into the eCRFs at screening, baseline/index procedure, at 48 - Hours, discharge, and at 30 - days post procedure or until death, and in accordance with the adverse event procedures described below. Sites will be requested to adhere to guidelines for the treatment and monitoring of these subjects. Planned Source Data Verification (SDV) will be 100% for all endpoint-related data.

8.2 STUDY VISITS

Table 4: Study Visits

Visit	Data Collection
Screening:	• Medical History • Demographics • Vital signs • Hematocrit/FiO_2/Creatinine/Platelets/INR/Troponin • CTA (RV:LV Ratio) • Concomitant Medications • Pregnancy Test • Hospital admission date
Baseline/Index Procedure (Day 1):	• AHC-HRSN Screening Tool[1] • Date of procedure • Vital signs (0- 48 Hours before the procedure) • Venous puncture for AlphaVac MMA $F18^{85}$ PE Procedure • Pre procedure Pulmonary Artery Pressure • Post procedure Pulmonary Artery Pressure • Concomitant Medications • Device Used • Time of Device Insertion • Bleeding: Major and Minor • Adverse Events
48 Hour Post – Procedure (±6 hr.):	• Vital signs • Hematocrit/FiO_2/Creatinine/Platelets/INR/Troponin • CTA (RV:LV Ratio) • Concomitant Medications • Bleeding: Major and Minor • Adverse Events
Discharge	• Vital signs • Concomitant Medications

	• Bleeding: Major and Minor • Adverse Events • Hospital Discharge Date
30 Day Follow-Up (± 7 days) (Virtual or In-Person)	• Vital signs (if the patient completes the 30-day follow up visit in person or if deemed necessary after the virtual visit) • Concomitant Medications • Symptomatic PE Recurrence • Adverse Events • The "Study Completion Form" CRF will be filled in at the end of the study (even if the patient is lost to follow-up before the 30-day visit, withdrew consent, or expired).

8.3 ADJUNCTIVE TREATMENTS

There may be circumstances for the need to use other treatments to aid the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE in recanalizing the targeted vessel.

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

9 PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 PARTICIPANT WITHDRAWAL

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Consent withdrawn
- Lost to follow-up

9.2 TERMINATION OF PATIENT PARTICIPATION

All patients have the right to terminate their participation at any point during the study. In addition, Principal Investigators also have the ability to terminate patient participation in the study. Reasons for termination include completion of study, patient withdrawal, physician directed patient withdrawal, lost-to-follow-up, and death. A description of the reason for their termination will be documented in the patient's medical file and in the appropriate study Case Report Forms (CRF).

9.3 SCREEN FAILURE

The reason for screen failure will be captured in the screening/enrollment section of the database.

- Subjects who were evaluated and do not meet the Entry Criteria
- Subjects who meet the Entry Criteria but decline to participate in the trial.
- Subjects who meet the Entry Criteria, but do not have any component of the study device (AlphaVac MMA F18[85] PE, described in Section 5.2) introduced into the body

9.4 LOST TO FOLLOW-UP

- A subject will be considered lost to follow-up if he or she fails to meet any of the following: return to the treating or care managing physician's office for scheduled routine follow-up visits, fail to be available remotely (e.g., by phone) to report safety (AEs and relevant medications) information, or) and is unable to be contacted by the study site staff.
- The site will attempt to contact the patient and reschedule the missed visit and counsel the patient on his/her obligation of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (e.g., 3 telephone calls to subject or next of kin, a certified letter to the participant's last known mailing address, email to subject or next of kin, inquiries to other known healthcare providers). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable and the reason for failure to respond has not been determined to be health related, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10 STUDY ASSESSMENTS AND ADVERSE EVENT REPORTING

Assessment and reporting of safety events will follow all national and local laws and requirements for the conduct of clinical studies.

10.1 ADVERSE EVENTS

For the purpose of this clinical investigation plan, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects whether or not related to the Investigational Product and includes events related to the procedures involved (any procedure in the clinical investigation plan). Safety events will refer to all peri procedural MAEs (PPMAEs), serious AEs (SAEs), Major AEs (MAEs), adverse device effects (ADEs) (including serious adverse device effects [SADEs]), and (severe) unanticipated adverse device effects (UADEs/SUADEs).

For the purposes of this study, any untoward medical occurrence that occurs in a subject is considered an AE.

Any medical conditions, problems, signs, symptoms, and findings that are occurring at the time of screening are to be reported as pre-existing conditions. Such conditions should be documented and reported on the Medical History eCRF as pre-existing conditions. If a pre-existing condition worsens during follow-up (frequency increases and/or severity grade increases), it should be documented as an AE per the definitions mentioned above.

At each evaluation from the time of enrollment, the investigator or designee will determine whether an AE as described has occurred. The AE description, date of onset, seriousness, severity, duration, treatment, outcome, and relationship to the underlying disease, procedure and investigational device will be recorded on the AE CRF. Adverse events will be assessed by a physician and monitored until they are adequately resolved, stabilized, or the subject has reached study completion.

All SAEs (including SADEs) and suspected UADEs will be documented for all patients, regardless of treatment, through the end of the period of evaluation for SAEs, or until the subject is withdrawn from study participation (for any reason).

The term "severity" refers to the intensity of a specific event (mild, moderate, or severe). An event can be severe but of relatively minor medical significance (such as severe erythema), thus not serious. Seriousness (as opposed to severity) serves as a guide for defining regulatory reporting obligations.

The Adverse Event Severity Scale, found in the table below, provides the definitions which will be used to determine the severity of each AE:

Table 5. Adverse Event Severity Scale:

Grade	Severity	Description
1	Mild	Awareness of a sign or symptom that does not interfere withthe patient's usual activity; or is transient (<48 hours) and resolves without medical intervention/therapy required.
2	Moderate	Interferes with the patient's usual activity (some assistance maybe needed) and/or no or minimal medical intervention/therapy is required.
3	Severe	Symptoms causing severe discomfort with marked limitationin activity, some assistance usually is required; medical intervention/therapy is required, and hospitalization is possible.
4	Life-threatening	Extreme limitation in activity, significant assistance required;significant medical intervention/therapy required, hospitalization or hospice care possible
5	Death	Death related to AE

For each corresponding AE identified in the study, an authorized investigator must assess the relationship of the AE to the study devices. Clinical investigators must determine whether there is a reasonable possibility that the study devices caused or contributed to an AE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and application of the study devices
- A plausible biological mechanism for the device to cause the AE,
- Another possible etiology for the AE
- Previous reports of similar AEs associated with the device or other devices in the same class, and
- Recurrence of the AE after re-application of the same device or conversion to another device, ifapplicable

10.1.1 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

Serious AEs are a subset of AEs. An SAE is one that:

1. Results in death
2. Results in life-threatening illness or injury
3. Results in a permanent impairment of a body structure or function
4. Requires inpatient hospitalization or prolongation of an existing hospitalization
5. Results in a medical or surgical intervention in order to prevent a permanent impairment to a body structure or function, or
6. Results in fetal distress, fetal death, or a congenital abnormality or birth defect
7. Important medical event

A planned inpatient hospitalization, without a serious deterioration in health, is not considered to be a serious adverse event. Reports relating to the subject's subsequent medical course must be submitted to the sponsor or sponsor's designee and the reviewing IRB (if required) until the event has subsided or, in the case of permanent impairment, until the event has stabilized and the overall clinical outcome has been ascertained. As for prolongation of hospitalization for the index procedure, the protocol considered an SAE of prolonged hospitalization if a subject is discharged from the facility more than 24 hours than the extended hospitalization (for the procedure) per hospital practice.

When an investigator determines that an event does meet the definition for a SAE (as defined above), the investigator or Research Coordinator must report the event within 10 days of becoming aware of the event to the sponsor or sponsor's designee and reporting at the number provided by the Contract Research Organization (CRO). Additionally, reports must be provided to the reviewing IRB per national and local requirements. All SAEs, including serious ADEs (SADEs) will be recorded as per investigator's reporting in the CRF.

10.2 ADVERSE DEVICE EFFECTS

Adverse device effects (ADEs) are a subset of adverse events. The ADEs are only those AEs caused by or related to Thrombectomy procedure performed by the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE (possibly, probably and definitely related), including any AE resulting, the lasing, or any malfunction of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE, including any event that is a result of a use error or intentional misuse.

With any procedure or treatment, there are known possible risks and complications. With the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE, all risks known for the proposed indication can be found in Section 10.11. A list of precautions and warning concerning use of the device is found in the device's IFU.

10.3 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

Investigators are required to submit a report of any suspected UADE occurring during an investigation to the sponsor or sponsor's designee as soon as possible, but not later than 10 working days after the

investigator first learns of the effect. Additionally, reports must be provided to the reviewing IRB per national and local requirements.

When an investigator suspects an event meets the definition for a UADE, then the event, date of onset, seriousness, severity, duration, treatment, outcome and relationship to investigational device will be recorded on the Adverse Event CRF.

The sponsor or sponsor's designee must then conduct an evaluation of the suspected UADE and report the results of the findings to the FDA and to all reviewing IRBs (if required) and participating investigators within 10 working days after the sponsor or sponsor's designee first receives notice of the effect. Thereafter, the sponsor or sponsor's designee shall submit such additional reports concerning the effect as FDA requests.

This information must be submitted via the CRF. Information includes:

- Clinical investigation plan number/identifier
- Subject identifying information
- Initial diagnosis (nature of suspected UADE) and results of any diagnostic tests supporting diagnosis
- Date(s) of use of investigational device
- Date of event, treatment, and outcome (current clinical status)
- Statement as to why event was unanticipated
- Relationship to the investigational device.
- Investigator's signature and date
- Other pertinent information as required by the sponsor or sponsor's designee.
- Reports relating to the subject's subsequent medical course must be submitted to the sponsor or sponsor's designee and the reviewing IRB (if required) until the event has subsided or, in the case of permanent impairment, until the event has stabilized, and the overall clinical outcome has been ascertained.

10.4 RELATIONSHIP TO STUDY DEVICE:

For each AE identified in the study, an authorized investigator must assess the relationship of the AE to the study devices. Clinical investigators and CEC review and adjudication must determine whether there is a reasonable possibility that the study devices caused or contributed to an AE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and application of the study devices
- A plausible biological mechanism for the device to cause the AE
- Another possible etiology for the AE
- Previous reports of similar AEs associated with the device or other devices in the same class, and
- Recurrence of the AE after re-application of the same device or conversion to another device, if applicable

The following definitions for Adverse Event Relationships, in the table below, will be used to determine the relationship of each event to the study device or study participation:

Table 6: Adverse Event Relationships

Not related	The cause of the **AE** is known and is not related to any aspect of study participation including the underlying condition or concurrent illness or effect of another device or drug.
Possibly related	There is a reasonable possibility that the event may have been caused by study participation. The AE has a **timely relationship** to the study procedure(s); **however, it follows no known pattern of response**, and an alternative cause seems more likely or there is significant uncertainty.
Probably related	It is probable that the event was caused by study participation. The AE has a **timely relationship** to the study procedure(s) and **follows a known pattern of response**, but a potential alternative cause may be present.
Definitely related	The event was definitely related to study participation. A related event has a strong temporal relationship, and an alternative cause is unlikely.

10.5 DEATH NOTICE

When a site becomes aware of a subject's death, it should be reported to the sponsor or sponsor's designee within 10 days, by way of completion of the appropriate CRF, and to the FDA and the reviewing IRB per local requirements.

The materials to be submitted for a death are due within 10 days of becoming aware of the death and consist of emailing or faxing the following reports to the sponsor or sponsor's designee:

- Death narrative: A short description by the treating physician regarding the circumstances of death and an assessment as to whether the death is related to study interventions.
- A copy of the patient's death certificate (If available).
- For reported deaths, the clinical investigator or designee should supply the sponsor or sponsor's designee and IRB with any additional requested information if available (e.g., hospital records and autopsy reports).

If the above reports are not available to the site within 10 working days, the site must notify the sponsor or sponsor's designee when they will be available.

10.6 DEVICE COMPLAINT AND MALFUNCTION

Device complaints include any deficiencies regarding the investigational device, IFU, and other product related documentation.

Device complaints may result in a safety event and if so should be reported and adjudicated as an adverse device effect (ADE or UADE). Complaints and malfunctions not adversely affecting the safety of the patient should be reported to the sponsor or sponsor's designee and properly collected in the Device Malfunction CRF. Where necessary, the sponsor may require that the device be returned for additional

evaluation. All device failures will be reported at the conclusion of the clinical study.

For any event involving suspicion of a device malfunction, the sponsor may request that the clinical investigator return the device (when possible) for further evaluation. Device malfunctions or failures are not to be reported as AEs. However, if there is an AE that results from a device failure or malfunction, that specific event would be recorded as described in Section 10.1.

10.7 MEDICAL MONITORING

It is the responsibility of the principal investigator to oversee the safety of the study at his/her site. If for example, the patient experiences clinical symptoms relating to a suspected PE recurrence in the treated vessel following the index procedure, the PE recurrence should be managed per institutional guidelines or at investigator discretion. This safety monitoring will include careful assessment by the principal investigator and appropriate reporting of all safety events as noted above.

The principal investigator or qualified delegate must review and verify the completed AE form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the device/procedure and the AE. When possible, the principal investigator should designate at least one other study physician who can perform the assessment of AE/SAE/SADE/UADE to provide uninterrupted coverage of monitoring of AEs which require expedited reporting.

Medical monitoring will also include a regular assessment of the number and type of safety events.

10.8 HANDLING AND REPORTING SAFETY EVENTS

Subjects will be carefully monitored during the study for possible safety events. All AEs will be collected actively and deliberately at predefined study intervals and shall be reported and documented on the appropriate eCRF (Adverse Events). All observations and clinical findings, including the nature, seriousness, severity, and relationship to the device and/or pulmonary embolism will be assessed by the investigator and provided on the CRF. This documentation will also include a detailed description of the event, treatments rendered in response to the event and outcomes of the treatment.

Additionally, an independent Data Monitoring Committee (DMC) will be established to monitor the safety and conduct of the clinical study, including adherence to the clinical investigation plan. The DMC will follow the statistical analysis plan (SAP) and the clinical investigation plan specific DMC Charter.

The investigator will report any and all safety events to the sponsor as soon as possible after becoming aware of the event. Reporting may occur by telephone at the number provided by the Sponsor.

10.9 DATA MONITORING COMMITTEE (DMC)

A DMC will be established to review cumulative study data to evaluate safety (interim and cumulative data for AEs), study conduct, and scientific validity and integrity of the trial. The DMC will consist of at least 3 independent subject matter experts who will be voting members and a Statistician (voting or non-voting). The three voting members will be physicians not associated with the study in any capacity or have any affiliations with the study sponsor or sponsor's designee, and without any direct business associations with the principal investigator of the trial. The physicians

may be selected from different disciplines but with an understanding of the study population and procedures. None of the members will have direct involvement in the conduct of the study or have any conflict of interests. The initial DMC meeting will develop the DMC Charter which will contain operational details including schedule for meetings, triggers set for data review or analyses, definition of a quorum, and stopping rules for safety.

The conduct of the DMC will be guided by the FDA guidance on the "Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors." The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the coordinating Investigator(s).

10.10 CLINICAL ENDPOINT ADJUDICATION COMMITTEE (CEC)

An independent CEC will be established for the purpose of reviewing clinical endpoints including safety and/or effectiveness data. The CEC will consist of medical doctors who will not have direct involvement of the conduct of the study. The CEC will meet regularly to review and adjudicate appropriate adverse events for causality and attribution.

10.11 RISK BENEFIT ANALYSIS

The clinical investigation plan has been designed to ensure that a subject's risks will be minimized. Specific processes include training of physicians on appropriate devise use, stopping rules, and ongoing DMC oversight. This device, as do all embolectomy systems and devices, has possible side effects, which include, but are not limited to infections, blood loss, thrombus formation, embolic events, vessel, ventricular or valvular damage and complications of percutaneous or surgical insertion techniques. These may occur if the Directions for Use are not followed.

Possible complications include those normally associated with large bore surgical and/or percutaneous vessel catheterization/cannulation, anticoagulation, and application of intravascularintroducer systems which include but are not limited to:

- Air Embolism
- Arrhythmia
- Arteriovenous Fistula
- Blood Loss/Blood Trauma
- Bradycardia
- Tachycardia
- General Discomfort, Tenderness, or Pain
- Hemorrhage/Bleeding
- Infection (Local or Systemic)
- Pleural Effusion
- Pericardial Effusion
- Pulmonary Embolism
- Pulmonary Infarction
- Injury to Blood Vessel
- Device Fracture with Distal Embolization
- Distal Embolization of Thrombus
- Hematoma

- Access Site Injury
- Vascular Thrombosis
- Valve Injury
- Perforation
- Vessel Spasm
- Hemoptysis
- Death
- Cardiac arrest
- Hemothorax
- Pulmonary Artery Injury/Wire Perforation

Benefits may include improvement in the subject's disease state.

11 STATISTICAL CONSIDERATIONS

11.1 GENERAL CONSIDERATIONS

Standard statistical methods will be employed to analyze all data. All data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, including counts, mean, median, standard deviation (SD), minimum and maximum. Where appropriate, 95% two-sided confidence intervals for the means will be presented. Categorical variables will be summarized by frequencies and percentages. Unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of unique patients.

11.2 DETERMINATION OF SAMPLE SIZE

This study is designed to assess the efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE with respect to the primary efficacy endpoint (reduction in RV/LV Ratio between baseline and 48 hours post procedure) as well as to assess the safety of the AlphaVac MMA F18[85] PE with respect to the primary safety endpoint (rate of any MAE within 48 hours of the procedure).

The safety performance goal is that less than 25% of study subjects experience an MAE (the primary safety endpoint). This is based on the upper limit of the 95% confidence interval for the average composite MAE rate (16.3%) observed across 7 RCTs in which acute PE was treated with thrombolysis versus an anticoagulant control.[6,8,10,11,12,13,14] For this study, the hypothesized composite MAE rate is expected to be approximately 15%. To detect a difference between an expected MAE rate of 15% and the performance goal of 25% with 80% power, the necessary sample size was calculated to be 103 (with a one-sided p-value = 0.05). A sample size of 103 patients was selected as a conservative sample size to assess safety with adequate statistical power. To account for attrition rate of 15%, 122 subjects will be enrolled.

Table 7: Sample Size Determination - Safety

Endpoint	Primary Analysis Population	Assumed Performance of Manual Mechanical Aspiration Catheter	Performance Goal	Power	Sample Size
Rate of any MAE	As treated	15%	25%	80%	103

The efficacy performance goal of 0.12mm reduction in the RV/LV Ratio from baseline was calculated using 4 randomized controlled trials that discuss the treatment of acute PE with anticoagulants, which is standard of care. The mean decrease in RV/LV ratio across the 4 trials was 0.12mm.[6,7,8,9] A standard deviation of 0.25mm was based on the standard deviation of the RV/LV ratio observed in the FLARE trial.[10]

Table 8: Sample Size Determination - Efficacy

Endpoint	Primary Analysis Population	Assumed Performance of Manual Mechanical Aspiration Catheter	Assumed Standard Deviation	Performance Goal	Power	Sample Size

Reduction in RV/LV Ratio	Modified as treated	0.20	0.25	0.12	80%	62

The SAS code and resulting output for each sample size calculation is included below:

```
proc power;
        pairedmeans sides = U
        test = diff
        nulldiff = 0.12
        meandiff = 0.20
        power = 0.8
        corr = 0.5
        npairs = .
        std = 0.25;
run;
```

The SAS System

The POWER Procedure
Paired t Test for Mean Difference

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Number of Sides	U
Null Difference	0.12
Mean Difference	0.2
Standard Deviation	0.25
Correlation	0.5
Nominal Power	0.8
Alpha	0.05

Computed N Pairs	
Actual Power	N Pairs
0.801	62

```
proc power;
        onesamplefreq test = z method = normal
```

```
Version Number: 5.1
Version Date: 07/18/23
        sides = 1
        alpha = 0.05
        nullproportion = 0.25
        proportion = 0.15
        ntotal = .
        power = .80;
run;
```

The SAS System

The POWER Procedure
Z Test for Binomial Proportion

Fixed Scenario Elements	
Method	Normal approximation
Number of Sides	1
Null Proportion	0.25
Alpha	0.05
Binomial Proportion	0.15
Nominal Power	0.8
Variance Estimate	Null Variance

Computed N Total	
Actual Power	N Total
0.802	103

11.3 ANALYSIS COHORTS

11.3.1 AS TREATED POPULATION

The As Treated population includes all subjects who meet the inclusion/exclusion criteria and in whom the F18[85] cannula is placed within the jugular or one of the common femoral veins. This population will serve as the primary analysis cohort for all safety endpoints and as a supportive analysis cohort for all efficacy endpoints.

11.3.2 MODIFIED AS TREATED POPULATION

The Modified As Treated population includes all subjects in the As Treated population who did not receive thrombolytics during the index procedure. This population will be used as the primary analysis cohort for all efficacy endpoints.

11.3.3 PER PROTOCOL POPULATION

Per Protocol population: This population includes all subjects in the Modified As Treated population who had no major protocol deviations. This population will serve as a supportive analysis cohort for all efficacy endpoints.

11.4 STUDY ENDPOINT ANALYSIS

11.4.1 PRIMARY EFFICACY ENDPOINT ANALYSIS

The primary efficacy analysis will be the reduction in the RV/LV Ratio between Baseline and 48 hours post procedure. The mean reduction in the RV/LV Ratio will be compared to a performance goal of 0.12. The hypothesis for reduction from baseline in RV/LV Ratio is as follows:

H_0: $R_{diff} < 0.12$
H_1: $R_{diff} \geq 0.12$

Where R_{diff} is the mean reduction in the RV/LV Ratio between Baseline and 48 hours post procedure.

The mean reduction in the RV/LV Ratio will be compared to the performance goal of 0.12 using a paired-samples t-test with a significance level of 0.05.

11.4.2 PRIMARY SAFETY ENDPOINT ANALYSIS

The primary safety analysis will be the rate of any MAE within the first 48 hours after the index procedure.

MAEs include:

- Device-related death
- Major bleeding
- Device-related SAEs which includes:
  - Clinical Deterioration
  - Pulmonary Vascular Injury
  - Cardiac Injury

Examples of major bleeding, clinical deterioration, pulmonary vascular injury, and cardiac injury are defined inAppendix I.

The proportion of subjects who experienced any MAE within 48 hours will be compared to a performance goal of 25%. The hypothesis for the rate of any MAE is as follows:

H_0: MAE > 0.25
H_1: MAE ≤ 0.25

Where MAE is the proportion of subjects who experienced any MAE within 48 hours of the procedure.

The rate of any MAE within 48 hours of the procedure will be compared to the performance goal of 25% using a one sample proportion test with a significance level of 0.05.

11.4.3 SECONDARY EFFICACY ENDPOINT ANALYSIS

The secondary efficacy endpoints will include the following:

1. Length of stay in ICU/Hospital setting within 30 Days
2. Use of thrombolytic within 48 hours of the index procedure
3. Change in modified miller index between baseline and 48 hours of the index procedure

Length of stay in the ICU/Hospital setting within 30 days and the change in modified miller index will be summarized descriptively. Point estimates will be reported. For all other secondary efficacy endpoints, the number and proportion of patients who experienced each endpoint will be presented.

11.4.4 SECONDARY SAFETY ENDPOINT ANALYSIS

1. Major bleeding within 48 hours
2. Device-related death within 48 hours
3. Device-related clinical deterioration within 48 hours
4. Device-related pulmonary vascular injury within 48 hours
5. Device-related cardiac injury within 48 hours
6. Any-cause mortality within 30 days
7. Device-related Serious Adverse Events within 30 days
8. Symptomatic recurrence of PE at 30 days (Recurrent pulmonary embolism is defined in the Study Definitions of Appendix I).

The number and proportion of patients who experienced each of the secondary safety endpoints will be presented.

11.4.5 EXPLORATORY ENDPOINT ANALYSIS

Exploratory analysis may be conducted to evaluate healthcare disparities, unmet healthcare needs with study enrollments and outcomes.

11.4.6 SUBGROUP ANALYSIS

Subgroup analyses are exploratory in nature and may include demographic information, baseline characteristics, and other factors to be determined after the study team reviews the final analyses of primary and secondary endpoints.

11.5 ADVERSE EVENT ANALYSIS

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects in the as treated population who experience each AE will be summarized by MedDRA system organ class and preferred terms. Serious adverse events will also be presented in a by-subject listing.

11.6 PROTOCOL DEVIATIONS

Patients with protocol deviations will be summarized in data listings. All enrolled patients will be included in the reporting of protocol deviations. Patients with major protocol deviations as defined in the Protocol Deviation Plan will be excluded from the Per Protocol analysis.

11.7 HANDLING MISSING DATA

Missing data are defined as data that are expected to be collected but are not available for the study at the time of the final analysis. In this study, missing data will not be imputed nor handled with the last observation carried forward. In general, data will be analyzed as they are recorded with the following specific methods apply to defining and handling missing data.

- Patients who drop out before study completion will not be replaced and all information obtained from them will be included in the analysis.
- Missed visits: If a patient missed a visit, information to be collected during that visit is considered as missing data. Patients with a missing visit will be removed fromthe analysis for that visit. For example, subjects without a 30-Day follow-up visit will not be included in the analysis of the symptomatic PE recurrence secondary endpoint.
- Missing data: We expect relatively few patients to be missing the primary endpoints due to withdrawal or refusal due to the short study follow-up period. The Electronic Data Capture (EDC) supports efficient data collection and management and facilitates rapid data closure. The frequency of missing data can be reduced by two mechanisms: the coordinators will receive a list of queries generated by the study monitors upon logging into the system, and any data required during a visit is immediately evident through the system and can be collected before closure of the visit window. Despite the screening and ongoing communication with patients regarding the importance of study endpoint assessment, we anticipate no more than 15% of subjects will be missing primary endpoint assessments due to technical issues/low-quality of the diagnostic pulmonary CTA images, procedural mortality, withdrawal, or refusal to continue participation in the study or lost to follow-up. Patients missing primary endpoint assessments due to lost to follow-up are accounted for in the sample size calculation.

11.8 SENSITIVITY ANALYSIS

Sensitivity analyses may be performed on the primary efficacy and primary safety endpoints to describe the potential impact of missing data on the observed study results. Subjects missing the primary efficacy endpoint and/or primary safety endpoint will be imputed using best-case and worst-case analyses. For subjects missing the primary efficacy endpoint, best-case imputation will use the best observed change in RV/LV ratio at 48 hours post procedure in the study population. Worst-case imputation of the primary efficacy endpoint will use the worst observed change in RV/LV ratio at 48 hours post procedure in the

study population. For subjects missing the primary safety endpoint, meaning they did not have a 48-hour visit, best-case imputation will assume the subject did not experience an MAE within the first 48 hours after the procedure. Worst-case imputation of the primary safety endpoint will assume the subject did experience an MAE within the first 48 hours after the procedure. Further, a tipping point analysis may be performed to assess sensitivity without need for postulating a specific set of assumptions regarding missing data. If there is evidence of non-normality of the primary efficacy endpoint based on a Shapiro-Wilk test at the 0.05 alpha level, a non-parametric sign test will be used.

11.9 POOLABILITY OF DATA

This study is designed and conducted as a multicenter clinical trial. All participating sites will be selected using the same criteria and trained prior to enrolling subjects. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results. Poolability of the data across centers in a multicenter study is assumed without burden of proof.

Nevertheless, poolability of data across sites will be examined for apparent violation of the poolability assumption. A logistic regression on the primary safety endpoint and a linear regression on the primary efficacy endpoint will be used to confirm the pooling of data across sites. For each regression model, a test for fixed site effect at the 0.15 alpha level will be used to assess potential heterogeneity. If there is evidence of heterogeneity of sites, a random site-effect model will be used to summarize the associated endpoint. The results of the poolability analysis will be used to assess the robustness of study results, not to change the study conclusion. Sites with fewer than five subjects will be combined and treated as a single site for these analyses.

12 DATA QUALITY ASSURANCE

A database will be overseen for this study in accordance with regulatory data integrity requirements, the Data Management Plan (DMP), and SOPs. All data elements for all subjects will be collected using electronic case report forms (eCRFs). In addition, electronic source data, meaning source data originally captured in electronic format, maybe used to populate eCRF data fields where it is possible to reduce unnecessary duplication of data and to reduce the possibility of transcription errors. All eCRF data fields that have data that is transmitted from electronic source data will have an attached and auditable Date Element Identifier in accordance with the Guidance for the Industry: Electronic Source Data in Clinical Investigations (September 2013). Data will be entered into the eCRFs at baseline, index procedure, 48 – hours, hospital discharge and 30 days after the index procedure. Data will be reviewed for accuracy and completeness by the sponsor or designee during all onsite and remote monitoring visits and throughout the data management process. Any discrepancies willbe resolved with the clinical investigator or designee, as appropriate. Access to the database shall be limited to appropriate trained personnel in order to preserve data integrity.

12.1 DATA MANAGEMENT

The standard procedures for handling and processing records will be followed per GCP and the SOPs.

For the duration of the study, the investigator and their delegates will maintain complete and accurate documentation, including but not limited to, medical records, study progress notes, laboratory reports, signed subject informed consent forms, correspondence with the reviewing IRB, correspondence with the sponsor or sponsor's designee and Study Monitor, adverse event reports, and information regarding subject discontinuation or completion of the study. For each enrolled subject, images will be appropriately de-identified, and sent to the imaging Core Lab for evaluation.

The investigator/institution will permit direct access to source data and documents in order for study-related monitoring, audits, IRB reviews, event adjudication and regulatory inspections to be performed. The investigator will obtain, as part of the informed consent process, permission for authorized sponsor employees, study monitors or regulatory authorities to review, in confidence, and records that identify subjects in this trial.

12.2 CONFIDENTIALITY OF DATA

Information about study subjects will be kept confidential and managed according to the requirements and regulations of the local and national governing bodies.

All data and information collected during this study will be considered confidential by the sponsor and their delegates. All data used in the analysis and summary of this study will be anonymous, and without reference to specific subject names. Access to subject files will be limited to authorized personnel of the sponsor and sponsor's designee, the investigator, clinical site research staff and authorized regulatory authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

12.3 SOURCE DOCUMENTS

Source data is all information, original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Examples of these original documents and data records include but are not limited to the following: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, subject files, and records kept at the pharmacy, and at the laboratories involved in the clinical trial.

Data will be entered into the eCRF using direct entry of data into the eCRF. For all data, the eCRF will be capable of recording metadata as data element identifiers (DEIs) that will identify the:

1. Originators of the data element (including those entered manually (e.g., by the clinical investigator(s)) or automatically by devices
2. Date and time that the data element was entered into the eCRF.

These data element identifiers allow sponsors, FDA, and other authorized parties to examine the audit trail of the eCRF data and to provide information that will allow FDA to reconstruct and evaluate the clinical investigation. All data entered in the eCRF, either directly or originating from an

electronic system will be available for review and updates by the investigator and not be final until electronically signed by the investigator.

Regulations require that the investigator maintain information in the subject's medical records that corroborate data collected for the study. To comply with these regulatory requirements, at a minimum, the following is a list of information that should be maintained.

- Medical history/general physical condition of the subject before involvement in the study of a sufficient nature to verify the clinical investigational plan (CIP) eligibility criteria
  - Dated and signed study/progress notes on the date of entry into the study documentingthe following:
    - The general health of the subject
    - The discussion of the study risks and benefits with the subject
    - Completion of the informed consent process
    - A statement the subject reviewed and signed the subject informed consentform
- Dated and signed notes from each subject visit to support all data recorded on theeCRFs
  - Adverse Events reported and their continuation or resolution at each visit, including supporting documents such as discharge summaries, lab results, non-invasive testing reports
  - Notes regarding CIP-required and prescription medications taken during the study (including start and stop dates if known)
  - Subjects general health and medical condition upon completion of or withdrawal from the study.

12.4 ELECTRONIC CASE REPORT FORMS

The eCRFs contain confidential material. Specific instructions to complete the eCRFs will be provided to the clinical investigator and other site personnel as appropriate. The clinical investigators or designees are responsible for reporting clinical study requested information in the eCRFs.

12.5 RECORD RETENTION

FDA regulations require that all study records, including those retained by the Site Institution, need to be retained for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such an indication, until 2 years after the investigation is discontinued and FDA is notified or as otherwise stated in the signed clinical trial agreement.

The investigator will retain study essential documents for a minimum of 2 years after formal closure of the trial. These documents must be retained for a longer period if required by an agreement with the sponsor or sponsor's designee or defined by local or national regulations. The sponsor or sponsor's designee will inform the investigator/institution as to when these documents no longer need to be retained. All clinical sites will maintain all records pertaining to this study for a minimum

of 2 years after the study is discontinued. The sponsor or sponsor's designee will notify the clinical sites of the date of discontinuation.

12.6 CLINICAL DATA MONITORING PROCEDURES

Clinical Research Associates (CRAs) will conduct site visits at the study facilities to monitor the study in compliance with the CIP, SOPs, GCP, ISO 14155 and the Monitoring Plan.

Monitoring visits will occur as defined in the Monitoring Plan and/or as required to conduct the study. The clinical study center agrees to allow these monitors and other authorized AngioDynamics personnel access to information and clinical supplies related to the study. CRAs will verify data entered into the CRFs against hospital records or other source documents to ensure accuracy and completeness of the CRFs for each subject. Clinical investigators and their staff agree to assist the monitors in their activities. Requests may be made to review subject charts by the sponsor or sponsor's designee so that CIP adherence and source documentation can be verified.

Monitoring visits will be performed at regular intervals throughout the course of the study to ensure compliance with the CIP. Monitoring activities may include, but are not limited to the following:

- Evaluation of subject screening and selection methods
- Verification of signed informed consent for each subject
- Verification of source documentation against completed case report forms for each subject
- Assurance that required study reports, including reports to the applicable IRB, are generated in a timely manner
- Monitoring of Safety Events, including device deficiencies that could have led to SAE
- Monitoring of device deficiencies irrespective of associated safety events
- Review of clinical investigation plan deviations
- Overall study compliance
- Review of the investigator site file.

13 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

13.1 INVESTIGATOR RESPONSIBILITIES

The investigator is responsible for the conduct of the study at the site. Prior to shipment of the first investigational device and first procedure, the investigator must do the following:

- Read and understand the CIP;
- Sign and complete the Investigator's Agreement;
- Provide an accurate financial disclosure, and file an update annually and 1 year after the completion of the study;
- Ensure appropriate IRB and institutional approvals are in place prior to completing any portion of the informed consent process or permitting

subject participation;

- Complete and file a fully executed clinical trial agreement between sponsor or sponsor's designee, investigator, and institution (as applicable); and
- Provide assurance of completed training on the investigational device and procedures being studied under the clinical investigation plan.

In addition, each investigator must have written approval by the sponsor or sponsor's designee to either use the investigational device being studied under this clinical investigation plan and/or perform the procedure being studied.

The study will be conducted in compliance with all relevant portions of 21 CFR Part 50 and 56: The study will be overseen by an IRB and all subjects will be consented. An IDEapplication in compliance with 21 CFR 812 will be submitted to FDA and approved prior to commencing the study. The study also complies with HHS' Policy for Protection of Human Research Subjects 45 CFR 46.

Throughout the course of the study, it is the investigator's responsibility to ensure thatthe investigation is conducted according to the signed Investigator's Agreement, the CIP, all applicable national and local regulations, and the respective IRB requirements, specifically:

- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Controlling devices under investigation
- Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50/ISO 14155.

Under no circumstances may an investigator provide an investigational device AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE for use to any personwho has not received training for use from the sponsor or sponsor's designee.

Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall control the device as the sponsor directs.

13.1.1 DEVIATIONS FROM INVESTIGATIONAL PLAN

A CIP deviation is defined as an event where the clinical investigator or site personnel deviate from the CIP or study procedures. It is the investigator's responsibility to ensure that there are no deviations from the clinical investigation plan. An investigator may deviate from the CIP without prior written approval from the sponsor or sponsor's designee in cases of medical emergencies to protect the life or physical well-being of a subject in an emergency. In that event, the investigator is required to notify the sponsor and the applicable IRB as soon as possible, but in no event later than 5 working days after the emergency occurred, of the deviation from the CIP by the Sponsor is required for changes in/or deviations from the CIP. Additionally, if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification is also required.

Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g., the subject was not available for a scheduled follow-up office visit or has moved without providing a forwarding address). These events, although outside the investigators control, are still required to be reported on the appropriate CIP deviation CRF in order to ensure that all deviations from the standard subject population are adequately documented and reported. The investigator will inform the sponsor or sponsor's designee of all deviations, and the reviewing IRB of all CIP deviations as per the IRB requirements for this study.

If the sponsor or sponsor's designee becomes aware that an investigator is not complying with any part of the CIP, including the signed Investigator's Agreement, the CIP, or any conditions of approval imposed by the reviewing IRB, the sponsor or sponsor's designee will immediately secure compliance, and may suspend the investigator's participation (including enrollment at the site), and may discontinue shipments/use of the device to the investigator until compliance is achieved and guaranteed. The sponsor may terminate an investigator's participation in the study at its discretion.

13.1.2 MAINTAINING RECORDS

The investigator will maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA.
2. Records of each subject's case history and exposure to the device, including:
    - documents evidencing informed consent and, for any use of a device by the investigator without informed consent,
    - any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
    - all relevant observations, including records concerning ADE (whether anticipated or not),
    - information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests,
    - a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy,
3. The CIP, with documents showing the dates of and reasons for each deviation from the CIP,
4. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

13.1.3 SUBMITTING REPORTS

In compliance with local and national laws, each investigator may be required to prepare and submit complete, accurate, and timely reports to the sponsor or sponsor's designee and the FDA/IRB. These reports may include:

1. Any UADE occurring during an investigation. (No later than 10 working days after the investigator first learns of the effect.)
2. Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurs. Except in emergency situations, a CIP deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
3. Any use of the device without obtaining informed consent. (Due within 5 working days after such use.)
4. Any further information requested by FDA or the IRB about any aspect of the investigation

The investigator will provide in writing any withdrawal of IRB approval of the study or an investigator within 5 working days of such action.

13.2 SPONSOR RESPONSIBILITIES

13.2.1 GENERAL DUTIES

The sponsor has the overall responsibility for the conduct of the study including assurance that the study satisfies the regulatory requirements of the appropriate regulatory agencies, ensuring IRB approvals, selecting investigators, ensuring proper monitoring, and ensuring informed consent is obtained. The sponsor will ensure oversight of the CRO according to local and national regulations. The sponsor will provide all information necessary to conduct the study, including the CIP, and any reports of prior investigations as appropriate. During the conduct of the clinical study, updates in information that may impact the clinical study will be made available to all the appropriate national and local regulatory authorities.

The sponsor will submit IDE progress reports to FDA at 6-month intervals.

13.2.2 SELECTION OF INVESTIGATORS

The sponsor will select investigators qualified by training and experience. Sites will be selected based upon a site assessment, appropriate facilities, clinical experience, and the qualifications of the Principal Investigator. Investigators will be evaluated by the sponsor based on the following:

1. A curriculum vitae, or other statement of investigator's relevant training and experience including type of experience with the intended procedure and clinical research, specifically;
2. Education and experience in the management of pulmonary embolism;
3. Whether the investigator has an adequate subject population to meet requirements of the

study;

4. Whether the investigator has adequate time to be personally involved in the conduct of the study, and adequate research staff and resources to support the study;
5. Whether the investigator's study center is associated with an IRB that satisfies all applicable regulatory requirements; and
6. Whether an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination must be provided.

Prior to site initiation, each investigator must also submit the following:

7. A certificate of human subject's protection training (if required by reviewing IRB)
8. A completed financial disclosure form (and annually up to one year after the completion of the study)
9. A signed Investigator's Agreement indicating an investigator's commitment to:
    - Conduct the investigation in accordance with the agreement, the CIP, Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA;
    - Supervise all testing of the device involving human subjects;
    - Ensure that the requirements for informed consent are met consistent with 21 CFR Part 50/ISO:14155;
    - Conduct the study according to the CIP.

The sponsor reserves the right to apply additional criteria to site and/or investigator selection.

13.2.3 TRAINING

Training may consist of a review of the IFU, hands-on training on the device, presentations, literature, etc. The training program will be standardized and will be documented. Additional training will include a review of the CIP, the regulations for medical device investigations and general study logistics required to complete the study.

Training of appropriate clinical study personnel will be the responsibility of the sponsor or sponsor's designee. To ensure uniform data collection and CIP compliance the sponsor or sponsor's designee will review the CIP (including the informed consent form), techniques for identification of eligible subjects, instructions on data collection, methods for scheduling follow-up visits in the window, etc. Detailed feedback regarding completion of the eCRFs, study requirements, and CIP compliance will be provided by the sponsor, CRO, and/or its Study Monitors as appropriate.

13.2.4 CHANGES IN THE CLINICAL INVESTIGATIONAL PLAN

The sponsor will obtain FDA approval for any change to the CIP that may affect the scientific soundness of the investigation or the rights, or the rights, safety and/or welfare of the subjects.

Approved CIP amendments will be provided to the investigators by the sponsor or sponsor's designee prior to implementing the amendment. The investigator will be responsible for notifying the reviewing IRB of the CIP amendment (administrative changes) or obtaining IRB approval of the CIP amendment (changes in subject care of safety), according to the instructions provided with the CIP amendment. The IRB acknowledgement/approval of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must be provided to the sponsor or sponsor's designee.

13.2.5 Withdrawal of Food and Drug Administration Approval

The sponsor will notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval of the investigation and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

14 Ethics and Regulatory Compliance

14.1 Conduct of the Clinical Study

Requires review from the regulatory affairs representative on the document development committee. Conduct of the clinical study will follow standard operating procedures (SOPs) from AngioDynamics and the CRO, as well as the Code of Federal Regulations, the Declaration of Helsinki, GCP, and other national and local laws. Each investigator must sign and date the Investigator's Agreement prior to the start of this study. With the signature, the investigator agrees to perform all study procedures according to the governing local and national regulations, and the CIP.

An independent CEC will be established to review and adjudicate all clinical study endpoints as defined in the CIP.

14.2 Conflict of Interest

If the FDA believes that the financial interest of any investigator raises a serious question about the integrity of the data, the FDA may take any action it deems necessary to ensure the reliability of the data including:

- Initiating agency audits of the data derived from the clinical investigator in question
- Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study
- Refusing to use the data from the covered clinical study as the primary basis for an agency action, such as 510(k) clearance.

Therefore, any investigator (or sub-investigator), their spouses, and/or dependent children who has a potential conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict evaluated by the sponsor. If a financial interest appears to exist, a management plan should be generated to minimize bias and must be approved by the study sponsor prior to participation in this study.

14.3 Institutional Review Board

A properly constituted, valid IRB must review and approve the CIP, the informed consent form, and related subject information and recruitment materials before the start of the study. It is the responsibility of the investigator to obtain approval of the CIP from the institution's IRB and to keep the IRB informed of any SAEs or SADEs and amendments to the CIP. Additional requirements imposed by the IRB/EC or other regulatory authority shall be followed if appropriate. All

correspondence with the IRB should be filed by the investigator and copies sent to the sponsor or sponsor's designee(s).

14.4 Clinical Study Informed Consent Approval

Informed consent shall be obtained in writing and documented before a subject is enrolled in the clinical study in accordance with the principles of Informed Consent, according to the Declaration of Helsinki, Good Clinical Practice (GCP), 21 Code of Federal Regulations (CFR) Part 50, the Medical Devices Directive 93/42/EEC, and International Organization for Standardization (ISO) 14155-.

It is the responsibility of the clinical investigator to ensure that written informed consent is obtained from the subject (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care. Information obtained during the conduct of the clinical that may impact the subject informed consent may require revisions to the informed consent. If so, revisions and approvals of such changes by the appropriate regulating authority are required. Documentation of the current versions of the informed consent shall be documented in the clinical study trial master file (TMF).

14.5 Subject Identification and Confidentiality

Subject identification and confidentiality will be ensured according to the terms and definitions in 21 CFR Parts 50, 56 and 812/ISO 14155. This includes but is not limited to the following:

- Subjects will be identified on all CRFs and source documents by a unique identification reference that may include the subjects' initials
- CRFs are confidential documents and will only be made available to the sponsor or sponsor's designee, the clinical investigator, the biostatistician, the CEC, and if requested, to advisory committees and regulatory authorities (including FDA)
- Data will be stored and analyzed by computer following national regulations for handling of computerized data

Each study center will maintain (anonymous to AngioDynamics) a list identifying all subjects entered into the trial. The list will be maintained as part of the investigation file.

This study will be conducted according to the US FDA standards of Good Clinical Practice (FDA Title 21 Code of Federal Regulations Part 11, 50, 54, 56 and 812), ISO: 14155, the Declaration of Helsinki, and the ICH Guidelines.

14.6 Site Qualification Visit

A site qualification visit will be performed to evaluate site facilities, investigator qualifications, and site knowledge of Good Clinical Practice (GCP) guidelines.

14.7 Site Initiation Visit

As available, study personnel will participate in a site initiation visit. Training will be provided to all applicable personnel not able to attend the site initiation visit. Components of this initiation visit may include:

- Introduction of the study design including the treatment and follow-up phase
- Product training to all end-users
- CRF completion training

- Safety reporting instructions
- Training on the regulations governing human research

14.8 INSURANCE

The sponsor shall maintain insurance coverage for this study. Pertinent information regarding the coverage shall be made available to the site upon request.

14.8.1 IMPACT ON MEDICARE BENEFICIARIES

It is widely understood that the risk of venous thromboembolism and the potential for pulmonary embolism increases with age. While clinical data indicate that most cases of PE occur at 60 to 70 years of age, autopsy data show the highest incidence among individuals 70 to 80 years of age.[16]

"This increasing risk is associated with a concurrent enhancement of coagulation activation and gradual development of a 'prethrombotic state'. This is reflected by increased levels of coagulation activation peptides in the elderly, as well as decreased activity of the fibrinolytic system. Moreover, with increasing age there is an increased incidence of comorbid conditions, which may, in themselves, be associated with an increased risk for the development of thrombosis. Accurate diagnostic techniques and strategies for treatment and prevention of deep vein thrombosis (DVT) are mandatory in order to prevent potentially fatal complications of DVT, such as pulmonary embolism." [17]

Further, in the past 18 months, the United States has seen that elderly patients are some of the most impacted by COVID-19. While vaccinations to prevent or mitigate the impact of COVID-19 are now available and a large percentage of Medicare beneficiaries are vaccinated, the medical community continues to learn about long-term effects of exposure to COVID-19 and about long-term efficacy of the vaccines as variants of the SARS COVID-19 virus are identified. What is clear in peer reviewed clinical literature is that there is a "link between COVID-19 and thrombotic complications, including a high incidence of acute PE and venous thromboembolism (VTE)."[1]

While Medicare is likely aware of thromboembolism risks for beneficiaries, heretofore, no study of this population has sought to identify potential healthcare disparities and social needs of the patients who develop pulmonary embolism. This study includes administration of Medicare's Accountable Health Communities Standardized Screening for Health-related Social Needs in Clinical Settings.[18] The findings of the screening will not only help identify individual patient social needs that may be addressed by provider referral to local services, but this clinical trial will summarize the finding across the enrolled populated to inform medical professional about the potential healthcare disparities and health-related social issues faced by patients treated for pulmonary embolism.

14.9 SITE AUDITS

There may be inspection and audits by government regulatory authorities, applicable compliance, and quality assurance offices. If these are requested, the investigator and study site personnel must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. If so requested, the investigator must provide the sponsor or sponsor's designee with copies of all correspondence that may affect the review of the current study or their qualification as an investigator in clinical studies conducted by the sponsor.

14.9.1 Internal Audits by Sponsor or Sponsor's Designee

In accordance with local and national regulations and the sponsor's or sponsor's designee's operating procedures, the sponsor or sponsor's designee may request access to all study records, including source documents, for inspection. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., cardiac catheterization laboratory, surgery suite, diagnostic laboratory.)

Internal quality assurance audits will be conducted at various sites during the trial. Selection of sites to undergo auditing will be determined by the sponsor per a pre-established audit plan.

14.10 External Audits

Requests by regulatory agencies to inspect the study sites may be made as well. The investigator or designee is required to report to the sponsor or sponsor's designee as soon as possible after receiving a request from and regulatory authority to perform an audit. The clinical investigator agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.11 Public Domain Access to the Clinical Study

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. Information regarding public access will be presented in the informed consent, as required by US Law.

15. General Considerations

15.1 Discontinuation of the Study

The study may be suspended or discontinued early if there is an observation of SAEs presenting an unreasonable risk to the study participants, inadequate subject enrollment, or determination that no statistically significant result can be obtained.

The sponsor may terminate investigator and site participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the CIP.

Notification of suspension or termination will occur no later than 5 working days after the sponsor makes the determination. In the event of study suspension or termination, the sponsor or sponsor's designee will send a report outlining the circumstances to the reviewing IRB the appropriate regulatory agencies, and to all participating investigators. Any suspension or termination may not be re-initiated without prior approval of the IRB and sponsor.

AngioDynamics reserves the right to discontinue this study for safety or administrative reasons at any time.

15.2 Use of Information and Publications

All information concerning the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE, AngioDynamics operations, patent applications, manufacturing processes, and basic scientific data supplied by AngioDynamics or the CRO to the clinical investigator and not previouslypublished, are considered confidential and remains the sole property of AngioDynamics. This includes all study

materials, CRF forms, worksheets and CRFs.

The information developed in this study may be used by AngioDynamics as support for a pre-market approval filing and in connection with the continued development and pre-market approval of the System. Any publication or other public presentation of the AlphaVac MMA $F18^{85}$ PE data resulting from this study will require prior review and written approval of AngioDynamics.

At the conclusion of the study, it is expected that the sponsor/investigators will promptly prepare and submit a multi-center manuscript for publication in a reputable scientific journal. The publication of the principal results (including abstracts) from any single site experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior written approval of the sponsor. The results of this study are intended to be published in a peer-reviewed journal. No individual investigator may publish on the results of this study, or his/her own patients, without prior approval from the Sponsor.

No participating physician may publish or present on the results of this study, or study data on his/her own patients, without prior approval from the Sponsor. If after 180 days from the conclusion of the study, the Sponsor has not published the results, the investigators may publish without prior approval from the Sponsor. This includes the release of negative outcomes and if the study is terminated early results will be hastened.

Further analyses, beyond those presented in the initial multi-center publication may be proposed to the sponsor. Many secondary manuscripts are anticipated. For purposes of timely abstract presentation and publication, such secondary publications may be delegated to the appropriate principal authors; however, any final analyses and manuscript review for all multi- center data will require the prior written approval of the sponsor.

None of the results, in whole or in part, of the study carried out under this CIP, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

16. APPENDIX I: STUDY DEFINITIONS

BLEEDING
Loss of blood from the vascular system. Bleeding was classified by the GUSTO[15](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
- Minor Bleeding includes GUSTO Mild bleeding:
  - GUSTO Mild bleeding that does not meet above criteria

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 • Pericardial Effusion

CLINICAL DETERIORATION
Also referred to as hemodynamic collapse[14] 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 mins, 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 SBP>90 mm Hg (including dopamine at the rate of >5 micrograms/kg per minute).

COMPLICATIONS
An undesirable clinical event that could result in Air Embolism, Cardiac Arrhythmia, Arteriovenous Fistula, Blood Loss/Blood Trauma, Bradycardia, Tachycardia, General Discomfort, Tenderness, or Pain, Hemorrhage, Infection (Local or Systemic), Pleural Effusion, Pericardial Effusion, Pulmonary Embolism, Pulmonary Infarction, Pulmonary Artery Injury/Wire Perforation, Damage to Blood Vessel, Distal Embolization, Hematoma, Vascular Thrombosis, Cardiac Valve Injury, Cardiac Perforation, Vessel Spasm, Hemoptysis, Death. Complications may or may not be related to the investigator product(s).

DEEP VEIN THROMBOSIS
A clot in a vein deep under the skin usually in a leg.

DISSECTION
Angiographic evidence of a tear in the arterial wall as defined by the occurrence of intramural hematoma.

DISTAL EMBOLIZATION
Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

ECMO
Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support (ECLS), is a means of providing both cardiac and respiratory support to persons whose heart and lungs are unable to provide an adequate amount of gas exchange to sustain life.

EMBOLI
Blood clots or thrombi transported by blood from a distant source.

PERFORATION
The piercing or rupturing of a blood vessel; perforations can be detected or observed angiographically.

PULMONARY EMBOLISM
A blood clot that dislodges and travels to the lungs resulting in complete or partial occlusion of the pulmonary arteries.

LOW-RISK PULMONARY EMBOLISM[19]
Acute PE in the absence of markers defining massive or submassive PE.

MASSIVE PULMONARY EMBOLISM[19]
Acute PE with presence of one of the following findings:

- Sustained hypotension (systolic BP <90 mm Hg for 15 min or requiring ionotropic support)
- Pulselessness
- Sustained heart rate <40 BPM with signs/symptoms consistent with shock

SUBMASSIVE PULMONARY EMBOLISM[19]
Acute PE with Systolic BP ≥90 mm Hg and RV dysfunction or myocardial necrosis defined by:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on CTA.
- RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT
- Elevation of BNP (B-type natriureic peptide) (>90 pg/mL), or N-terminal pro-BNP (>500 pg/mL)
- EKG changes (new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)
- Elevation of troponin I (>0.4 ng/mL) or troponin T (>0.1 ng/mL)

RECURRENT PULMONARY EMBOLISM
Symptomatic PE objectively confirmed on contrast-enhanced chest CT, ventilation perfusion lung scan, or invasive contrast pulmonary angiography.

PULMONARY VASCULAR INJURY
Pulmonary vascular injury may include the following events occurring in the pulmonary vasculature:

- Arterial Venous Fistula

- Dissection
- Hemorrhage (Intrapulmonary/ Intrapleural)
- Hemoptysis
- Intimal flap
- Perforation
- Rupture
- Thromboembolic occlusion resulting in permanent damage i.e., infarction

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18 ATTACHMENTS

Investigator's Protocol Signature Page:

CLINICAL INVESTIGATION PLAN NUMBER:	2021-EVT-01
CLINICAL INVESTIGATION PLAN TITLE:	Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) $F18^{85}$ PE for Treatment of Acute Pulmonary Embolism.
FINAL CLINICAL INVESTIGATION PLAN:	07/18/2023

I have read this clinical investigation plan and agree to conduct this clinical trial as outlined herein. I will ensure that all sub investigators and other study staff members have read and understand all aspects of this clinical investigation plan. I agree to cooperate fully with AngioDynamics and the CRO during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials during and after study completion.

Principle Investigator Name:

Date:

Signature:

MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) $F18^{85}$ PE for Treatment of Acute Pulmonary Embolism
Protocol Number:	2021-EVT-01
Protocol Version History:	Version 5.1 / 18 July 2023 Version 5.0 / 13 June 2023 Version 4.0 / 15 August 2022 Version 3.0 / 22 February 2022 Version 2.0 / 03 September 2021
Investigational Product:	AlphaVac Multipurpose Mechanical Aspiration (MMA) $F18^{85}$ PE
Sponsor:	AngioDynamics, Inc.
SAP Version/Date:	1.0, 07-Dec-2023

SIGNATURE PAGE

Protocol Title:	Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE for Treatment of Acute Pulmonary Embolism.
Protocol Number:	2021-EVT-01
SAP Version/Date:	1.0, 07-Dec-2023

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature		**Date**
Md Nazir Uddin	*Electronically signed by: Md Nazir Uddin* *Reason: Approved* *Date: Dec 8, 2023 12:47 EST*	
Md Nazir Uddin **Biostatistician** **Medpace, Inc.**		
Ariel Bloch	*Electronically signed by: Ariel Bloch* *Reason: Approved* *Date: Dec 19, 2023 16:32 EST*	
Ariel Bloch **Senior Data Scientist** **AngioDynamics, Inc.**		
Elizabeth Manning	*Electronically signed by: Liz Manning* *Reason: Approved* *Date: Dec 19, 2023 16:34 EST*	
Liz Manning **Director, Clinical Affairs** **AngioDynamics, Inc.**		

VERSION HISTORY

Version	Version Date	Description
1.0	07-Dec-2023	Original signed version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AHC	Accountable Health Communities
ATC	Anatomical Therapeutic Chemical
ADE	Adverse Device Effects
ADAM	Analysis Data Model
AE	Adverse Event
CSR	Clinical Study Report
CTA	Computed Tomography Angiography
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
HRSN	Health- related Social Needs Screening Tool
ICU	Intensive Care Unit
LV	Left Ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Multipurpose Mechanical Aspiration
MAE	Major Adverse Event
PE	Pulmonary Embolism
RCT	Randomized Control Trial
RV	Right Ventricle
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SDTM	Study Data Tabulation Model
TFL	Tables, Figures, and Listings
UADE	Unanticipated Adverse Device Effect

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the AngioDynamics protocol 2021-EVT-01, "Evaluating the Safety and Efficacy of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18^{85} PE for Treatment of Acute Pulmonary Embolism." If circumstances arise during the study such that more appropriate analytic procedures become available, the SAP may be revised. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY DESIGN

2.1 Study Description

This is a prospective, multicenter, single arm study. This study will include up to 122 patients at up to 30 centers in the United States. Each subject will be in the trial for approximately 30 days.

2.2 Device Description

The AngioDynamics' AlphaVac MMA F18^{85} PE has five main components, a flexible cannula (F18^{85}), sheath, tapered obturator, aspirator handle, and waste bag. The AlphaVac MMA F18^{85} PE is a mechanical aspiration thrombectomy device with a nitinol basket reinforced, self-expandable funnel shaped distal tip, that is collapsed using an over-sheath that is advanced though a 22 Fr sheath and over a guidewire into the venous system percutaneously.

2.3 Indication for Use

The AlphaVac MMA F18^{85} PE System is a commercially available device (marketed under K213388). At present, the device is not cleared for the specific submassive acute PE indication for which it is being tested.

Current Indication:

The Cannula is indicated for:

- The non-surgical removal of thrombi or emboli from venous vasculature.
- Aspiration of contrast media and other fluids from venous vasculature.

The Cannula is intended for use in the venous system.

The Handle is indicated as a vacuum source for the AlphaVac MMA System.

During use the cannula is placed within the jugular or one of the common femoral veins and connected to the aspirator handle. Once access is gained, the cannula is advanced under image guidance towards the undesirable intravascular (i.e., thrombus or emboli) until it is engaged, the aspirator is then pulled back creating suction pulling the material into the cannula, removing it from the vasculature. The aspirated material is then moved from the aspiration handle into the waste bag for disposal.

2.4 Study Population

This study will collect data on symptomatic patients with acute intermediate-risk PE. The enrolled patients will be treated with aspiration thrombectomy by the AlphaVac MMA F18^{85} PE.

2.5 Study Enrollment

Patients presenting with signs and symptoms of acute intermediate risk PE will be screened for possible enrollment as a patient into the trial based on Inclusion/Exclusion Criteria.

2.6 Enrollment Procedure

Consecutive patients presenting with acute intermediate-risk PE will be screened for this trial. Those who do not meet the study's Inclusion/Exclusion Criteria will not be enrolled with the reason recorded.

A patient is considered enrolled once the patient informed consent form and HIPAA Authorization are signed by the patient, and in whom the AlphaVac MMA F18[85] PE has been introduced into their body.

Any patient enrolled into the trial, but in whom the AlphaVac MMA F18[85] PE is not able to access a pulmonary embolus is considered an as treated patient and will be monitored per protocol until the end of required follow-up period of 30 days.

Any patient that experiences an adverse event after venous puncture but in whom the Cannula is not inserted will be monitored through discharge for safety.

2.7 Study Objective

The objective of this clinical study is to determine the safety and effectiveness of mechanical aspiration thrombectomy using the AlphaVac MMA F18[85] PE in a prospective trial of patients with acute intermediate-risk PE.

2.8 Study Procedure

All data elements for all subjects will be collected using electronic case report forms (eCRFs). Source data originally captured in electronic format may be used to populate eCRF data fields where possible to reduce unnecessary duplication of data and to reduce the possibility of transcription errors. Data will be entered into the eCRFs at screening, baseline/index procedure, at 48-Hours, discharge, and at 30-days post procedure or until death, and in accordance with the adverse event procedures described below. Sites will be requested to adhere to guidelines for the treatment and monitoring of these subjects. Planned Source Data Verification (SDV) will be 100% for all endpoint-related data.

2.9 Adjunctive Treatment

There may be circumstances for the need to use other treatments to aid the AlphaVac MMA F18[85] PE in recanalizing the targeted vessel. Adjunctive treatments will be considered as a protocol deviation unless used to treat clinical deterioration. These adjunctive treatments will be recorded on the CRF.

3 PRIMARY SAFETY AND EFFICACY

3.1 Primary Endpoints

	Outcome
Primary Efficacy:	Reduction in the right ventricle (RV)/left ventricle (LV) ratio at 48 hours post-procedure assessed by computed tomography angiography (CTA). The primary efficacy analysis will be the difference between the baseline and the 48-hour RV/LV diameter ratio.

Primary Safety:	Rate of major adverse events post-procedure, defined as:
	• Device-related death within 48 hours
	• Major bleeding within 48 hours
	• Device-related serious adverse events (SAEs) within 48 hours, which includes:
	  o Clinical deterioration
	  o Pulmonary vascular injury

	○ Cardiac injury Some examples of major bleeding, clinical deterioration, pulmonary vascular injury, and cardiac injury are defined in the study definitions of Appendix I of the protocol.

3.2 Secondary Endpoints

	Outcome
Secondary Efficacy:	• Length of stay in intensive care unit (ICU)/Hospital setting within 30 days • Use of thrombolytics within 48 hours • Change in Modified Miller Index at 48 hours post-procedure assessed by CTA
Secondary Safety:	• Device-related death within 48 hours • Major bleeding within 48 hours • Clinical deterioration within 48 hours • Pulmonary vascular injury within 48 hours • Cardiac injury within 48 hours • Any-cause mortality within 30 days • Device-related SAEs within 30 days • Symptomatic PE recurrence within 30 days Refer to Appendix I of the protocol for definitions.

3.3 Exploratory Endpoint

This study will collect baseline data to identify unmet social related needs such as housing instability, violence, financial strain, etc. Exploratory analysis may be conducted to evaluate healthcare disparities, unmet healthcare needs with study enrollments and outcomes. Specifically, a linear regression model will be generated to assess if the number of unmet healthcare needs has an impact on the primary efficacy endpoint, namely the change in RV/LV ratio between Screening and 48 Hours Post Procedure.

The accountable health communities (AHC) health-related social needs screening tool (HRSN) will be completed by all enrolled patients at their baseline visit.

4 STATISTICAL METHODOLOGY

4.1 General Considerations

Standard statistical methods will be employed to analyze all data. All data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, including counts, mean, median, standard deviation (SD), minimum and maximum. Where appropriate, 95% two-sided confidence intervals for the means will be presented. Categorical variables will be summarized by frequencies and percentages. Unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of unique patients.

4.2 Determination of Sample Size

This study is designed to assess the efficacy of the AlphaVac MMA F18[85] PE with respect to the primary efficacy endpoint (reduction in RV/LV ratio between baseline and 48 hours post procedure) as well as to

assess the safety of the AlphaVac MMA F18[85] PE with respect to the primary safety endpoint (rate of any major adverse event (MAE) within 48 hours of the procedure).

The safety performance goal is that less than 25% of study subjects experience an MAE (the primary safety endpoint) within 48 hours after the index procedure. This is based on the upper limit of the 95% confidence interval for the average composite MAE rate (16.3%) observed across 7 randomized control trials (RCTs) in which acute PE was treated with thrombolysis versus an anticoagulant control. For this study, the hypothesized composite MAE rate is expected to be approximately 15%. To detect a difference between an expected MAE rate of 15% and the performance goal of 25% with 80% power, the necessary sample size was calculated to be 103 (with a one-sided p-value = 0.05). A sample size of 103 patients was selected as a conservative sample size to assess safety with adequate statistical power. To account for attrition rate of 15%, 122 subjects will be enrolled.

Sample size determination - Safety:

Endpoint	Primary Analysis Population	Assumed Performance of Manual Mechanical Aspiration Catheter	Performance Goal	Power	Sample Size
Rate of Any MAE	As Treated	15%	25%	80%	103

The SAS code for safety sample size calculation is included below:

```
proc power;
onesamplefreq test = z method = normal
sides = 1
alpha = 0.05
nullproportion = 0.25
proportion = 0.15
ntotal = .
power = .80;
run;
```

The efficacy performance goal of 0.12mm reduction in the RV/LV ratio from baseline was calculated using 4 randomized controlled trials that discuss the treatment of acute PE with anticoagulants, which is standard of care. The mean decrease in RV/LV ratio across the 4 trials was 0.12mm. A standard deviation of 0.25mm was based on the standard deviation of the RV/LV ratio observed in the FLARE trial.

Sample size determination – Efficacy:

Endpoint	Primary Analysis Population	Assumed Performance of Manual Mechanical Aspiration Catheter	Assumed Standard Deviation	Performance Goal	Power	Sample Size
Reduction in RV/LV Ratio	Modified as treated	0.20	0.25	0.12	80%	62

The SAS code for safety sample size calculation is included below:

```
proc power;
pairedmeans sides = U
```

```
test = diff
nulldiff = 0.12
meandiff = 0.20
power = 0.8
corr = 0.5
npairs = .
std = 0.25;
run;
```

4.3 Analysis Day

Analysis day will be calculated from the date of the first index procedure. The day of the index procedure will be Day 1 and the day immediately before Day 1 will be Day -1. There will be no Day 0.

4.4 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the eCRF. There are five visits considered for this study: Screening, Baseline/Index Procedure, 48-Hours Post-Procedure, Discharge, and 30 Day Follow-Up. Any unscheduled visits will not be considered for the summary statistics but will be included in listings.

4.5 Definitions of Baseline

Baseline is defined as the last assessment obtained prior to the index procedure.

4.6 Summary Statistics

For tables, categorical data will generally be summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, SD, minimum, and maximum.

In summary tables, data from the scheduled visits, including conditional follow-up visits, will be included.

Listings will include all data from scheduled and unscheduled/End of Study visits and will serve as data sources for all tables and figures.

4.7 Poolability of Data

This study is designed and conducted as a multicenter clinical trial. All participating sites will be selected using the same criteria and trained prior to enrolling subjects. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results. Poolability of the data across centers in a multicenter study is assumed without burden of proof.

Nevertheless, poolability of data across sites will be examined for apparent violation of the poolability assumption.

A logistic regression on the primary safety endpoint and a linear regression on the primary efficacy endpoint will be used to confirm the pooling of data across sites. For each regression model, a test for fixed site effect at the 0.15 alpha level will be used to assess potential heterogeneity. If there is evidence of heterogeneity of sites, a random site-effect model will be used to summarize the associated endpoint. The results of the poolability analysis will be used to assess the robustness of study results, not to change the study conclusion. Sites with fewer than five subjects will be combined and treated as a single site for these analyses.
Sample SAS code for the logistic regression can be found below:

```
/*****************************
MAEDATA is the data set that includes MAE as a binary response variable and
SITE as a categorical predictor variable.

MAE=1,if the subject experienced an MAE
```

```
MAE=0, otherwise
SITE=Study site
*****************************/
proc logistic data = MAEDATA;
class SITE;
model MAE = SITE;
run;
```

The effect of AHC-HRSN will be evaluated through a simple linear regression model. The AHC-HRSN score will be calculated by following the AHC-HRSN manual and will be equivalent to the number of domains in which the subject has an unmet health-related social need.

Sample SAS code for the linear regression can be found below:

```
/*****************************
RVLVDATA is the data set that includes RVLVCHG, a variable representing the
change in RV/LV ratio, and SITE as a categorical predictor variable.

RVLVCHG=Change in RV/LV ratio at 48 hours post procedure from baseline
SITE=Study site
AHC_HRSN=1, if subject's AHC-HRSN score > median score
AHC_HRSN=0, if subject's AHC-HRSN score ≤ median score
*****************************/
PROC GLM DATA = RVLVDATA;
  CLASS SITE;
  MODEL RVLVCHG = SITE AHC_HSRN;
  RUN;
```

4.8 Handling Missing Data

Missing data are defined as data that are expected to be collected but are not available for the study at the time of the final analysis. In this study, missing data will not be imputed nor handled with the last observation carried forward. In general, data will be analyzed as they are recorded with the following specific methods apply to defining and handling missing data.

- Patients who drop out before study completion will not be replaced and all information obtained from them will be included in the analysis.
- Missed visits: If a patient missed a visit, information to be collected during that visit is considered as missing data. Patients with a missing visit will be removed from the analysis for that visit. For example, subjects without a 30-Day follow-up visit will not be included in the analysis of the symptomatic PE recurrence secondary endpoint.
- Missing Data: We expect relatively few patients to be missing the primary endpoints due to withdrawal or refusal due to the short study follow-up period. The Electronic Data Capture (EDC) supports efficient data collection and management and facilitates rapid data closure. The frequency of missing data can be reduced by two mechanisms: the coordinators will receive a list of queries generated by the study monitors upon logging into the system, and any data required during a visit is immediately evident through the system and can be collected before closure of the visit window. Despite the screening and ongoing communication with patients regarding the importance of study endpoint assessment, we anticipate no more than 15 % of subjects will be missing primary endpoint assessments due to technical issues/low-quality of the diagnostic pulmonary CTA images, procedural mortality, withdrawal, or refusal to continue participation in the study or lost to follow-up. Patients missing primary endpoint assessments due to lost to follow-up are accounted for in the sample size calculation.

4.9 Analysis Populations

4.9.1 As Treated Population

The As Treated population includes all subjects who met the inclusion/exclusion criteria and in whom the F18[85] cannula is placed within the jugular or one of the common femoral veins. This population will serve as the primary analysis set for all safety endpoints and supportive analysis set for all efficacy endpoints.

4.9.2 Modified As Treated Population

The Modified as Treated population includes all subjects in the as treated population who did not receive thrombolytics during the index procedure. This population will be used as the primary analysis set for all efficacy endpoints.

4.9.3 Per Protocol Population

Per Protocol population includes all subjects in the Modified As Treated population who had no major protocol deviations. This population will serve as a supportive analysis cohort for all efficacy endpoints.

4.10 Subject Data

4.10.1 Subject Disposition

Counts and percentages of participants who completed the study, discontinued from the study along with the reason for discontinuation from study will be summarized for all population as defined in Section 4.9.

A by-participant listing will be provided.

4.10.2 Protocol Deviations

Protocol deviations will be identified based on the clinical data as defined in the Protocol Deviation Plan. The Protocol Deviation Plan will define all protocol deviations as either major or minor deviations. Patients with protocol deviations will be summarized in a table by deviation category and deviation type as well as in data listings. All enrolled patients will be included in the reporting of protocol deviations. The summarization will be repeated for all population as defined in Section 4.9.

4.10.3 Analysis Population

Counts and percentages of subjects in each analysis population will be summarized.

4.10.4 Demographic Characteristics

The following demographic characteristics will be summarized:

- Age (years)
- Gender
- Race
- Ethnicity
- Smoking status
- Year of smoking
- Cigarettes/day

Demographic information will be summarized with descriptive statistics or counts and percentages of subjects, as appropriate for all population defined in Section 4.9.

4.10.5 Medical History

Counts and percentages of participants with relevant medical history will be summarized by category and condition based on the as treated population. In addition, all other medical history will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Participants will be counted only once for each system organ class and preferred term level. The summarization will be repeated for all population as defined in Section 4.9.

4.10.6 Concomitant Medications

Concomitant medications are defined as any medication that was used at least once after the administration of the study device. Medications that were stopped on the same date as the administration of the study device will be analyzed as concomitant medications.

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug B3.

Counts and percentages of participants taking concomitant medications by ATC class and preferred term will be summarized using the as treated population. Participants who used the same medication on multiple occasions will only be counted once in the specific category (preferred term). The summarization will be repeated for all population as defined in Section 4.9.

4.11 Efficacy and Safety Assessment

The analysis for all efficacy endpoints will be performed based on the Modified As Treated population. Supportive analysis for all efficacy endpoints will be performed based on the As Treated population and the Per Protocol population. The analysis for all safety endpoints will be performed based on the As Treated population.

4.11.1 Primary Efficacy Endpoints Analysis

The primary efficacy analysis will be the reduction in the RV/LV ratio between Baseline and 48 hours post procedure. The mean reduction in the RV/LV ratio will be compared to a performance goal of 0.12mm. The hypothesis for reduction from baseline in RV/LV ratio is as follows:

$$H_0: R_{diff} < 0.12$$
$$H_1: R_{diff} \geq 0.12$$

Where, R_{diff} is the mean reduction in the RV/LV ratio between Baseline and 48 hours post procedure. The mean reduction in the RV/LV ratio will be compared to the performance goal of 0.12mm using a paired samples t-test with a significance level of 0.05.
Sample SAS code for the paired sample t-test can be found below:

```
/*************************************
Note:
BASE=RV/LV ratio at baseline
POSTHRS=RV/LV ratio at 48 hours post baseline
*************************************/
proc ttest data=RVLVDATA sides=u alpha=0.05 h0=0.12;
      title "Paired sample t-test";
      paired BASE * POSTHRS;
   run;
```

4.11.2 Primary Safety Endpoint Analysis

The primary safety analysis will be the rate of any MAE within the first 48 hours after the index procedure.

MAEs are defined as:

- Device-related death
- Major bleeding
- Device-related serious clinical deterioration
- Device-related serious pulmonary vascular injury
- Device-related serious cardiac injury

Examples of major bleeding, clinical deterioration, pulmonary vascular injury, and cardiac injury are defined in Appendix I of the protocol.
The proportion of subjects who experienced any MAE within 48 hours will be compared to a performance goal of 25%. The hypothesis for the rate of any MAE is as follows:

$$H_0: MAE > 0.25$$
$$H_1: MAE \leq 0.25$$

Where MAE is the proportion of subjects who experienced any MAE within 48 hours of the procedure.
The rate of any MAE within 48 hours of the procedure will be compared to the performance goal of 25% using a one sample proportion test with a significance level of 0.05.

Sample SAS code for one sample proportion test can be found below:

```
/*************************************
Note:
IMAE='Yes' if subject had an MAE
IMAE='No' No MAE
*************************************/
proc freq data=MAEDATA;
 tables IMAE / binomial(p=0.25 level="Yes");
run;
```

4.11.3 Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoints will include the following:

1. Length of stay in ICU/Hospital setting within 30 days
2. Use of thrombolytic within 48 hours of the index procedure
3. Change in Modified Miller Index between baseline and 48 hours of the index procedure

Length of stay in the ICU/Hospital setting within 30 days and the change in Modified Miller Index will be summarized descriptively. Point estimates will be reported. For all other secondary efficacy endpoints, the number and proportion of patients who experienced each endpoint will be presented.

4.11.4 Secondary Safety Endpoint Analysis

1. Major bleeding within 48 hours
2. Device-related death within 48 hours
3. Device-related clinical deterioration within 48 hours
4. Device-related pulmonary vascular injury within 48 hours
5. Device-related cardiac injury within 48 hours
6. Any-cause mortality within 30 days
7. Device-related serious adverse events within 30 days
4. Symptomatic recurrence of PE at 30 days (Recurrent pulmonary embolism is defined in the Study Definitions of Appendix I of protocol).

The number and proportion of patients who experienced each of the secondary safety endpoints will be presented.

4.11.5 Subgroup Analysis

Subgroup analyses are exploratory in nature and may include demographic information, baseline characteristics, and other factors to be determined after the study team reviews the final analyses of primary and secondary endpoints.

4.11.6 Sensitivity Analysis

Sensitivity analyses may be performed on the primary efficacy and primary safety endpoints to describe the potential impact of missing data on the observed study results. Subjects missing the primary efficacy endpoint and/or primary safety endpoint will be imputed using best-case and worst-case analyses. For subjects missing the primary efficacy endpoint, best-case imputation will use the best observed change in RV/LV ratio at 48 hours post procedure in the study population. Worst-case imputation of the primary efficacy endpoint will use the worst observed change in RV/LV ratio at 48 hours post procedure in the study population. For subjects missing the primary safety endpoint, best-case imputation will assume the subject did not experience an MAE within the first 48 hours after the procedure. Worst-case imputation of the primary safety endpoint will assume the subject did experience an MAE within the first 48 hours after the procedure.

Further, a tipping point analysis may be performed to assess sensitivity without need for postulating a specific set of assumptions regarding missing data. Missing data for the RV/LV ratio will be imputed for the primary efficacy analysis using multiple imputation methodology in two steps. Initially, 25 data sets will be imputed for non-monotone missing values in the original dataset. In the second step, the remaining monotone missing values will be imputed. Generally, the number of imputations should be at least as much as the percentage of cases that are incomplete. Therefore, twenty-five imputations were selected for the primary analysis. Upon completion of the trial, if the percentage of cases with incomplete data is larger than initially anticipated then the number of imputations will be increased for the final analysis.

The variable for the imputation model will consist of the RV/LV ratio at Baseline. For each imputation dataset, the mean reduction in the RV/LV ratio between Baseline and 48 hours post procedure will be analyzed using the paired t-test model described above. The results from these 25 analyses will be combined to construct the mean estimates using the parameter estimates and associated standard errors. The combined parameter estimates will then be used to test the hypothesis for the reduction from baseline in RV/LV ratio as described above (meaning, against a hypothesis test cut-off value of 0.12). Randomly chosen seed numbers will be selected for the analysis and will be retained.

The analysis will be performed using a tipping point approach under the missing not at random assumption by adding a shift (delta) to the RV/LV ratio at 48 hours post procedure. The delta values will range from -1.0 to 1.0 by 0.05 increments. If the tipping point (i.e., delta value for which statistical significance is lost) is outside of this range, it will be extended to the value at which statistical significance is lost, as appropriate.

Example SAS® code for performing this analysis is as follows:

```
/*************************************
Multiple Imputation for Non-Monotone missing values
Assuming a shift of 0.00 that will be adjusted up or down during the tipping
point analysis
Note:
BASE=RV/LV ratio at baseline
POSTHRS=RV/LV ratio at 48 hours post baseline
*************************************/
proc mi data=RVLV_temp seed=12141619 out=data_impMCMC nimpute=25;
   var BASE POSTHRS;
```

```
   mcmc impute=monotone chain=single;
run;
proc mi data=data_impMCMC seed=07071107 out=data_impMONO nimpute=1 simple;
   by _Imputation_;
   monotone reg;
   var BASE POSTHRS;
   mnar adjust (POSTHRS / shift=0.00);
run;

/*************************************
Paired T-test
*************************************/
ods select none;
proc ttest data= data_impMONO sides=u alpha=0.05;
      by  _Imputation_ ;
      paired BASE * POSTHRS;
      ods output Statistics = ttest_parms;
run;
ods select all;

/*************************************
MIANALYZE to combine results of imputed data sets
*************************************/
proc mianalyze data=ttest_parms theta0=0.12;
   modeleffects mean;
   STDERR stderr;
   ods output ParameterEstimates = mi_parms;

run;
```

If there is evidence of non-normality of the primary efficacy endpoint based on a Shapiro-Wilk test at the 0.05 alpha level, a non-parametric sign test will be used.

4.12 Safety Assessment

4.12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects whether or not related to the Investigational Product and includes events related to the procedures involved (any procedure in the clinical investigation plan). Safety events will refer to all peri procedural MAEs, serious AEs (SAEs), Major AEs (MAEs), adverse device effects (ADEs) (including serious adverse device effects [SADEs]), and (severe) unanticipated adverse device effects (UADEs/SUADEs). A detailed description of the how AEs are identified and reported can be found in Section 10.1 in the protocol.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects in the As Treated population who experience each AE will be summarized by MedDRA system organ class and preferred terms. Adverse events will also be presented in by-participant listings.

4.12.2 Serious Adverse Events

Serious AEs are a subset of AEs. An SAE is one that:

1. Results in death
2. Results in life-threatening illness or injury
3. Results in a permanent impairment of a body structure or function

4. Requires inpatient hospitalization or prolongation of an existing hospitalization
5. Results in a medical or surgical intervention in order to prevent a permanent impairment to a body structure or function, or
6. Results in fetal distress, fetal death, or a congenital abnormality or birth defect
7. Important medical event

4.12.3 Adverse Device Effects

Adverse device effects (ADEs) are a subset of adverse events. The ADEs are AEs caused by or related to thrombectomy procedure performed by the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE (possibly, probably and definitely related), including any AE resulting in a malfunction of the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE or any event that is a result of a use error or intentional misuse. With any procedure or treatment, there are known possible risks and complications. With the AlphaVac Multipurpose Mechanical Aspiration (MMA) F18[85] PE, all risks known for the proposed indication can be found in Section 10.11 of the protocol. A list of precautions and warnings concerning the use of the device is found in the device's IFU.

4.12.4 Unanticipated Adverse Device Effects (UADE)

Overall summary statistics and by participant listings will be provided.

4.12.5 Adverse Event Severity

Overall summary statistics and by participants listings will be provided for all adverse events by maximum severity.

4.12.6 Deaths

Overall summary statistics and by participants listings will be provided for all deaths.

4.12.7 Device Malfunctions

Overall summary statistics and by participants listings will be provided for all device malfunctions.

4.13 Clinical Laboratory Tests

Results of clinical laboratory tests will be descriptively summarized. Laboratory test results at each scheduled visit as well as changes from baseline for each test will be displayed. Shift tables showing the categorical results at baseline and 48 hours post procedure will also be provided.

By-participant listings will be provided by clinical laboratory test, and values outside the reference ranges will be flagged.

4.14 Vital Signs

Vital sign parameters including height, weight, body mass index (BMI), blood pressure, shock index, heart rate, respiratory rate, body temperature, oxygen saturation, and FiO2 will be summarized descriptively.

By-participant listings will also be provided.

5 INTERIM ANALYSIS

There are no planned interim analyses for the purposes of early stopping for success, sample size modification, or other trial design changes. Analyses of accruing data for regulatory submissions in different geographies may be performed at different points during the study. These analyses are only intended to support geographic specific regulatory requirements. Since there is no planned early stopping or sample size adjustment planned, there are no type I error concerns.

To protect against the introduction of operational bias, distribution of aggregate results from such analyses will be restricted on a "need-to-know" basis. Access to aggregate results will be restricted to those persons necessary to complete the associated regulatory submission. Aggregate results will specifically not be provided to study sites, investigators, or staff or to those involved with the management of the study.

6 DATA MONITORING COMMITTEE

A data monitoring committee (DMC) will be established to review cumulative study data to evaluate safety (interim and cumulative data for AEs), study conduct, and scientific validity and integrity of the trial. The DMC will consist of at least 3 independent subject matter experts who will be voting members and a Statistician (voting or non-voting). The three voting members will be physicians not associated with the study in any capacity or have any affiliations with the study sponsor or sponsor's designee, and without any direct business associations with the principal investigator of the trial. The physicians may be selected from different disciplines but with an understanding of the study population and procedures. None of the members will have direct involvement in the conduct of the study or have any conflict of interests. The initial DMC meeting will develop the DMC Charter which will contain operational details including schedule for meetings, triggers set for data review or analyses, definition of a quorum, and stopping rules for safety.

The conduct of the DMC will be guided by the Food and Drug Administration guidance on the "Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors." The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the coordinating Investigator(s).

7 CLINICAL ENDPOINT COMMITTEE

An independent CEC will be established for the purpose of reviewing clinical endpoints including safety and/or effectiveness data. The CEC will consist of medical doctors who will not have direct involvement of the conduct of the study. The CEC will meet regularly to review and adjudicate appropriate adverse events for causality and attribution.

8 END OF STUDY ANALYSIS

Upon completion of the study, the database will be locked, and the final analysis will be generated. The end of study analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP. In addition to TFLs, standard data tabulation model (SDTM) data and ADaM data along with associated files will be provided. Associated files may include the following: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, analysis data model (ADaM) programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

The results of this analysis will be used for the CSR.

9 CHANGE FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSIS

This SAP does not deviate from the statistical analysis described in v5.1 of the protocol. Any deviations from the protocol or SAP will be described in the CSR.

10 PROGRAMMING SPECIFICATION

Analyses will be performed using SAS® version 9.4 or higher.

All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed programming specifications will be provided in the separate documents.