COVERSHEET

The Aortix™ CRS Pilot Study

An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome

Protocol	PVP017
NCT#	NCT04145635
Title	Clinical Investigation Plan, Version G
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Clinical Investigational Plan

The Aortix™ CRS Pilot Study

An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome

Protocol Number	PVP017
Version	G
Sponsor	Procyrion Inc 3900 Essex Lane, Suite 850 Houston, TX 77027 USA
Australian Sponsor	Procyrion Australia Pty Ltd C/O Prime Accounting & Business Advisory Floor 17, HWT Tower 40 City Road Southbank, VIC, 3006

Revision History Table		
Rev.	**Description of Change**	**Effective Date**
A	Initial Release.	31-May-2018
B	Added Australian sponsor information; updated device descriptions including indication for use; updated study duration; replaced study flow chart; significantly revised Study Procedures; updated risk, safety and adverse event wording; significant updates to data collection requirements.	06-Sept-2019
C	Clarified a few inclusion/exclusion criteria; added echo parameters; minor edits and clarifications.	01-Oct-2019
D	Clarified objective wording; added endpoints; revised inclusion/exclusion criteria; revised protocol to provide more clarity on data collection requirements.	17-Feb-2020
E	Clarified wording; added information to patient withdrawal section; updated lowest pump speed to 18krpm. Added wording to section 4 to further explain required data collection specified in Appendix A. Added clarifications to Appendix A and updated Appendix B. Modifications to wording for inclusion/exclusion criteria.	14-Feb-2021
F	Corrected anticoagulation ACT value, included wording for vascular steal	19-Apr-2021
G	Clarified wording; updated exclusion criteria; modified schedule of assessments and data collection.	24-July-2021

INVESTIGATOR STATEMENT

Study Product Name	The Aortix System
Clinical Investigation Plan Identifier	PVP017
Version	Rev G
I have read and have been trained on the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Procyrion. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Procyrion. I will discuss this material with them to ensure that they are fully informed about the product and the study.	
Investigator's Signature:	
Investigator's Name (PRINT):	
Institution:	
Date:	

Abbreviations

ACC — American College of Cardiology

ACS — Aortix Control System

ACT — activated clotting time

ADE — adverse device effect

ADHERE — Acute Decompensated Heart Failure National Registry

ADHF — acute decompensated heart failure

ADS — Aortix Delivery System

AE — adverse event

AF — atrial fibrillation

AHA — American Heart Association

AKI— acute kidney injury

AKIN — acute kidney injury network

AP — anterior-posterior

aPTT — activated partial thromboplastin time

AR — aortic regurgitation

ARS — Aortix Retrieval System

ASA — aspirin

ASADE — Anticipated Serious Adverse Device Effect

AWS CLI — Amazon Web Services Command Line Interface

BARC — Bleeding Academic Research Consortium

BNP — Brain Natriuretic Peptide (or b-type Natriuretic Peptide)

BP — blood pressure

BUN — blood urea nitrogen

CBC — complete blood count

CEC — clinical events committee

CFR — Code of Federal Regulations

CMP — comprehensive metabolic panel

CO — cardiac output

CPO — cardiac power output

CPT — Current Procedural Terminology

Cr — creatinine

CRF — case report form

CRRT — continuous renal replacement therapy

CRS — cardiorenal syndrome

CT — computed tomography

CVP — central venous pressure

EC — Ethics Committee

ECMO — extracorporeal membrane oxygenation

eCRF — electronic case report form

EDC — electronic data capture

EF — ejection fraction

eGFR — estimated glomerular filtration rate

eIFU — electronic instructions for use

EMI – Electromagnetic Interference

EO — Ethylene Oxide

EQ5D — the EuroQol-5D, an instrument developed in Europe and widely used, which evaluates the generic quality of life.

F, FR — French (size)

FIH — first-in-human

GI — Gastrointestinal

Hb — hemoglobin

HCPCS — The Healthcare Common Procedure Coding System

Hct — hematocrit

HFpEF — heart failure with preserved ejection fraction

HFrEF — heart failure with reduced ejection fraction

HFmEF— heart failure with mid-range ejection fraction

Hgb — hemoglobin

HIPAA — Health Insurance Portability and Accountability Act

HIT — Heparin Induced Thrombocytopenia

HITRUST — a privately held company located in Frisco, Texas, that, in collaboration with The HITRUST CSF is a prescriptive set of controls that was designed to meet the requirements of multiple regulations and standards provides a way to comply with standards such as ISO/IEC 27000-series and HIPAA.

HR — heart rate

HR-PCI — high risk percutaneous coronary intervention

IABP — intra-aortic balloon pump

ICD-10 — 10th revision of the International Statistical Classification of Diseases and Related Health Problems, a medical classification list by the World Health Organization

ICH — International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICMJE — International Committee of Medical Journal Editors

ID — inner diameter

IEC — independent ethics committee

INR — International Normalized Ratio

INTERMACS — Interagency Registry for Mechanically Assisted Circulatory Support

IRB — Institutional Review Board

IS — Introducer Set

ISO 14155 — Clinical investigation of medical devices for human subjects – Good clinical practice

IT — Information Technology

IU/L — International Units Per Litre

IV — intravenous

KCCQ — Kansas City Cardiomyopathy Questionnaire

LA — left atrial

LDH — lactate dehydrogenase

LFTs — liver function test

LVAD — left ventricular assist device

LVEDV — left ventricular end-diastolic volume

LVESD — left ventricular end-systolic dimension

LVESV — left ventricular end-systolic volume

MAP — mean arterial pressure

MCS — mechanical circulatory support

MR — mitral regurgitation

NSAIDS — nonsteroidal anti-inflammatory drugs

NT-pro-BNP — N-terminal pro b-type Natriuretic Peptide

NYHA — New York Heart Association

OD — outer diameter

PA — pulmonary artery

PAC — pulmonary artery catheter

PAP —pulmonary artery pressure

PCWP — pulmonary capillary wedge pressure

pfH — Plasma free hemoglobin

PICF — patient information and consent form

QoL — quality of life

RBCs — red blood cells

RPM — revolutions per minute (1,000 RPM = 1KRPM)

RR — respiratory rate

RVIDD — right ventricular internal diameter in diastole

SADE — serious adverse device effect

SAE — serious adverse event

SSAE 16 — Statement on Standards for Attestation Engagements no. 16

SV — stroke volume

TAPSE — tricuspid annular plane systolic excursion

TAVR — transcatheter aortic valve replacement

TLS — transport layer security

TR — tricuspid regurgitation

UADE — unanticipated adverse device effect

UFH — unfractionated heparin

UOP — urine output

USADE — unanticipated serious adverse device effect

VAD — ventricular assist device

VARC — The Valve Academic Research Consortium

WRF — worsening renal function

Summary and General Information

Title:	The Aortix CRS Pilot Study: An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome
Investigational Plan:	PVP017
Investigational Device:	The Aortix System
Study Design & Purpose:	The study is a prospective, multi-center, non-randomized feasibility study to evaluate the safety and performance of the Aortix System in patients hospitalized with acute decompensated heart failure (ADHF) irrespective of ejection fraction and worsening renal function refractory to medical management with persistent congestion.
Objectives:	To evaluate the Aortix System, specifically to assess: ▪ Safety: o Observe the nature, severity, and frequency of adverse events associated with the delivery, use, and retrieval of the Aortix Pump. ▪ Performance: o Successfully deliver the Aortix Pump to the descending thoracic aorta using the Aortix Delivery System; o Aortix Pump shall function as programmed for the duration of therapy; o Manage the Aortix Pump Power Lead and access site over the course of therapy without significant complications; o Successfully retrieve and remove the Aortix Pump using the Aortix Retrieval System. ▪ Effectiveness: o Evaluate hemodynamic decongestion (CVP, PCWP) during Aortix therapy; o Evaluate the effect of the Aortix therapy on kidney function; o Evaluate the impact of the Aortix Pump on clinical biomarkers of congestion.
Patient Population:	This study will enroll up to 60 patients in order to treat 30 patients using Aortix with ADHF (irrespective of ejection fraction) refractory to medical management with persistent clinical signs of congestion and worsening renal function.

Inclusion Criteria:

1) Admitted to the hospital with a primary diagnosis of acute decompensated heart failure, either heart failure with reduced or preserved ejection fraction (HFrEF, HFpEF or HFmEF);
2) Worsening renal function (serum creatinine increase by ≥0.3 mg/dl [≥27 µmol/L]) despite 48 hours of intravenous diuretic therapy. Increase can be compared to a baseline value taken within 90 days of hospitalization or during hospitalization;
3) Objective measure of congestion (Elevated PCWP [≥20 mmHg] OR Elevated CVP [≥12 mmHg]) obtained via catheter measurement;[i]
4) Persistent clinical signs and/or symptoms of congestion despite diuretic therapy (one or more of the following):
    a) dyspnea at rest or with minimal exertion,
    b) paroxysmal nocturnal dyspnea,
    c) orthopnea,
    d) lower extremity edema (≥2+),
    e) elevated jugular venous pressure,
    f) pulmonary rales,
    g) enlarged liver or ascites,
    h) pulmonary vascular congestion on chest x-ray;
5) Age >21 years and able to provide written informed consent.

Exclusion Criteria:

1) Treatment with high dose IV inotropes within the last 48 hours. High dose is defined as > 1 unit of inotrope (excluding digoxin) as follows:
   5 µg/kg/min dopamine = 1 unit,
   5 µg/kg/min dobutamine= 1 unit,
   0.375 µg/kg/min milrinone = 1 unit,
   (for example, dopamine 2.5 µg/kg/min + dobutamine 2.5 µg/kg/min = 1 unit; dobutamine 2.5 µg/kg/min + milrinone 0.1875 µg/kg/min = 1 unit);
2) Treatment with vasopressors to maintain blood pressure as per exclusion #3;
3) Active and ongoing hypotension defined as a systolic blood pressure < 90 mmHg lasting more than 30 minutes or a mean arterial pressure (MAP) < 60 mmHg lasting more than 30 minutes;
4) Acute Kidney Failure defined as increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) within the last 48 hours before enrollment;
5) Exposure to intravenous contrast, aminoglycosides or high dose NSAIDS in the 48 hours before enrollment;
6) Known or suspected contrast induced nephropathy;

[i] This assessment requires patient to sign informed consent.

7) Prior kidney transplant, isolated single kidney, stage V Chronic Kidney Disease (eGFR ≤15) at admission OR use of dialysis, continuous renal replacement therapy (CRRT) or aquapheresis (ultrafiltration) in last 90 days;
8) Urologic intervention (except indwelling urinary (Foley) catheter)) within the last 7 days;
9) Known cirrhosis or shock liver;
10) Presence of an active infection;
11) Prior heart transplant in the last 2 years, heart failure due to rejection of a previous heart transplant, planned heart transplantation before the 30-day follow-up visit;
12) Current or previous support with a durable LVAD at any time or use of an intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), or percutaneous ventricular assist devices (e.g. Impella or TandemHeart) currently or within the last 30 days;
13) Patient has known hypo- or hyper coaguable state such as disseminated intravascular coagulation or heparin induced thrombocytopenia (HIT);
14) Known cardiac amyloidosis;
15) Acute myocardial infarction Type 1 within 30 days of enrollment, or planned coronary revascularization;
16) Stroke within 30 days of enrollment;
17) Severe Bleeding Risk (any of the following):
    a) Previous intracranial bleed unless there is documentation in the medical record (from a physician that is not part of the study) that the patient can safely use anticoagulation for 7 days,
    b) GI bleeding within 6 months requiring hospitalization and/or transfusion,
    c) Recent major surgery within 6 months if the surgical wound is judged to be associated with an increased risk of bleeding,
    d) Endovascular procedure with ilio-femoral access > 6 FR within 30 days,
    e) Platelet count <75,000 cells/mm^3, [ii]
    f) Uncorrectable bleeding diathesis or coagulopathy (e.g. INR ≥2 not due to anticoagulation therapy);
18) Current endovascular stent graft in the descending aorta or any femoro-iliac vessels;
19) Contraindicated Anatomy:[iii]
    a) Descending aortic anatomy that would prevent safe placement of the device [<18mm or >31mm aorta diameter at deployment location

[ii] If patient doesn't have a, b, c, d or f, but the platelet count at time of enrollment is <75,000 cells/mm3, patient can be enrolled and the platelet count re-assessed at the time of the procedure. The platelet count at time of procedure should be ≥75,000 cells/mm^3. If platelet count at time of procedure is <75,000 cells/mm^3, patient would be a screen failure.
[iii] Anatomy assessment requires patient to sign informed consent.

(measured between the superior aspect of the T10 vertebra and superior aspect of the L1 vertebra)],

b) Ilio-femoral diameter or peripheral vascular anatomy that would preclude safe placement of a 21F (outer diameter) introducer sheath,

c) Abnormalities or severe vascular disease that would preclude safe access and device delivery (e.g. aneurysm with thrombus, marked tortuosity, significant narrowing or inadequate size of the abdominal aorta, iliac or femoral arteries, or severe calcification),

d) Known connective tissue disorder (e.g. Marfan Syndrome) or other aortopathy at risk of vascular injury;

20) Known hypersensitivity or contraindication to study or procedure medications (e.g. anticoagulation therapy) or device materials (e.g. history of severe reaction to nickel or nitinol);
21) Positive pregnancy test if of childbearing potential;
22) Participation in any other clinical investigation that is likely to confound study results or affect the study;
23) Unable or unwilling to undergo screening (imaging, PA Catheter placement), device implant and retrieval procedures.

Follow-up schedule: Patients with the pump successfully implanted will be followed for 30 days (± 7 days) post device retrieval for protocol required data collection. Patients with the pump implanted will be followed for adverse events for 30 days (± 7 days) post device retrieval. Patients that have an attempted implant but do not have the pump implanted will be followed for adverse events for 30 days (± 7 days) post attempted implant. If implanted or attempted implant patients are still hospitalized at 30 days due to an adverse event relating to the device or any study related procedures, they must be followed until resolution of the adverse event, resolution with sequelae, or until a terminal event.[iv] Patients who are enrolled and undergo anatomy screening and/or invasive hemodynamic measurements who do not have an attempted implant will be followed for adverse events for 7 days (± 2 days) post anatomic screening or invasive hemodynamics (whichever is later) or until hospital discharge, whichever is first.

Study Duration: It is expected that study patients will be enrolled over a period of approximately 12-24 months within Australia and the USA. The total duration of a patient's participation in the study is approximately 1.5 months including screening, enrollment, therapy and follow-up.

[iv] Terminal events are death, LVAD implantation, heart and/or kidney transplantation, dialysis, ultrafiltration or CRRT.

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Australian Sponsor:	Procyrion Australia Pty Ltd C/O Prime Accounting & Business Advisory Floor 17, HWT Tower 40 City Road Southbank, VIC, 3006

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1. Introduction and Rationale

1.1 Background

In partnership with clinical experts, Procyrion, Inc. (Procyrion) has developed a partial Mechanical Circulatory Support (MCS) system to treat patients with Acute Decompensated Heart Failure (ADHF).

Heart failure (HF) is common, affecting more than 6 million adults and resulting in over 1 million annual hospitalizations in the United States alone.[1] HF is a chronic, progressive condition, marked by episodes of acute decompensation typically requiring hospitalization for stabilization and improvement in symptoms. Unfortunately, outcomes after a hospitalization for decompensated heart failure are poor. The 1-year mortality rate after a heart failure hospitalization has remained high at 20-30%,[2] and there is additive risk with each subsequent hospitalization.[3,4]

For patients with chronic, stable HF there are multiple pharmacologic and device-based treatment options.[1,5–7] However, for patients with ADHF, many medical therapies have been tested in this patient population without success[8–10] and, as a result, acute HF care remains largely homogenous and unchanged over the past 40 years.[11,12] The majority of acute HF patients are treated with intravenous loop diuretics with consideration of vasodilator therapies.[13] High-risk patients with decompensated HF failing conventional therapies are rarely (<2%[14,15]) considered for temporary or permanent MCS due to a lack of evidence in this population, risk, and cost.[11] Positive inotropes are similarly uncommon, used in only 6-12% of these patients due to evidence showing worsened outcomes and higher mortality.[16,17] Despite optimal medical therapy, 33% of ADHF patients are discharged with persistent congestion.[18]

Some degree of renal dysfunction occurs in 91% of ADHF admissions, with 64% of patients having at least moderate (Stage III) dysfunction.[16] These patients represent a particularly high-risk population with poor outcomes. Data from the ADHERE registry of over 110,000 ADHF admissions showed that in-hospital mortality increased from 1.9% for patients with normal renal function to 7.6% in patients with severe dysfunction.[16] In these patients, outcomes are poor due to persistent congestion (90% have persistent congestion after 3 days of pharmacologic therapy[19]), increased dose of diuretics,[20] and decreased diuretic efficiency.[21]

Cardiorenal syndrome (CRS) encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. The pathophysiology underlying CRS is poorly understood and probably multifactorial, reflecting underlying renal dysfunction from heart failure and other conditions, side effects of acute therapies including diuretics, impaired renal perfusion, and renal congestion.[22] The degree of renal dysfunction has not been shown to be directly correlated with the degree of left ventricular systolic dysfunction (reduced ejection fraction), and may also be associated with diastolic dysfunction (preserved ejection fraction). Therefore, the renal dysfunction represents a separate and distinct risk factor for patients with heart failure resulting in reduced (HFrEF) or preserved (HFpEF) ejection fraction patients.[16] Therapies that reduce congestion without causing worsening renal function (WRF) have been elusive, as evidenced from the data in recent trials using low-dose dopamine and nesiritide.[23] There is an urgent need to develop new treatment strategies that will favorably alter the course of this common condition. In fact, the most recent version of the ACC/AHA Heart Failure Guidelines identified the lack of recognition and

treatment of CRS as a key gap in heart failure knowledge and evidence.[11] A clinical need exists for a minimally invasive device for treating HF that provides both cardiac and renal support to improve outcomes in the ADHF patient population.

Existing percutaneous impeller pumps and pulsatile balloon pumps placed in the heart have not been shown to be effective in this patient population. Additionally, existing continuous flow percutaneous impeller pumps are placed across the aortic valve, lack sufficient anchoring for patient mobility and safety, and have a high incidence of hemolysis.[24]

The investigational device, the Aortix System, includes an electrically driven micro-pump with an integrated nitinol stabilization system. The 18F device is deployed trans-femorally to the descending thoracic aorta where the struts, once deployed, expand to stabilize the Aortix Pump to the vessel wall. Once implanted and activated, the Aortix Pump is designed to reduce load on the heart and increase end-organ perfusion, in particular improving flow to the kidneys. When therapy is complete, the device is retrieved via catheter in a similar procedure.

The Aortix System has undergone extensive pre-clinical verification and validation studies to confirm device performance and safety requirements following internationally recognized standards and guidance. The Aortix System has also been tested *in vivo* using large-animal (porcine and ovine) models, successfully demonstrating deployment, retrieval, and acute efficacy. Initial safety and efficacy data were obtained in a porcine model and demonstrated proof of concept (n=9).[25] In an ovine model of chronic HF (n=4), the Aortix Pump decreased the energy consumption of the heart by 39%, shifting it to a more efficient operating point. Cardiac output (+14%) and ejection fraction (+28% [relative]) were significantly increased, as were key measures of renal function, eGFR (+23%) and urine output (+100%). These *in vivo* data supported the use of the Aortix System in a first-in-human (n=6) study for acute use during high risk percutaneous coronary intervention (HR-PCI) which demonstrated procedural and device feasibility and safety followed for 14 days.

1.2 Clinical Experience

Procyrion completed a first-in-human (FIH) study (n=6) with the Aortix System in the setting of high-risk percutaneous coronary intervention (HR-PCI) procedures.[26] The mean number of lesions treated during the procedure was 1.5 (range 1-4).

The Aortix Pump supported the patients during the HR-PCI procedure and was removed at the end of the procedure. The Aortix Pump operated for an average of 70 min (range 47-95) and was deployed in less than 10 minutes in all cases with no device failures. The Aortix Pump operated continuously at an average of 3.5 L/min of estimated pump flow. Angiographic success was achieved in all patients and no episodes of hemodynamic compromise or hemolysis occurred on Aortix Pump support.

Safety, procedural, and efficacy outcomes were assessed. No adverse events or safety issues occurred, and the study generated clinical data suggesting that the Aortix Pump improved both hemodynamics and kidney function.

During therapy, urine output increased an average of 10-fold (n=4 with available data) and serum creatinine decreased an average of 0.12 mg/dL at discharge (n=6) despite contrast load from the HR-PCI procedure.[v] Hemodynamics including heart rate and proximal and distal aortic pressures were maintained during and after the HR-PCI procedure.

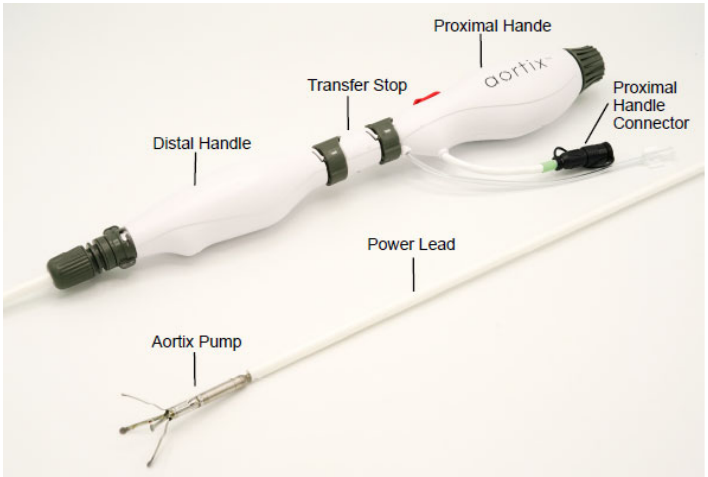
In summary, the Aortix Pump was acutely deployed and retrieved in a simple percutaneous procedure in the setting of HR-PCI (n=6) with 100% angiographic success and no clinical adverse events, adverse device effects, device deficiencies or incidents of hemodynamic compromise were observed. Acute signals from the HR-PCI patient population point to a potential for hemodynamic improvement and a reno-protective effect that could benefit ADHF patients.

2. Device Description

Brief descriptions of the following components of the Procyrion Aortix System are provided below: the Aortix Delivery System, the Aortix Pump, the Aortix Control System, and the Aortix Retrieval System. The Aortix System is investigational. Refer to the Aortix System Instructions for Use (PPL004) for detailed product specifications and instructions for use.

The Aortix Delivery System, Introducer Set and Aortix Pump

The Aortix Delivery System (ADS) is comprised of the Aortix Pump and the Aortix Delivery Tool. The Introducer Set (IS) is comprised of a sheath and a dilator. As described in the Instructions for Use, the Aortix Pump is introduced through the 18F ID/21F OD sheath. The Aortix Delivery Tool allows the Aortix Pump to be connected to and controlled by the Aortix Control System before the Aortix Pump is released from the Aortix Delivery Tool.

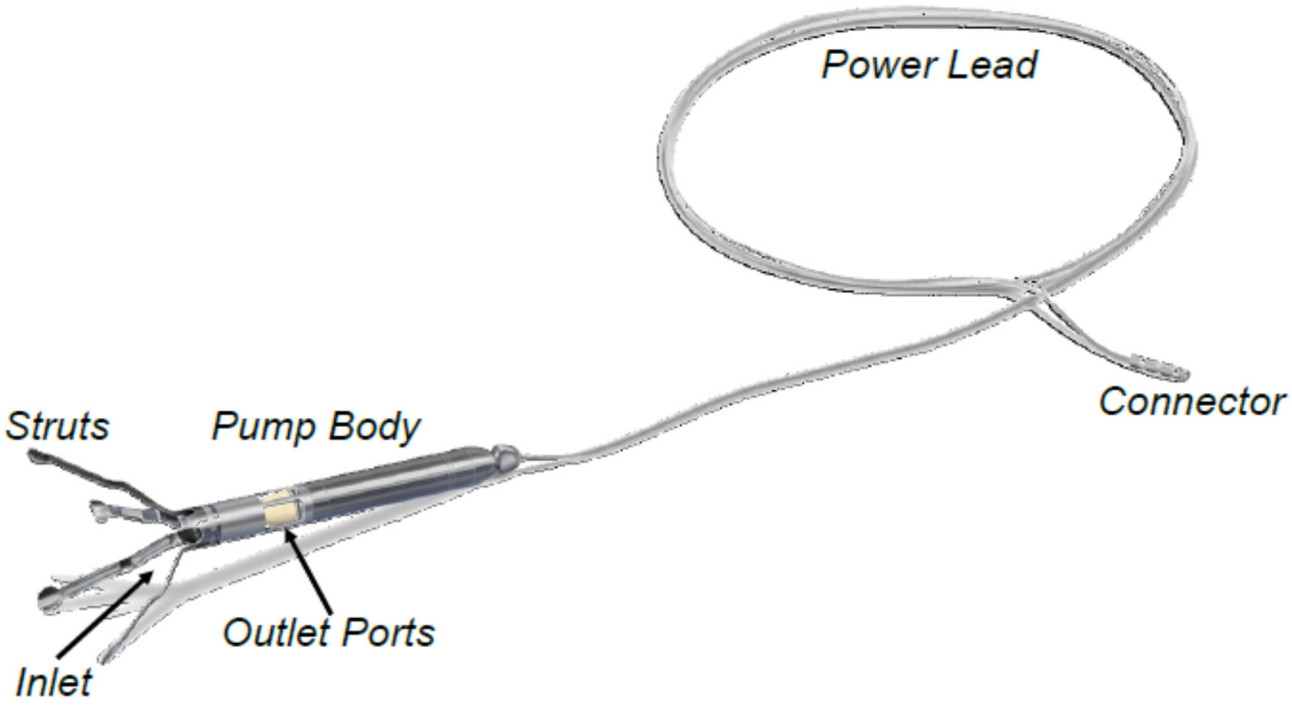


[v] Note the current study protocol for the use of Aortix in ADHF patients with CRS does not require the use of contrast.

Aortix Pump

The Aortix Pump is packaged in the Aortix Delivery System. The Aortix pump is an impeller pump that is approximately 6.5cm long, 6mm (18 F) in diameter (pump body) and implanted in the descending aorta superior to the renal arteries via a femoral approach. Expandable struts maintain the position of the device in the descending aorta while the Aortix Pump provides partial circulatory support at a nominal flow of 3.5 liters per minute. The Aortix Pump has an integral Power Lead (6F in diameter) that exits the arteriotomy and connects to the Aortix Control System. The 6F Power Lead is the only part of the system that exits the arteriotomy; a sheath is not left in for the duration of therapy.

Aortix has no gradient to pump against and uses fluid entrainment to augment pressure and flow in the aorta. In this approach, only a portion of the native blood flow enters the Aortix device. This portion is accelerated by the pump and exits in high velocity jets that entrain, or transfer momentum to, the flow that bypasses the pump. Entrainment allows Aortix to pump effectively while maintaining pulsatile flow. Aortix pumps blood from the aortic root into the abdominal aorta. This decreases aortic root pressure which allows higher cardiac output with less energy required. Downstream of the pump, aortic pressure is higher, driving increases in renal perfusion (flow and pressure).

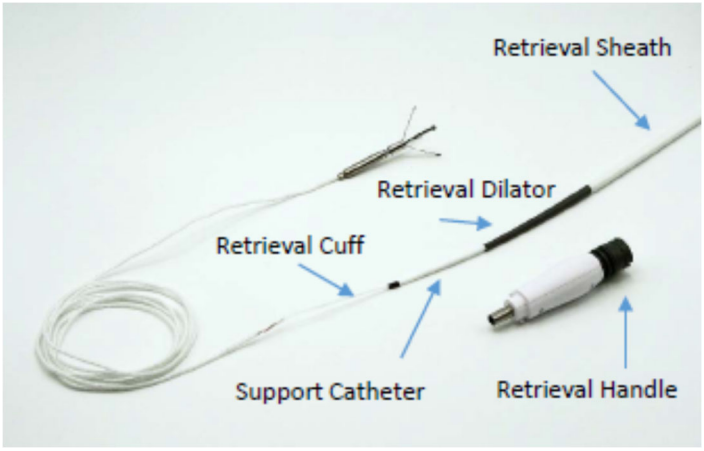


Aortix Control System

The Aortix Control System (ACS) consists of the Aortix Cradle and Aortix Controller. The Aortix Controller is connected to the Power Lead Connector of the Aortix Pump, provides up to approximately 1 hour of battery support when not mounted within the Aortix Cradle, and includes alert indicators. The Aortix Cradle is used to set the Aortix Pump speed, is IV pole mountable, and provides power to the Aortix Controller. The Aortix Cradle displays Aortix Pump operating information and alerts.

The Aortix Retrieval System

The Aortix Retrieval System (ARS) includes (amongst other components) an 18F ID/21F OD Retrieval Sheath and Dilator. The ARS is used to retrieve the Aortix Pump in a second, separate procedure following completion of therapy.



2.1 Indication for Use

Aortix is a circulatory support device for chronic heart failure patients on medical management who have been hospitalized for acute decompensated heart failure (ADHF) with worsening renal function (WRF). Aortix may aid in the treatment of ADHF by providing cardiac and renal circulatory support to decrease congestion and improve renal function resulting in increased urine output and reduced fluid overload.

Currently, the Aortix System is for Clinical Investigational use only**,** in accordance with this *Clinical Investigation Plan* and subject to required approvals.

2.2 Packaging/Labeling

The Aortix Delivery System and pre-loaded Aortix Pump are packaged together within a sterile barrier and placed in a shelf carton. Product labels are affixed to the pouch and the shelf carton and the electronic *Instructions for Use* (eIFU) card are placed within the shelf carton. The Aortix Introducer Set is packaged separately with an introducer sheath and a dilator. The Aortix Retrieval System components are packaged and labeled in the same way. The Aortix Control System components are packaged together in a foam inset and placed within a shelf carton. Product labels are affixed to the components and the shelf carton and the *Instructions for Use* are placed within the shelf carton.

All product labels include the statement: "Caution: Investigational Device. Limited by Federal (or United States) law to investigational use. Exclusively for clinical investigations." to comply with United States and international requirements. This device has not been approved for use in any country.

2.3 Sterilization

The Aortix Delivery System (including the Aortix Pump), Introducer Set and the Aortix Retrieval System are provided sterile. The Aortix Delivery System, Introducer Set and Aortix Retrieval System are single-use only and are not to be re-used and are not to be re-sterilized.

The Aortix Control System is packaged in non-sterile packaging. The Aortix Control System components (Cradle and Controller) may be re-used after appropriate cleaning. Refer to the Aortix System Instructions for Use (PPL004) for additional details.

2.4 Shipping/Storage

Good Clinical Practice guidelines require accounting for the disposition of all investigational devices received by each clinical site. Information on device disposition consists of the date received, date used, and the patient in whom the device was used. The Investigator is responsible for accounting for all used and unused devices.

The Aortix System will be hand carried or shipped to the sites at intervals dependent on the rate of patient enrollment. The site will use device accountability forms to document the inventory and study device disposition.

All Aortix System devices for this study must be stored at room temperature in an area free of environmental extremes and with limited, controlled access. Procyrion will inspect the storage area and will ensure study device accountability prior to device use.

Unused product should be returned to the sponsor following final patient enrollment. Expired product can be returned to the sponsor at any time. See Section 4.6 for instructions on returning used product.

3. Study Design

3.1 Study Purpose

The study is a prospective, multi-center, non-randomized feasibility study to evaluate the safety and performance of the Aortix System in patients hospitalized with acute decompensated heart failure (ADHF) irrespective of ejection fraction and worsening renal function refractory to medical management with persistent congestion.

3.2 Study Objectives

To evaluate the Aortix System, specifically to assess:

- Safety:
    - Observe the nature, severity, and frequency of adverse events associated with the delivery, use, and retrieval of the Aortix Pump.
- Performance:
    - Successfully deliver the Aortix Pump to the descending thoracic aorta using the Aortix Delivery System;
    - Aortix Pump shall function as programmed for the duration of therapy;
    - Manage the Aortix Pump Power Lead and access site over the course of therapy without significant complications;
    - Successfully retrieve and remove the Aortix Pump using the Aortix Retrieval System.
- Effectiveness:
    - Evaluate hemodynamic decongestion (CVP, PCWP) during Aortix therapy;
    - Evaluate the effect of the Aortix therapy on kidney function;
    - Evaluate the impact of the Aortix Pump on clinical biomarkers of congestion.

3.3 Study Endpoints

3.3.1 Primary Safety Endpoints

1 Rate of Occurrence of Serious Adverse Events (rate will be calculated and reported) [timeframe: enrollment to 30 day visit]

2 Rate of Occurrence of Serious Procedure Related Adverse Events (rate will be calculated and reported) [timeframe: procedure to 30 day visit]

3.3.2 Device Performance

1. Deployment (implant) and retrieval procedures success rates (rates will be calculated and reported)

2. Rate of occurrence of ADS, ARS and pump device-related adverse events (includes device malfunctions) (rate will be calculated and reported) [timeframe: implant attempt/implant to 30 day visit]

3.3.3 Primary Effectiveness Endpoints

1. Clinically significant decongestion as measured by the PA catheter. Decrease in CVP or PCWP of $\geq$ 20%. [timeframe: pre-implant vs when congestion target is met or therapy deemed ineffective].

2. Change in Urine Output Assessed as the hourly rate of urine output before pump implanted vs hourly rate of urine output over the Aortix therapy period (until congestion target met or therapy deemed ineffective)

3. Decrease in BNP or NT-pro-BNP by 20% (pre-implant vs when congestion target is met or therapy deemed ineffective)

3.3.4 Other Data to Be Characterized and Reported

- Rate of occurrence of all adverse events
- Utilization of continuous renal replacement therapy (CRRT), ultrafiltration and dialysis
- Change in serum creatinine
- Change in eGFR
- Change in diuretic doses
- Change in urine sodium excretion
- Changes in cardiac output and cardiac power output[vi]
- QoL changes from KCCQ and EQ5D
- Change in dyspnea assessment
- Changes in echo parameters (includes CO)
- Rates of hemolysis as measured by Lactate Dehydrogenase (LDH), Plasma Free Hb (pfH) and urine hemoglobin

[vi] Cardiac Output (CO) and Cardiac Power Output (CPO) will be calculated by the sponsor. CPO parameters to be collected: SaO_2 (as measured by pulse oximeter), SvO_2 (as measured on mixed venous gas from PA catheter), hemoglobin (from CBC), weight, height, blood pressure [to calculate mean arterial pressure (MAP)], and heart rate.

3.4 Study Population

This study will enroll up to 60 patients in order to treat 30 patients using Aortix with ADHF (irrespective of ejection fraction) refractory to medical management with persistent clinical signs of congestion and worsening renal function.

3.4.1 Inclusion Criteria

The patient must meet **ALL** of the following criteria:

1) Admitted to the hospital with a primary diagnosis of acute decompensated heart failure, either heart failure with reduced or preserved ejection fraction (HFrEF, HFpEF or HFmEF);
2) Worsening renal function (serum creatinine increase by ≥0.3 mg/dl [≥27 μmol/L]) despite 48 hours of intravenous diuretic therapy. Increase can be compared to a baseline value taken within 90 days of hospitalization or during hospitalization;
3) Objective measure of congestion (Elevated PCWP [≥20 mmHg] OR Elevated CVP [≥12 mmHg]) obtained via catheter measurement;[vii]
4) Persistent clinical signs and/or symptoms of congestion despite diuretic therapy (one or more of the following):
    a) dyspnea at rest or with minimal exertion,
    b) paroxysmal nocturnal dyspnea,
    c) orthopnea,
    d) lower extremity edema (≥2+),
    e) elevated jugular venous pressure,
    f) pulmonary rales,
    g) enlarged liver or ascites,
    h) pulmonary vascular congestion on chest x-ray;
5) Age >21 years and able to provide written informed consent.

[vii] This assessment requires patient to sign informed consent.

3.4.2 Exclusion Criteria

1) Treatment with high dose IV inotropes within the last 48 hours. High dose is defined as > 1 unit of inotrope (excluding digoxin) as follows:

   5 µg/kg/min dopamine = 1 unit,
   5 µg/kg/min dobutamine= 1 unit,
   0.375 µg/kg/min milrinone = 1 unit,
   (for example, dopamine 2.5 µg/kg/min + dobutamine 2.5 µg/kg/min = 1 unit; dobutamine 2.5 µg/kg/min + milrinone 0.1875 µg/kg/min = 1 unit);

2) Treatment with vasopressors to maintain blood pressure as per exclusion #3;
3) Active and ongoing hypotension defined as a systolic blood pressure < 90 mmHg lasting more than 30 minutes or a mean arterial pressure (MAP) < 60 mmHg lasting more than 30 minutes;
4) Acute Kidney Failure defined as increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) with in the last 48 hours;
5) Exposure to intravenous contrast, aminoglycosides or high dose NSAIDS in the 48 hours before enrollment;
6) Known or suspected contrast induced nephropathy;
7) Prior kidney transplant, isolated single kidney, stage V Chronic Kidney Disease (eGFR ≤15) at admission OR use of dialysis, continuous renal replacement therapy (CRRT) or aquapheresis (ultrafiltration) in last 90 days;
8) Urologic intervention (except indwelling urinary (Foley) catheter)) within the last 7 days;
9) Known cirrhosis or shock liver;
10) Presence of an active infection;
11) Prior heart transplant in the last 2 years, heart failure due to rejection of a previous heart transplant, planned heart transplantation before the 30-day follow-up visit;
12) Current or previous support with a durable LVAD at any time or use of an intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), or percutaneous ventricular assist devices (e.g. Impella or TandemHeart) currently or within the last 30 days;
13) Patient has known hypo- or hyper coaguable state such as disseminated intravascular coagulation or heparin induced thrombocytopenia (HIT);
14) Known cardiac amyloidosis;
15) Acute myocardial infarction Type 1 within 30 days of enrollment, or planned coronary revascularization;
16) Stroke within 30 days of enrollment;
17) Severe Bleeding Risk (any of the following):
    a) Previous intracranial bleed unless there is documentation in the medical record (from a physician that is not part of the study) that the patient can safely use anticoagulation for 7 days,
    b) GI bleeding within 6 months requiring hospitalization and/or transfusion,
    c) Recent major surgery within 6 months if the surgical wound is judged to be associated with an increased risk of bleeding,

d) Endovascular procedure with ilio-femoral access > 6 FR within 30 days,

e) Platelet count <75,000 cells/mm^3, [viii]

f) Uncorrectable bleeding diathesis or coagulopathy (e.g. INR ≥2 not due to anticoagulation therapy);

18) Current endovascular stent graft in the descending aorta or any femoro-iliac vessels;

19) Contraindicated Anatomy:[ix]

a) Descending aortic anatomy that would prevent safe placement of the device [<18mm or >31mm aorta diameter at deployment location (measured between the superior aspect of the T10 vertebra and superior aspect of the L1 vertebra)],

b) Ilio-femoral diameter or peripheral vascular anatomy that would preclude safe placement of a 21F (outer diameter) introducer sheath,

c) Abnormalities or severe vascular disease that would preclude safe access and device delivery (e.g. aneurysm with thrombus, marked tortuosity, significant narrowing or inadequate size of the abdominal aorta, iliac or femoral arteries, or severe calcification),

d) Known connective tissue disorder (e.g. Marfan Syndrome) or other aortopathy at risk of vascular injury;

20) Known hypersensitivity or contraindication to study or procedure medications (e.g. anticoagulation therapy) or device materials (e.g. history of severe reaction to nickel or nitinol);

21) Positive pregnancy test if of childbearing potential;

22) Participation in any other clinical investigation that is likely to confound study results or affect the study;

23) Unable or unwilling to undergo screening (imaging, PA Catheter placement), device implant and retrieval procedures.

3.5 Study Duration

It is expected that study patients will be enrolled over a period of approximately 12-24 months within Australia and the USA. The total duration of a patient's participation in the study is approximately 1.5 months including screening, enrollment, therapy and follow-up.

3.6 Subject Withdrawal and Discontinuation

Every effort shall be made to keep all patients in the study for the duration. However, the patient's participation in this study is completely voluntary. If the patient decides not to participate or to withdraw from the study, their decision will have no effect on any services or treatment the patient is currently receiving and will not affect their relationship with their doctor. Additionally, the Principal Investigator may withdraw or choose not to enroll a patient if they feel they do not meet the protocol defined criteria or if it is in the best medical interest of the

[viii] If patient doesn't have a, b, c, d or f, but the platelet count at time of enrollment is <75,000 cells/mm^3, patient can be enrolled and the platelet count re-assessed at the time of the procedure. The platelet count at time of procedure should be ≥75,000 cells/mm^3. If platelet count at time of procedure is <75,000 cells/mm^3, patient would be a screen failure.

[ix] Anatomy assessment requires patient to sign informed consent.

patient in question. A patient may also be withdrawn if they have a terminal event, defined as a heart or kidney transplant, death, dialysis, ultrafiltration or CRRT or LVAD implant.

In cases of voluntary patient withdrawal, all data collected from the time of informed consent to the time of voluntary withdrawal may be used. If a patient chooses to withdraw from the study prematurely, the reason for withdrawal will be documented on the applicable electronic case report form (eCRF). If patient requests to withdraw after the investigational Aortix Pump is deployed, the Aortix Pump must be retrieved, and the patient shall be instructed and encouraged to continue follow-up visits for evaluation of the patient's health status.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records). If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. Procyrion or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at study closure from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study closure in all patients is crucial for the integrity of the study.

In the event the patient withdraws consent during the study, the date of withdrawal will be documented. If the investigator voluntarily removes a patient from further study participation, supporting documentation must be in place for the rationale and date of removal. Every attempt will be made to contact patients who are noncompliant to the follow-up requirement. Patients will be considered lost to follow-up once the following steps have been taken:

- At least three (3) phone calls should be made to the patient. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured. Additionally, sites should send a certified letter to the most recent known address if unable to reach the patient by phone.
- Contact the patient's family doctor (if known) to obtain survival status and information on adverse events (if any).
- If there is no response, the patient will be considered lost to follow-up. The sponsor should be notified, and the Study Exit form should be completed.

3.7 Subject Identification and Confidentiality

A study patient's medical record, including patient identification, will be made available for review by the study Sponsor, their representatives, and appropriate regulatory authorities. Any copies of medical records or eCRFs used to collect study data by the Sponsor will only identify patients by a unique patient identifier. Study results or information about the study that is made public will in no way disclose any patient's identity.

4. Study Procedures

The following sections outline the details of the clinical study methods for the Aortix CRS Pilot study. **Figure 1** summarizes the study design.

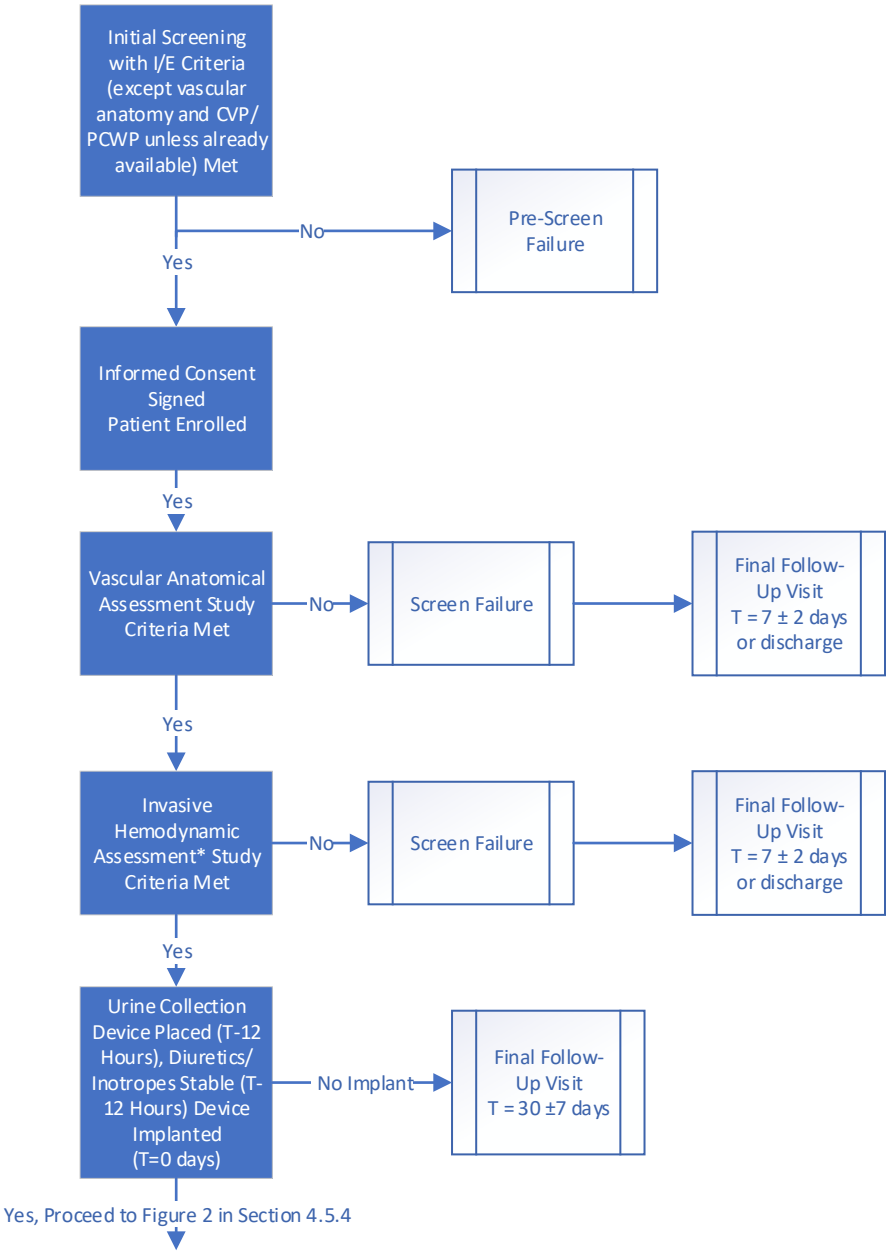


Figure 1: Study Design Summary

Refer to **Appendix A: Schedule of Visits and Procedures** for detailed procedure schedule. For details on specific use of the Procyrion Aortix System refer to the Aortix System Instructions for Use (PPL004).

4.1 Screening

Prior to consent, it is possible to review medical records to see if many of inclusion and exclusion criteria are present. If patients have worsening renal function and persistent congestion as defined in the inclusion/exclusion criteria, despite treatment with the institution's standard of care medical therapy, then he/she may be considered for the Study. During the study clinicians should avoid the use of nephrotoxic drugs. Prior to anatomical imaging and Swan-Ganz pulmonary artery catheter (PAC) placement, the patient will be evaluated for inclusion in the Study (pre-screening). If patient meets all other eligibility criteria, he/she will be approached for Informed Consent prior to final screening. Patients must sign informed consent before undergoing new PAC placement or study-related anatomical imaging assessments. Patients must be treated with optimal heart failure medical therapy per the institution's standard of care. Patients should be on intravenous diuretics for at least 48 hours before enrollment.

4.2 Enrollment

The patient is considered enrolled in the study when they sign the informed consent and before imaging screening is initiated. Following Informed Consent, imaging of ilio-femoral and aortic anatomy will be obtained to verify appropriate diameter and evaluate for any abnormalities that would preclude device placement. Imaging modality is up to the site, but one or more of the following modalities are recommended: non-contrast CT, intravascular ultrasound (IVUS) or external arterial ultrasound. Magnetic Resonance Angiography (without contrast) or CO2 angiography may also be considered.[x]

If not done previously, PAC placement can occur any time after informed consent is signed and before device placement to confirm inclusion criterion for objective measure of congestion. Alternatively, PAC placement can occur in the cath lab before the Aortix device implant procedure.

4.3 Baseline Monitoring

Once patient is enrolled, baseline monitoring will begin. The following shall be done:

- Collect a medical history
- Perform a cardiovascular exam
- Collect vital signs (heart rate-HR, blood pressure-BP, respiratory rate-RR), NYHA classification, height
- Administer KCCQ and EQ5D assessments
- Collect baseline blood labs (See **Appendix A**).
- Echocardiogram (for the baseline echocardiogram, an echocardiogram taken during the current hospitalization may be used if the required parameters are recorded and no clinically significant changes are suspected from time of the echocardiogram to the baseline visit)

Echocardiogram parameters to be recorded: severity of AR, TR and MR, EF, LVESV, LVEDV, LVEDD, LVESD, CO, SV, LA diameter, TAPSE, and RVIDD. The selection of the echocardiogram technique and views are left to the

[x] If the patient has had imaging within the last 12 months, this can be used in lieu of repeating the imaging if no clinically significant change is suspected.

institution. A report should be generated and kept as source documentation. Baseline assessments will be made in accordance with the schedule of assessments in **Appendix A**.

In addition to baseline monitoring, the following shall be done:

- Urinary collection device placement at least 12 prior to implant
    - Begin careful fluid intake and output (I/O) monitoring starting at least 6 hours prior to Aortix implant)
- Document current renal and cardiovascular medications
    - Cease to adjust diuretics and inotropes 12 hours prior to Aortix implant

The following categories of medications should be recorded, at a minimum: ACE inhibitor, ARNI, angiotensin receptor blocker, antiarrhythmic, beta blocker, digoxin, diuretic, inotrope, nitrate, MRA, SGLT2, thiazide diuretic, nitroprusside. Medication dose changes will be tracked through the 72 hour/discharge visit. Medications at the follow-up will also be recorded.

After signing informed consent, a urinary collection device will be placed, if not already present. A Foley catheter is recommended, but an external urine collection device may be used per institution requirements. The urine collection device will be placed (do not measure the urine collected during catheter placement) at least twelve (12 hours) before the Aortix Pump placement. If a urinary collection device is already in place, urine should be discarded. Output and intake should be strictly observed starting twelve hours prior to the scheduled implant. The urine collection device and the strict ins/outs monitoring will continue until the Aortix pump is retrieved. The first measurement of intake and output should occur at least six hours prior to Aortix placement and should be recorded every two hours until the pump is turned on. Measurements will occur at the frequency outlined in **Appendix A**.

Fluid ins should be monitored (IV and Oral) for the entire duration the urine collection device is in place with final measurements taken at the time of device retrieval.

Patients will receive standard medical therapy throughout the study. Patients should be on optimized medical therapy prior to being considered for Aortix Pump placement. To characterize the effect of the experimental device, physicians should not adjust the diuretic or inotrope dosing regimen during the twelve (12) hours prior to or the twelve (12) hours after Aortix Pump placement, unless medically necessary. **Diuretics and inotropes should not be adjusted for twelve (12) hours after the Aortix pump is turned on, however, after that point, while the Aortix pump is running, cessation of medications or down titration of diuretics, inotropes or other medications are allowed.** Adjustments of medical therapy can otherwise be made at any point during the study period at the discretion of the treating physician. All medications and medications adjustments will be captured on eCRFs.

4.4 Day of Implant

4.4.1 Pre-Implant

Prior to Aortix Pump placement, placement of a pulmonary artery (PA) catheter is required to confirm hemodynamic congestion inclusion criteria. In addition, patients should have a pulse oximeter for periodic oxygen

saturation (SaO2) measurements. The following serial PA catheter measurements will be performed throughout the study per **Appendix A**:

- Central Venous Pressure (CVP)
- Pulmonary Artery (PA) Pressure Systolic
- Pulmonary Artery (PA) Pressure Diastolic
- Pulmonary Artery (PA) Pressure Mean
- Pulmonary Capillary Wedge Pressure (PCWP)
- SvO2 (As measured on mixed venous gas from PA catheter)

On the day of the implant procedure, prior to the deployment of the Aortix device, the following assessments should be made (note: any baseline tests that were done on the day of implant do not need to be repeated and it is acceptable to enter the same data into the respective CRF):

- Cardiovascular exam (edema, pulmonary auscultation, weight)
- Vital Signs (HR, BP, RR)
- Dyspnea evaluation
- Fluid Ins and Outs
- Hemodynamics to include the following:
    - CVP
    - PA systolic
    - PA diastolic
    - PA mean
    - PCWP
    - SvO2 as measured by the PA catheter
    - SaO2 as measured by the pulse oximeter
- Blood and urine labs should be collected as per **Appendix A**.

4.4.2 Aortix Implant Procedure

Refer to the Aortix System Instructions for Use (PPL004) for all details of the Aortix Pump implant (deployment) technique, monitoring, management, and retrieval technique.

Anticoagulation should be initiated prior to the deployment of Aortix Pump in accordance with the Instructions for Use and **Appendix B: Anticoagulation Protocol**.

Ultrasound or another imaging modality should be used before and after implanting the pump to verify the femoral artery is not compromised (no vascular damage or clots).

Due to the potential for developing contrast induced nephropathy, if the use of iodinated contrast is required, then use the lowest dose possible and dilute 1:1 with saline.

Fluoroscopy should be used to aid in device placement and images of final device position should be captured and sent to Procyrion.

If Aortix Pump is not positioned or functioning satisfactorily, the device may be repositioned or replaced as appropriate. After Aortix Pump implantation, anticoagulation should be maintained per **Appendix B**.

A fluoroscopic image of the final pump position should be taken, downloaded and the image documented. The image should be sent to Procyrion.

During the procedure, patients should be monitored for any adverse events, including fever and anaphylaxis.

Any components of the Aortix Delivery System or Delivery Tool Kit that malfunction or are associated with an Adverse Event should be returned to the sponsor using the supplied Aortix Return Kit. Any device deficiencies should be reported.

4.5 Aortix Post-Deployment Monitoring and Management

The Aortix Pump has been tested to operate safely for 7 days of use. Aortix therapy should continue until objective signs of hemodynamic congestion have resolved, alternative / escalated therapy is required, or if device related safety concerns arise. The duration of Aortix pump use should be dictated by the physician's target for diuresis (net fluid and weight loss). In addition, the pre-specified target for pump effectiveness is a **minimum** 20% decrease in the patient's CVP and PCWP from pre-implant. **Diuretics and inotropes should not be adjusted for twelve (12) hours after the Aortix pump is turned on. After that point, while the Aortix pump is running, cessation of medications or down titration of diuretics, inotropes or other heart failure medications are allowed.** Adjustments of other medical therapy can otherwise be made at any point during the study period at the discretion of the treating physician. All medications and medications adjustments will be captured on eCRFs.

Refer to the Aortix System Instructions for Use (PPL004) for details of the Aortix Pump management.

If clinically significant device migration is suspected, use x-ray or another imaging modality to verify pump position.

It is recommended that the patient's vital signs be monitored frequently post procedurally (e.g., vitals checked every 15 minutes for the first hour, then every 30 minutes for the second hour). The patient's pedal pulses should be monitored post procedurally frequently for distal limb perfusion, ideally but not limited to, every fifteen (15) minutes times four (4), every thirty (30) minutes times two (2) and every hour (1) for two (2) hours and then as frequently as signs and symptoms warrant. In addition, the access site should be monitored for bleeding, hematoma, swelling or signs of infection.

Patients should be closely monitored during Aortix therapy and evaluated for any signs of vascular steal, including hearing loss, decrease in mental acuity, tinnitus, blurred vision, dizziness, vertigo, loss of muscle coordination, neurologic changes, or fainting. If any of these symptoms are observed, consider evaluating carotid circulation with doppler ultrasound and/or turning the pump speed down. In addition, report these signs as adverse events in accordance with Section 6. Since patient vital signs are monitored every 6 hours while the Aortix pump is implanted, it is recommended to evaluate the patient for signs of vascular steal while their vital signs are being monitored.

4.5.1 Initial Data Collection

Following the implant procedure (time zero), the following data will be collected and entered on the eCRFs while the pump is implanted:

- Two (2) hours post implant:
    - Vital signs (HR, BP, RR)
    - Fluid Ins and Outs since last reading
    - Hemodynamics
        - CVP
        - PA Systolic
        - PA Diastolic
        - PA Mean
        - PCWP
        - SvO2 as measured by the PA catheter
        - SaO2 as measured by pulse oximetry
    - Document any medication changes and adverse events
    - Urine labs per Appendix A
- Six (6) hours post implant and every 6 hours for 24 hours post implant:
    - Vital signs (HR, BP, RR)
    - Fluid Ins and Outs since last reading
    - Hemodynamics
        - CVP
        - PA Systolic
        - PA Diastolic
        - PA Mean
        - SvO2 as measured by the PA catheter
        - SaO2 as measured by pulse oximetry
    - Document any medication changes and adverse events
- Twelve (12) hours post implant and every 12 hours until Pump retrieval:
    - Blood and urine labs per Appendix A
- Twenty-four (24) hours post implant and every 24 hours until Pump retrieval:
    - Cardiovascular exam (edema, pulmonary auscultation, weight)
    - Vital signs (HR, BP, RR)
    - Fluid Ins and Outs since last reading
    - Hemodynamics
        - CVP
        - PCWP
        - PA Systolic
        - PA Diastolic
        - PA Mean
        - SvO2 as measured by the PA catheter
        - SaO2 as measured by pulse oximetry

- Dyspnea evaluation
- Document any medication changes and adverse events
- Blood labs per Appendix A

BMI will be calculated by the sponsor. Patient should be maintained on anticoagulation and antiplatelet therapy per **Appendix B**.

If the Aortix Pump is suspected to be malfunctioning or mal-positioned, imaging studies, diagnostic procedures, or access site exam may be performed as needed.

Prior to any unplanned retrieval of the Aortix Pump, hemodynamic and laboratory assessments should be repeated, and a fluoroscopic image of the pump position should be taken, and the image documented.

Refer to **Appendix A** for a detailed study monitoring schedule.

4.5.2 Programming the Aortix Pump/Pump Speed Changes:

4.5.2.1 Programming the Pump

The Aortix Pump should initially be operated at a speed of 25 krpm for a minimum of two days. The pump may be stopped once congestion and hemodynamic targets have been achieved for that patient as assessed by the investigator. The pump should be left in place for a sufficient time to achieve the diuresis and hemodynamic goals for the patient. All adjustments are at the discretion of the investigator according to their clinical judgement. Once congestion and hemodynamic targets have been achieved, diuretic or other therapies may be down titrated or discontinued, at the physician's discretion, but the pump should be kept running at 25 krpm. **If a decision is made to reduce the Pump speed, vital signs, hemodynamic measurements and fluid ins and outs must be recorded before speed reduction in accordance with Appendix A.**

If congestion and hemodynamic targets have not been achieved after 2 days, the pump speed may be turned up in 1 krpm increments to see if running the pump at a higher speed will provide benefit to the patient.

4.5.2.2 Monitoring Hemolysis and Adjusting Pump Speed

Careful monitoring for hemolysis should be coincident with adjusting the pump speed. Plasma free hemoglobin (pfH) (every 24 hours), LDH (every 12 hours) and urine hemoglobin[xi] (every 12 hours) measurements should be taken while the pump is implanted to confirm there is no hemolysis. After every speed change (before the congestion target met/therapy deemed ineffective timepoint), pfH/LDH and urine hemoglobin measurements should be assessed before contemplating an additional speed change. As such, speed changes should only be made every 12 hours. Patients should be regularly monitored for signs of hemolysis (e.g. hemoglobinuria, cramping) as hemolysis may occur and not be recognized until the next pfH/LDH measurement. The maximum speed is 28k rpm.

Aortix Pump speed may be reduced to the last speed with no hemolysis if hemolysis or safety concerns arise.

[xi] Only required if collected as part of routine standard of care urinalysis.

4.5.3 Congestion Target Met/Therapy Deemed Ineffective Data Collection

Once the congestion target has been met or therapy has been deemed ineffective, before weaning begins, the following assessments should be made within 12 hours of beginning weaning:

- Cardiovascular exam (edema, pulmonary auscultation, weight)
- Vital Signs (HR, BP, RR)
- Dyspnea evaluation
- Fluid Ins and Outs since last reading
- Hemodynamics:
    - CVP
    - PA Systolic
    - PA Diastolic
    - PA Mean
    - PCWP
    - SvO2 as measured by the PA catheter
    - SaO2 as measured by pulse oximeter
- Echocardiogram
- Blood and urine labs per Appendix A
- Document any medication changes and adverse events

If the congestion target timepoint overlaps with a scheduled assessment (e.g, an every 24 hour hemodynamic measurement), the scheduled assessment value can be used and also entered on the congestion target met timepoint eCRF.

4.5.4 Weaning the Pump Speed

Once the decision has been made to cease therapy, the pump speed may be adjusted down gradually (in increments of 2-5 krpm) while monitoring the patient's hemodynamics and urine output. The pump speed may be reduced to 18-20 krpm before it is retrieved. This process should ideally be conducted over a **minimum timeframe** of three hours with a minimum of two hours to reduce the speed to 18-20 krpm and a minimum of one hour of observation of the patient before removal. Only once in the cath lab and ready for retrieval should the Pump be turned OFF.

Figure 2 summarizes the pump programming steps.

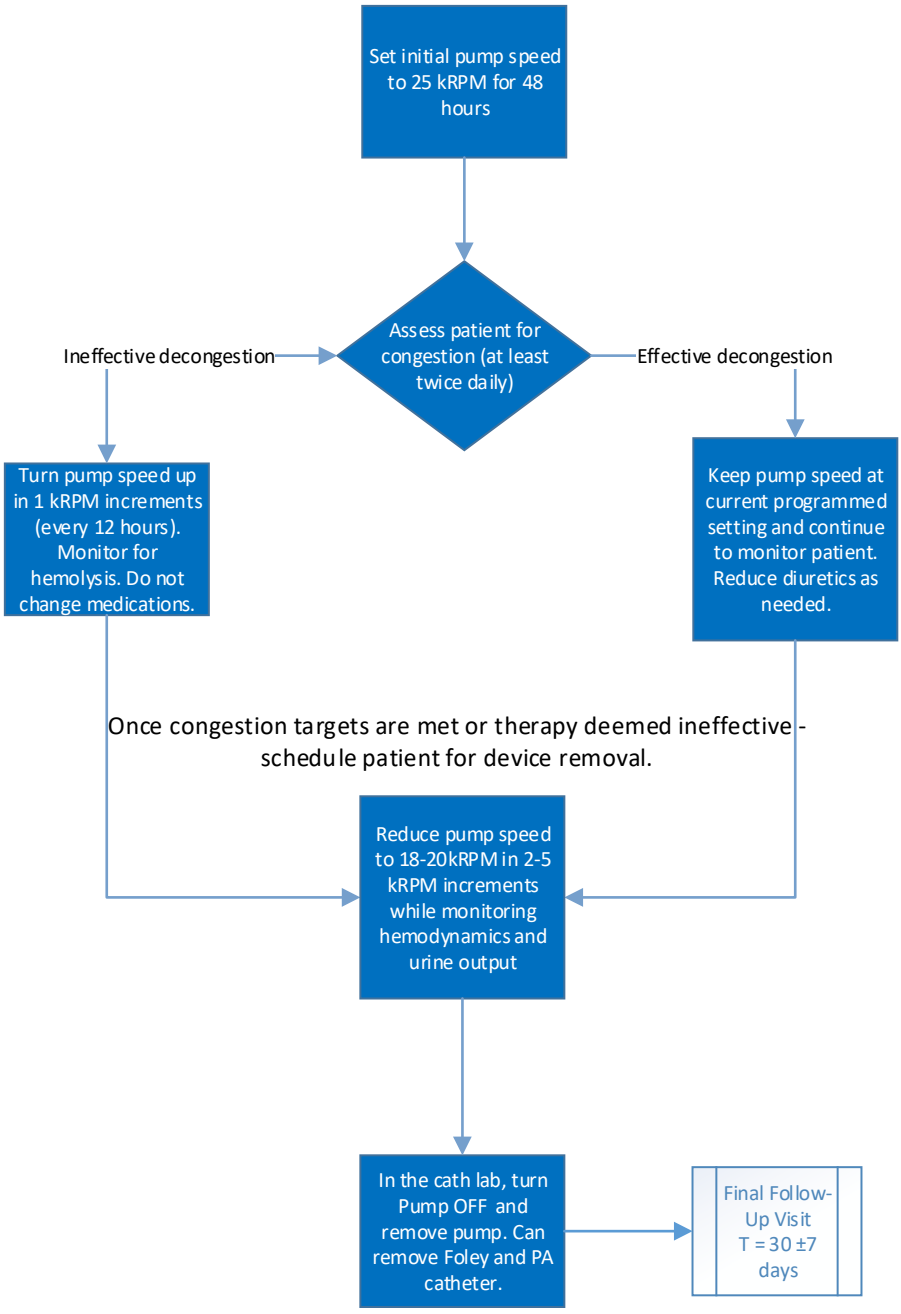


Figure 2: Pump Programming

4.6 Day of Retrieval/Aortix Retrieval Procedure

4.6.1 Prior to Retrieval

The day of the Pump retrieval, before the Pump is retrieved, the following assessments should be made:

- Document any medication changes and adverse events

Before the Pump is retrieved, *in the cath lab*, the following assessments should be made:

- Vital Signs (heart rate, blood pressure, respiratory rate)
- Hemodynamics:
    - CVP
    - PA Systolic
    - PA Diastolic
    - PA Mean
    - PCWP
    - SvO2 as measured by the PA catheter
    - SaO2 as measured by pulse oximeter
- Fluid Ins and Outs since last reading
    - Fluid Ins and Outs should be recorded at the current pump speed per **Appendix A**.
- Blood labs per **Appendix A**.

After these measurements are taken, the Pump can be programmed to OFF and the retrieval procedure can commence.

4.6.2 Retrieval Procedure

A fluoroscopic image of the final pump position should be taken and documented before the pump is retrieved. The image should be sent to Procyrion.

Accessing the arteriotomy for Aortix Pump retrieval should be performed via a percutaneous technique or a cutdown, at the physician's discretion. Following pump retrieval with the Aortix Retrieval System, the arteriotomy should be closed using percutaneous or surgical techniques. Ultrasound or another technique should be used after retrieving the pump to verify the femoral artery is not occluded after closure (no vascular damage or clots). Careful post procedure assessment of peripheral pulses should follow the same protocol as the initial procedure. The retrieval site should be monitored for bleeding and hematoma. Prophylactic antibiotics according to standard of care are recommended.

Refer to Aortix System Instructions for Use (PPL004) for details of the Aortix Pump retrieval.

All Aortix Pumps and Aortix Control Systems should be returned to the sponsor using the supplied Aortix Return Kit. Any components of the Aortix Delivery System or Aortix Retrieval System that malfunction or are associated with an Adverse Event should also be returned to the sponsor using the supplied Aortix Return Kit.

4.7 Post Device Retrieval Monitoring

Following Aortix Pump retrieval, the patient will continue to receive routine standard of care for ADHF. After removal of the Aortix pump, the femoral artery should be monitored using hospital standard operating procedures for care of large bore arterial access procedure sites.

Following the retrieval procedure, the patient will be monitored until discharge as follows:

- Twenty-four (24) hours post retrieval and every 24 hours until discharge/seventy-two hour post retrieval timepoint:
    - Measure and record fluid ins and outs (if urine collection device still in place)
    - Blood labs per Appendix A
    - Document any medication changes and adverse events
- Once at seventy-two (72) hours (± 4 hours) post retrieval or at discharge (whichever is earlier):
    - NYHA classification
    - Cardiovascular exam (edema, pulmonary auscultation, weight)
    - Vital signs (HR, BP, RR)
    - Dyspnea evaluation
    - Blood and urine labs per Appendix A
    - Document any medication changes and adverse events

4.8 Follow-Up

Patients with the pump implanted will be followed for adverse events for 30 days (± 7 days) post device retrieval. If implanted patients are still hospitalized at 30 days due to an adverse event relating to the device or any study related procedures, they must be followed until resolution of the adverse event, resolution with sequelae, or until a terminal event. Protocol required data collection for patients with the pump implanted will be for 30 days post device retrieval (± 7 days) per **Appendix A.**

The following data will be collected:

- NYHA classification
- Cardiovascular exam (edema, pulmonary auscultation, weight),
- Vital signs (HR, BP, RR)
- Dyspnea evaluation
- KCCQ, EQ5D
- Document current cardiovascular/renal medications and adverse events
- Blood and urine labs per **Appendix A**

Patients that have an attempted implant but do not have the pump implanted will be followed for adverse events for 30 days (± 7 days) post attempted implant. If attempted implant patients are still hospitalized at 30 days due to an adverse event relating to the device or any study related procedures, they must be followed until resolution of the adverse event, resolution with sequelae, or until a terminal event.

Terminal events are death, LVAD implantation, heart and/or kidney transplantation, dialysis, ultrafiltration or CRRT.

Patients who are enrolled and undergo anatomy screening and/or invasive hemodynamic measurements who do not have an attempted implant will be followed for adverse events for 7 days (± 2 days) post anatomic screening or invasive hemodynamics (whichever is later) or until hospital discharge, whichever is first.

Every attempt should be made to perform follow-up visits in person. Should extenuating circumstances (e..g, COVID-19 global pandemic travel restrictions) impact a site's ability to perform follow-up visits in person, notify the sponsor and make every attempt to collect the protocol required data via other means (e.g., telephone, video conference, blood and urine labs at a non-hospital lab).

4.9 Health-Economic Data Collection (US Sites Only)

In order to further quantify resource utilization and health care costs in the study population and to complement data from the medical records, hospitalization and follow-up resource utilization and cost data may be collected and analyzed by an independent core laboratory. Data to be collected may include, but are not limited to, copies of the patients' hospital bills (UB04) and/or itemized hospital bills. The data will be redacted prior to analysis.

The following personal health information from the billing forms may be collected, but not limited to:

- Patient's hospital admission date
- Patient's hospital discharge date
- ICD-10 diagnosis and procedure codes, HCPCS and CPT codes
- Total charges for hospitalizations
- Number and duration of admissions to rehabilitation hospitals, nursing homes and other chronic care facilities
- Self-reported measures of outpatient medical resource utilization including the number of emergency room visits during each follow-up period

4.10 Subject Death

If a patient dies during or after deployment of the Aortix Pump, the Investigator will make every effort to have an autopsy performed to help determine the extent to which the patient's death was related to the device/procedure. The Aortix pump should be returned to Procyrion.

All subject deaths which occur in subjects prior to study exit/withdrawal, regardless of causality or study relationship, must be reported to Procyrion. Investigator must provide a detailed narrative summary to include as much detail that is known regarding the circumstances surrounding the death. All deaths will be brought to the clinical event committee for adjudication and will be reported using standard mortality classifications.

4.11 Study Termination

The study may be terminated by the Sponsor at any time with suitable written notice to the Principal Investigator, the reviewing EC/IRB, and applicable regulatory agencies. Similarly, the Principal Investigator may withdraw from

the study at any time, provided that written notice to the Sponsor 30 days prior to the date they intend to withdraw is provided. Scheduled follow-up, as described in **Section 4.8**, should continue for all patients who were treated prior to the termination of the study.

4.12 Protocol Deviations

The Principal Investigator must make every effort to follow the protocol, collect all data required and maintain adequate source documentation. The integrity of the study is dependent on the quality of the data collected. Deviations from the protocol will be documented on a Protocol Deviation eCRF and reviewed with the Principal Investigator to ensure compliance.

The investigator must notify Procyrion or its designee and the reviewing EC/IRB of any deviation from the protocol when specific to the protection of the life or physical well-being of a patient in an emergency. Such notice must be given no later than 5 working days after the emergency occurred.

If a pattern of non-compliance is noted, Procyrion or its designee will determine the course of action to take, assess root cause, review relevant protocol procedures and, as applicable, retrain and verify understanding of the issue in question. This will be documented in the Trial Master Files. In the case of repeated or serious non-compliance, Procyrion or its designee reserves the right to disqualify the offending site.

5. Risk/Benefit Analysis

Procyrion has conducted an analysis of the benefits and risks of the Aortix System and procedure. Below is a summary of the potential risks and benefits of this study.

5.1 Potential Benefits

The Aortix Pump has been designed to reduce the load on the heart, improve cardiac hemodynamics, and improve kidney function. While these benefits have been validated in preclinical studies and n=6 acute clinical implants, the benefits have not yet been evaluated in this ADHF patient population or over the course of multiple days. It is possible that the device may benefit the patient by unloading the heart and improving kidney function more rapidly than with standard care and thereby could possibly reduce the hospital length of stay. These potential benefits are not known and will be evaluated in the study. In addition to the potential benefits to patients enrolled in the study, we expect the information gathered will benefit future heart failure patients.

5.2 Potential Risks

The risks associated with trans-femoral interventions and mechanical circulatory support (MCS) are the predominant risks of the study. Most of the risks of the investigational Aortix System procedure are similar to the risks associated with other percutaneous MCS devices. The likelihood of these risks is unknown since the use of MCS in this patient population has not been rigorously studied. These potential risks include, but are not limited to, the following:

- Allergic Reaction or Hypersensitivity
- Aortic Injury (including aortic puncture, tear, dissection or perforation)

- Anemia
- Bleeding (from the access site or due to anticoagulation therapy)
- Bruising at the Access Site
- Death
- Device Failure
- Device Malfunction
- Device Migration or Dislodgment
- Embolism
- Hematoma
- Hemolysis
- Hepatic Injury
- Immune reaction
- Infection
- Insertion Site Hematoma
- Limb Ischemia
- Need for Additional Intervention (Surgical or Non-Surgical)
- Neurological Event
- Nerve Injury
- Pain
- Pump Thrombosis
- Renal Injury
- Sepsis
- Syncope
- Thrombocytopenia
- Thromboembolic Complication
- Thrombotic Vascular Complication
- Vascular Injury (non-Aortic)
- Vascular steal
- Wound Dehiscence

The risks of the investigational Aortix System procedure are similar to the risks listed above; however, the frequency of some may be increased or decreased with the Aortix System procedure or device. For example, the risks of bleeding may be increased by the large diameter Aortix Delivery and Retrieval Systems and the delivery and retrieval procedures, and the risk of infection as compared to the chronic use of IABP or Impella has not yet been established. Other risks, such as hemolysis, may be reduced due to the unique design and fixation of the Aortix Pump.

Given the size of the 18F ID/21F OD Aortix Delivery System and Aortix Retrieval System, potential vascular complications (as listed above) will be carefully monitored. Prior studies of cardiac devices requiring large-bore vascular access have demonstrated higher rates of vascular access complication with increasing size. In the transcatheter aortic valve replacement (TAVR) pivotal trials, major vascular access complications occurred in 5.9%

(Medtronic CoreValve Revalving System – 18F delivery sheath) to 15% (Edwards SAPIEN valve – 22-24F delivery system) of subjects.[27] Although the Aortix Pump may be deployed percutaneously by an interventional cardiologist, for this pilot study, the physician may obtain direct vascular access to the femoral artery via cutdown and direct visualization. During vascular access, ultrasound guided placement, micropuncture needles, and microangiography may be considered to ensure proper placement of the guidewire and minimize vascular injury and bleeding.

Upon retrieval of the Aortix Pump, the femoral artery may undergo primary surgical closure. Additionally, at follow-up visits, the femoral artery and descending aorta may be non-invasively imaged to ensure vessel patency and structural integrity.

Vascular imaging, clinical monitoring, and clinical mitigation steps will be used to minimize the occurrence of these risks. The likelihood of these risks is unknown, as this is the first introduction of the investigational Aortix Pump into a human population with a duration of treatment more than 90 minutes. However, bench-top testing and large animal studies have demonstrated that the Aortix Pump can be safely implanted and retrieved after multiple days of use. Simulated use testing has demonstrated acceptable performance of the device under clinical use conditions and/or repeated use.

There may be other, unknown complications that may occur as a result of this procedure. If these or any of the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or, in rare cases, death. The study doctor and/or the research staff will make every effort to minimize additional risks.

There are also risks associated with the pulmonary artery catheter insertion procedure, which is non-investigational, but required by the study protocol. The most common risks are bruising at the site of the PAC insertion, excessive bleeding and vein injury or tear. Pneumothorax can also occur as a result of a puncture to the lung. This is more common when the catheter is inserted into the neck or chest veins.

The Sponsor has designed the device to be inherently safe. Failure modes due to the user, the device, or the software were studied and risks were mitigated through safe design, provision of information to the user, or protective measures in the medical device itself, software, or in the manufacturing process. The Aortix System is within acceptable risk levels as determined by the risk analysis conducted on potential hazard use, design, and software conditions.

5.3 Risk Mitigation

In addition, this protocol provides steps to mitigate risk to study patients. These include the following:

- Limited Study Size: A limited number of patients will receive the Aortix Pump in this study to determine performance and safety.
- Treatment Duration: The Aortix Pump will only remain implanted up to the point the investigator determines therapeutic goals have been reached. Alternatively, if the investigator determines Aortix Pump therapy is ineffective or unsafe, Aortix Pump may be retrieved at any time.
- Follow-up Assessments: Patients will be monitored closely for device performance, effectiveness, and adverse events.
- Investigator Selection: The investigators in this study are selected based on their experience in performing large bore cardiovascular interventional procedures and experience treating patients with ADHF with worsening renal function.
- Site Selection: Study sites will have sufficient expertise and resources to manage adverse events and provide appropriate alternative therapies if needed.
- Investigator Training: Investigator(s) will be trained in proper device operation prior to study start. Training will include didactic and hands-on training with the Aortix System.
- Subject Screening: The study protocol includes appropriate precautions in patient selection. For example, patients with known anatomic incompatibilities, significant co-morbidities or uncontrolled cardiovascular or other disease will be excluded.
- Adverse Event Monitoring: Timely detection, treatment, and reporting of all adverse events.
- Adverse Event Monitoring: Enrollment pause based on occurrence of procedural related death or serious procedural related adverse events (see Section 6).
- Independent Safety Monitoring. Use of an external clinical events committee for safety monitoring with timely adjudication of adverse events.

6. Adverse Events

Adverse event definitions used in the study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice) as defined below. Specific definitions of key Adverse Events are listed in **Appendix C: Key Adverse Event Definitions**. The Clinical Event Committee may elect to further modify or add to the definitions.

For this clinical study, adverse events will be collected post informed consent when invasive or non-standard-of-care screening begins (i.e. imaging or invasive hemodynamics). For safety reporting, all adverse events will be reported until the patient exits the study. Any unresolved procedural or device related adverse events that are still ongoing past study exit will be reported as being unresolved or unresolvable.

Enrollment will pause if any of the following serious, procedure related adverse events occur:

- Death (Aortix procedure related only)
- Aortic Injury Requiring Surgical Intervention to Repair (Aortix procedure related only)

Enrollment will be paused until the event can be evaluated and discussed with regulatory agencies if appropriate and approval is granted to continue enrollment.

For purposes of this study, minor clinical changes which would normally occur for this patient during the course of having heart failure which are not related to the device, the procedure or the therapy, need not be reported. Examples include but are not limited to ongoing poor appetite, weakness or fatigue. Investigator discretion is expected. If unsure, report as an adverse event.

It is anticipated that due to underlying baseline conditions, all laboratory values may not remain in the range of normal for a given participant. Investigator discretion is required to determine if a laboratory value that remains out of range is associated with an untoward clinical finding that should be reported as an adverse event.

6.1 Event Reporting Requirements

Adverse events should be reported to Procyrion on the appropriate eCRF using one CRF per AE.

The Investigator must report SADEs and SAEs to Procyrion as soon as possible, but in no circumstances later than 24 working hours after the Investigator first learns of the event, at the following email address:

By email to: safety@procyrion.com

The initial report must be followed by as much information is available and ideally should include complete documentation, including the time and date of onset, description of the event, severity, duration, actions taken and outcome (if known).

All AEs (regardless of severity or relationship to the study device) will be recorded on the eCRF.

Table 1: Timeline for Reporting of Adverse Events

Type	Report to	Reporting Timeframe (from time of learning of event)
Device Deficiency	Sponsor	Within 2 working days
AE / ADE	Sponsor	Within 2 working days
	EC/IRB	Per EC/IRB reporting requirements
SAE / SADE / USADE / UADE	Sponsor	Within 1 working day
	EC/IRB	Per EC/IRB reporting requirements

6.2 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the investigational medical device.

Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE):

A Serious Adverse Event is an adverse event that:

a. led to death

b. led to serious deterioration in the health of the participant, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Note: Device deficiencies include malfunctions, user errors, and inadequate labeling. They can be, but do not have to be, associated with an ADE or AE. Device deficiencies also include effects of electromagnetic interference (EMI). EMI effects can be intermittent; EMI related device effects, degradations, or malfunctions should be reported.

Unanticipated Serious Adverse Device Effect (USADE) / Unanticipated Adverse Device Effect (UADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (or protocol or instructions for use)

Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

AEs or SAEs will also be classified as to their relationship to the Investigational Medical Device or procedure, as follows:

Not Related: The event is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the investigational device or procedure.

Related: The event could be attributed to the use of the investigational device or procedure.

Note: The Clinical Event Committee may further categorize relatedness categories such as likely related and definitely related for better understanding of AEs.

If an AE or SAE is determined to be related to the investigational device or procedure, the expectedness of the event would further be classified as anticipated or unanticipated. Expectedness is based on the current literature and experience documented in the risk analysis report and/or contained in the *Investigational Plan, Investigator's Brochure, Report of Prior Investigations, or Instructions for Use*.

6.3 Clinical Event Committee (Safety Committee)

An independent clinical events committee (safety committee) (CEC) will be utilized in this study for adverse event adjudication. All clinical events will be reviewed by the committee. The committee will consist of three physicians who are not participating in the clinical study. The physicians will either be heart failure or interventional specialists. A charter will be developed governing the working of the committee. A chairperson will be designated to run the committee meetings and to work with the committee to ratify the CEC charter prior to any event review. CEC meetings will be scheduled based on the number of events or on trial milestones, but no less than twice a year while the study is ongoing. The last CEC meeting will occur after all subjects have been enrolled and have completed the protocol required follow up period and when all adverse event forms and source documentation have been received by the sponsor.

The sponsor will ensure that adequate source documentation is gathered prior to bring an event before a committee. Additionally, the sponsor will remove all identifiers to site and patient. If an event goes to the CEC and the committee requests additional source documentation, the event will be listed as pending and every attempt will be made to bring the event back to the next meeting.

Reports will show the CEC classification, once final as the final classification. In interim reports, pending events will be listed with the investigator classification. Deaths will be reported separately and the event leading to the death will be shown separately only if designated by the CEC as a separate event. Example, death from cardiac arrest is not reported as both a cardiac arrest and a cardiac arrest death.

7. Statistical Considerations

For the primary purposes of this pilot study, each patient's data will be reviewed individually. Systolic (HFrEF) and diastolic (HFpEF) heart failure patients may be analyzed as distinct subgroups. Study results will be summarized using standard statistical analyses (e.g. means and standard deviations compared to baseline, event rates, absolute and relative changes). The sample size of up to thirty (30) implanted patients is based upon industry standards for early stage studies of medical devices; the sample size was not statistically derived. The study will provide data to be used for demonstrating initial device safety and effectiveness in this patient population, as well as providing input for design of future clinical studies of the device. It is estimated that approximately 33% of patients enrolled may not receive the pump due to anatomical requirements or right PA catheterization requirements not being met or inability to implant the pump. Therefore, we plan to enroll up to 60 patients to yield 30 implanted patients. An interim report may be generated prior to completion of enrollment for regulatory or publication purposes. Enrollment at a given site may be restricted to ensure a balanced enrollment across sites and geographies.

8. Ethical, Regulatory, and Administrative Considerations

8.1 Informed Consent

A Patient Information and Consent Form (PICF) template is provided in **Appendix D: Participant Information and Consent Form**. The Investigator is responsible for obtaining an EC/IRB approved version of the PICF prior to enrolling any patients into the study.

The Sponsor will review the site's draft forms prior to submission to the IRB/IEC and the final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

The Investigator must ensure that each study patient provides written informed consent for their inclusion in the study after explaining the rationale for and the details, aims, and objectives of the study, the risks and benefits of participation, alternative treatments, and the extent of the patient's involvement. Patients will also be informed that their participation in the study is voluntary and that they may refuse to participate or withdraw from the study at any time. Any data collected will be used in the study and stored in the electronic data capture system. Each study patient must sign and date the informed consent, and the person obtaining consent must sign and date the consent confirming that he/she fully explained the study to the patient and the consent process must be documented accordingly. The Investigator must ensure that no patient is subject to any non-standard, study-required procedures before the patient has given his/her written informed consent.

After obtaining signature of the patient, duly signed informed consent forms, as well as written information given to patients, shall be kept and archived in the Investigator file according to the requirements of the country's regulations and site's requirements.

In circumstances where there is new information available that may affect a patient's willingness to continue to take part in the study, this information will be discussed with the patient.

Pediatric, legally incompetent, or other vulnerable patients are not eligible for the study.

8.2 Release for Medical Billing Information

Patients in the United States will be asked to sign a medical billing release form in order to support health economic data collection. If patients choose to not release their medical billing information, they can still provide informed consent to participate in the study.

8.3 Investigator Responsibilities

The Investigator is responsible for the management of patients involved in this clinical study as well as for the clinical use of the Aortix System at the study site. The Investigator will assume overall responsibility and accountability for the research team and for the clinical data obtained from patients participating in the study. The Investigator will be responsible for:

- Ensuring EC/IRB approval for this Investigational Plan and any amendments are obtained prior to commencement.
- Ensuring that the clinical study is conducted according to this Investigational Plan, federal, state, and local regulations, ICH Good Clinical Practices, applicable standards and the signed Investigator Agreement.
- Obtaining informed consent on the approved EC/IRB Informed Consent Form prior to any study participation.
- Collecting all data as required per the protocol and maintaining source documentation for data supplied
- Reporting adverse events to the EC/IRB, regulatory agencies, and the Sponsor, as required.
- Controlling any investigational device(s) stored at their site. This includes monitoring and return of devices to Sponsor.
- Protecting the rights, safety, and welfare of the patients.
- Maintaining records and reports as outlined in Section 8.3.1.

8.3.1 Investigator Records

The investigator will maintain complete, accurate, and current study records during the course of the clinical trial. The Sponsor will notify the Investigator when the records can either be destroyed or forwarded to the Sponsor, in accordance with applicable regulations. The clinical trial records must be maintained by the site until that notice is provided. All records should be made available if requested by relevant authorities. These records include:

Subject Records: Signed informed consent forms, copies of all completed eCRFs and supporting documentation (laboratory reports, angiograms, etc.) and records of exposure of each patient to the device (procedure note for example).

Investigational Plan: A current copy of the Investigational Plan and any amendments, including the Instructions for Use and the Investigator's Brochure.

USADE / UADEs: Record of all reports and information pertaining to unanticipated device effects.

Ethics Committee (EC) / Institutional Review Board (IRB): All information and correspondence pertaining to EC/IRB review and approval of this clinical study, including a copy of the EC/IRB approval letter and a blank informed consent form approved by the EC/IRB.

Investigator Agreements: Copies of the signed Investigator's Agreement with the Investigator's *Curriculum Vitae* attached.

Other: Any pertinent correspondence and/or records that may be require by applicable laws and regulations

8.3.2 Compliance to Regulations

The investigational study will be performed in accordance with this Investigational Plan, ISO 14155, applicable national and local regulations, the ethical requirements defined in the Declaration of Helsinki, ICH Good Clinical Practices and any conditions of approval imposed by the reviewing Ethics Committee or Institutional Review Board. Failure to comply with and/or inability to meet applicable national regulations may jeopardize continued participation in this study by the investigator or the study site.

8.4 Sponsor Responsibilities

The Sponsor of this clinical study, Procyrion or its designee, is responsible for the following:

- Selecting qualified Investigators and study centers and providing them with the information they need to conduct the investigation properly including adequate training on use of the device and inclusion / exclusion criteria.
- Providing study centers and investigators with new risk information.
- Ensuring that EC/IRB review and approval are obtained and remain current.
- Registering the trial and submitting applications to the appropriate regulatory authorities, as required.
- Ensuring that national regulatory bodies are duly informed of and allow the clinical trial to commence.
- Ensuring that EC/IRBs and any applicable national regulatory bodies are informed of significant new information about the clinical study.
- Reviewing the investigator's assessments of adverse events and reviewing all device deficiency reports
- Conducting evaluations of adverse events, especially USADE / UADEs and reporting to EC/IRBs and regulatory bodies as required.
- Controlling the device(s) under investigation.
- Maintaining adequate contact with the Investigator and conducting periodic on-site monitoring visits to ensure compliance with the Investigational Plan and to ensure the facility continues to be adequate for this study.

8.4.1 Study Monitoring

Clinical monitoring will be performed per Procyrion's DOP031 "Procedure, Clinical Monitoring" by an authorized Procyrion representative to ensure appropriate investigators and sites are selected, to protect the rights and well-being of the patients, to ensure the study data are accurate, complete, and verifiable, and to ensure study conduct

is compliant with the approved protocol, current ICH Good Clinical Practices, the respective local and national government regulations and guidelines (if applicable), and Procyrion requirements.

Procyrion will conduct a Site Initiation visit with the Investigator and Research Team to review the details of the protocol, study procedures, device instructions, and to confirm all required study documentation is in place prior to enrollment of the first patient. Sites visits will be conducted by an authorized Procyrion representative at regular intervals throughout the study per the monitoring plan. Procyrion will also contact or visit the investigator at the end of the study and arrange for the return shipment of all unused devices and any other study related equipment.

8.4.2 Data Management

Procyrion or its designee will be responsible for data management. Procyrion will use an electronic database, electronic case report forms (eCRF), and electronic signatures. The eCRFs will be provided by Procyrion or its designee. All data requested on the eCRF are considered required. Pertinent records in connection with the study, including patient charts, laboratory data, and related information will be made available to the sponsor on request while protecting the confidentiality of patient information.

To accurately collect all information, patient worksheets will be used for study specific data not otherwise found in the medical records and will be considered the source documents.

The most current version of MedNet Solution's iMedNet EDC will be used for this study. The Principal Investigator, or his/her designee, must e-sign each patient's case book to confirm the accuracy and completeness of all data. Each patient enrolled in the study will be assigned a unique patient identifier. Completed eCRFs will be submitted to Procyrion.

Manual and automatic data review will be performed to identify discrepancies and queries will be issued manually or created within the EDC system. Site staff will be responsible for resolving all queries in a timely fashion, within the EDC system.

iMedNet is a web-based EDC system for the collection and management of clinical trial data developed and provided by MedNet Solutions. MedNet Solutions is responsible for the creation, validation, and development of 21 Code of Federal Regulations (CFR) Part 11 compliant clinical trial databases. The iMedNet EDC is a secure site that is compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations for patient privacy. MedNet utilizes Amazon Web Services provided by ClearDATA to host and protect production data. Data is redundantly backed up utilizing automated routines and AWS CLI Scripts. The primary data center is SSAE 16 Type 2 certified and HITRUST certified. MedNet utilizes transport layer security (TLS) encryption on all data transmissions to and from their servers. MedNet Solutions IT staff performs regularly scheduled vulnerability scans against IT resources to ensure compliance with regulatory standards and industry best practices.

8.4.3 Publication Policy

Publication and Authorship will be aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Procyrion will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of the clinical study. While study results are owned by Procyrion, all data on which

a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, with sponsor permission, data may be published or used by study investigators provided that such publication or use is in accordance with this protocol, the Investigator Agreement and Procyrion's Publication and Authorship Guidelines.

8.5 Steering Committee

A Steering Committee will oversee the study and will provide oversight. Members of the study steering committee may be investigators participating in the study. Responsibilities of the steering committee include, but may not be limited to:

1) Providing medical and scientific input
2) Reviewing clinical data
3) Overseeing enrollment
4) Provide input on analyses and publication planning

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Appendix A: Schedule of Visits and Procedures

	Pre-Therapy		Aortix Therapy								Post-Therapy		
Category	**Pre-Implant Period (Baseline Monitoring)**	**Day of Implant (Pre-implant)**	**Implant to Pump Retrieval**					**Once Congestion Target is Met and Within 12 hours of Beginning Weaning $^{\alpha}$**	**Day of Pump Retrieval (Pre-Pump Retrieval)**	**Cath-Lab Pre-Pump Retrieval**	**Post-Pump Retrieval Monitoring**		**Follow-Up: 30 days (± 7 days) from Pump retrieval**
	Current hospitalization once	once	Once (after pump deployed)	2 hours post implant ✪ (± 30 min)	6 hours post implant (± 30 min) and Every 6 hours (± 1 hour) for 24 hours post implant	Every 24 h (± 2 hours)♦	Pump Speed Changes #	once	once	once	Every 24 h (± 2 hours)	Once at 72 hours post retrieval (± 4 hours) or discharge (whichever is earlier)	once
Informed Consent[1]	X												
Med History	X												
NYHA Class	X											X	X
Cardiovascular exam (edema, pulm auscultation, weight)	X	X				X		X				X	X
Vital Signs: HR, BP, RR #	X	X		X	X	X	X	X		X		X	X
Height	X												
Fluid Ins and Outs*		X*		X	X	X	X	X		X	X^{β}		
Dyspnea Evaluation		X				X		X				X	X
KCCQ, EQ5D	X												X
HEMODYNAMICS													
CVP, PAP #		X		X	X	X	X	X		X			
PCWP #		X		X		X	X	X		X			
SvO2, SaO2**		X		X	X	X		X		X			
IMAGING													
Anatomy Screening	X												
Echo	X							X					
Fluoro Image			X							X			
MEDICATIONS	X	Record all cardiovascular/renal medications and medication changes.****											X
OTHER EVENTS***	Record all adverse events, readmissions and mortality.												

1 Patient must sign informed consent before undergoing PA catheter placement for verification of inclusion criteria for objective measure of congestion or before undergoing imaging to assess anatomy for exclusion criteria for contraindicated anatomy.

αOne time assessments to be taken once congestion targets are met or therapy has been deemed ineffective (decision has been made to retrieve device). These assessments should be performed before the pump speed is turned down; within 12 hours of beginning weaning.

*Urine collection device should be inserted at least 12 hours before pump implant. Urine collection device may be removed at time of pump retrieval. Urine output measurement should exclude volume collected as part of urine collection device placement procedure. Fluid ins should be monitored (IV and Oral) for the entire duration the urine collection device is in place with final measurements for UOP and fluids in at the time of removal of the urine collection device. The "Day of Implant (Pre-implant)" UOP measurements should be taken every 2 hours before the pump is turned on. The first measurement of intake and output should occur at least six hours prior to Aortix placement and should be recorded every two hours until the pump is turned on.

** Cardiac Output (CO) and Cardiac Power Output (CPO) will be calculated by the sponsor. CPO parameters to be collected: SaO2 (as measured by pulse oximeter), SvO2 (as measured on mixed venous gas from PA catheter), hemoglobin (from CBC), blood pressure (to calculate MAP), weight, height, and heart rate.

HR, BP, PCWP, CVP and PAP – these values should also be collected any time the speed of the pump is adjusted. For PCWP it should be within 2 hours (+/- 30 min) of a speed change. For HR, BP, CVP and PAP it should be within 1 hour (+/- 30 min) of a speed change.

***For United States patients, hospital billing information will be collected post-patient discharge.

β Data collection at this time point is optional. Urine Output and Fluids IN required post device retrieval ONLY if urine collection device is still in place.

****All heart failure and renal medications/medication adjustments should be recorded from baseline to discharge/72 hours post-device retrieval (whichever is first). At the 30 day follow-up, current medications should be recorded. Medication changes between discharge/72 hours post-device retrieval and follow-up do not need to be recorded.

✪2 hours from time pump turned on during the deployment procedure.

♦First measurement should be made 24 hours after pump is turned on. Subsequent every 24 hour measurements can be made during daily rounds or another convenient time as long as the first every 24 hour measurement is made at least 12 hours after the initial measurement 24 hours after the pump is turned on.

Hemodynamics Data Collection

Category	Pre-Therapy		Aortix Therapy								Post-Therapy		
	Pre-Implant Period (Baseline Monitoring)	**Day of Implant (Pre-implant)**	**Implant to Pump Retrieval**					**Once Congestion Target is Met and within 12 Hours of Beginning Weaning$^{\alpha}$**	**Day of Pump Retrieval (Pre-Pump Retrieval)**	**Cath-Lab Pre-Pump Retrieval**	**Post-Pump Retrieval Monitoring**		**Follow-Up: 30 days (± 7 days) from Pump retrieval**
	Current hospitalization once	once	Once (after pump deployed)	2 hours post implant (± 30 min)	6 hours post implant (± 30 min) and Every 6 hours (± 1 hour) for 24 hours post implant	Every 24 h (± 2 hours) ♦	Pump Speed Changes #	once	once	once	Every 24 h (± 2 hours)	Once at 72 hours post retrieval (± 4 hours) or discharge (whichever is earlier)	once
HEMODYNAMICS													
CVP#		X		X	X	X	X	X		X			
PA Pressure Systolic#		X		X	X	X	X	X		X			
PA Pressure Diastolic#		X		X	X	X	X	X		X			
PA Pressure Mean#		X		X	X	X	X	X		X			
PCWP #		X		X		X	X	X		X			
CO, CPO**		X		X	X	X		X		X			
• SvO2		X		X	X	X		X		X			
• SaO2 via pulse oximeter		X		X	X	X		X		X			

PCWP, CVP and PA Pressures – these values should also be collected any time the speed of the pump is adjusted. For PCWP it should be within 2 hours (+/- 30 min) of a speed change. For CVP and PA Pressures it should be within 1 hour (+/- 30 min) of a speed change.

** Cardiac Output (CO) and Cardiac Power Output (CPO) will be calculated by the sponsor. CPO parameters to be collected on the hemodynamics case report form: SaO2 (as measured by pulse oximeter), SvO2 (as measured on mixed venous gas from PA catheter).

♦First measurement should be made 24 hours after pump is turned on. Subsequent every 24 hour measurements can be made during daily rounds or another convenient time as long as the first every 24 hour measurement is made at least 12 hours after the initial measurement 24 hours after the pump is turned on.

αOne time assessments to be taken once congestion targets are met or therapy has been deemed ineffective (decision has been made to retrieve device). These assessments should be performed before the pump speed is turned down; within 12 hours of beginning weaning.

Blood and Urine Labs

Category	Pre-Therapy		Aortix Therapy					Post-Therapy		
	Pre-Implant Period (Baseline Monitoring)	**Day of Implant (Pre-implant)**	**Implant to Pump Retrieval**			**Once Congestion Target is Met and Within 12 hours of Beginning Weaning$^{\alpha}$**	**Cath-Lab Pre-Pump Retrieval**	**Post-Pump Retrieval Monitoring**		**Follow-Up: 30 days (± 7 days) from Pump retrieval**
	Current hospitalization once	once	2 hours✪ post implant (± 30 min)	Every 12h (± 1 hour)	Every 24 h (± 2 hours)	once	once	Every 24 h (± 2 hours)	Once at 72 hours post retrieval (± 4 hours) or discharge (whichever is earlier)	once
White Blood Cells, Platelets		X		X		X			X	X
Hemoglobin, Hematocrit		X		X		X	X	X	X	X
Sodium, Potassium, CO2, Chloride	X	X		X		X			X	X
Bilirubin (total)	X	X		X		X			X	X
ALP, ALT/SGPT, AST/SGOT	X	X		X		X			X	X
Serum BUN or Urea	X	X		X		X			X	X
Serum Creatinine	X	X		X		X	X	X	X	X
eGFR	X	X		X		X	X	X	X	X
Plasma Free Hb (pfH)*		X			X	X	X	X	X	
LDH *		X		X		X	X	X	X	
aPTT + INR	X	X		X		X			X	
NT-pro-BNP or BNP**		X		X		X	X	X	X	X
Urine sodium (NA+)		X	X	X		X			X	X
Urine creatinine		X	X	X		X			X	X
Urine urea		X	X	X		X			X	X
Urine osmolality		X	X	X		X			X	X
Urine Blood (Hemoglobin)*♦		X		X		X			X	
Urine albumin		X	X	X		X			X	X

*these values will be monitored if the pump speed is adjusted before weaning begins (see protocol section 4.5.2)

**clinical site may report either NT-pro-BNP or BNP for a patient, but should be consistent with all measurements for that patient during the study (do not mix NT-pro-BNP and BNP measurements for a given patient during the study). BNP is the preferred measurement.

✪2 hours from time pump turned on during the deployment procedure.

♦ only required if collected per institution's standard of care urinalysis

αOne time assessments to be taken once congestion targets are met or therapy has been deemed ineffective (decision has been made to retrieve device). These assessments should be performed before the pump speed is turned down; within 12 hours of beginning weaning.

Appendix B: Anticoagulation Protocol

Follow your institution's protocol for percutaneous MCS devices.

The following targets are recommended:

Device Implant:

1. Once sheath is inserted into the femoral artery, administer unfractionated heparin (UFH) to a target ACT of 250 seconds.
2. After insertion of the sheath and until end of pump implantation procedure, ACT should be maintained at 250 seconds.

Anticoagulation Maintenance:

Note: High inter- and intra-patient variability is common with these devices. Selection of the goal anticoagulation range and titration of heparin should be done in the context of the patient's overall clinical status and should include evaluation of all applicable hematologic markers (e.g., aPTT, ACT, platelets, fibrinogen, Hgb, Hct, anti-Xa UFH).

1. Titrate systemic heparin dose to achieve a goal aPTT of 45-60 seconds or a goal Anti-Xa UFH level of 0.5-0.7 IU/mL.
2. Monitor Platelet count daily for Heparin Induced Thrombocytopenia (HIT)
3. If issues with bleeding observed, down titrate heparin/Anti Xa UFH as needed.

Anti-Platelet Maintenance:

1. Patients are to be maintained on any oral anti-platelet therapy they may have been receiving prior to study participation (e.g. aspirin, ticagrelor, prasugrel or clopidogrel).
2. For patients not already on an antiplatelet agent, aspirin (ASA) should be started at a dose such as 81 mg/day within 24 hours after implant if there are no postoperative bleeding complications. The aspirin can be continued until device retrieval.
3. For patients not an alternative antiplatelet agent or who have an aspirin allergy or are otherwise intolerant, clopidogrel 75 mg daily is a viable alternative until device retrieval.

Note: All anticoagulation titrations will be documented on the Aortix eCRF.

Appendix C: Key Adverse Event Definitions

Minor Hemolysis	A plasma free Hemoglobin (pfH) greater than 20 mg/dL or a serum lactate dehydrogenase (LDH) greater than two and one half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant in the absence of clinical symptoms or findings of hemolysis or abnormal pump function (see Major Hemolysis for a list of symptoms and findings) and thought not attributable to laboratory error.
Major Hemolysis	A pfH value greater than 20 mg/dl or a serum LDH greater than two and one half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis or abnormal pump function. Major Hemolysis requires the presence of at least one of the following conditions: • Hemoglobinuria ("tea-colored urine") • Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state) • Hyperbilirubinemia (total bilirubin above 2 mg/dL, with predominately indirect component) • Pump malfunction and/or abnormal pump parameters
Bleeding: **Life Threatening or Disabling**	• Fatal bleeding *(BARC type 5)* OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR • Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units∗ *(BARC type 3b)*
Bleeding: **Major Bleeding (BARC type 3a)**	• Overt bleeding accompanied by hemoglobin drop of 3 to < 5 g/dL (1.86 to 3.1 mmol/L SI Units) (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding

Bleeding: **Minor bleeding (*BARC type 2)***	• Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major
Acute kidney injury (AKIN classification) **Stage 2**	• Increase in serum creatinine** to 200%-300% (2.0-3.0 fold increase compared with baseline) OR • Urine output <0.5 mL/kg/h for >12 h
Acute kidney injury (AKIN classification) **Stage 3†**	• Increase in serum creatinine** to >300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR • Urine output <0.3 ml/kg/h for ≥24 h OR • Anuria for ≥12 h
Major vascular complication	• Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding,¥ visceral ischemia, or neurological impairment OR • Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention *associated* with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by subject symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury

Minor vascular complication	• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding,¥ visceral ischemia, or neurological impairment OR • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure	• Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

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

**The increase in creatinine must occur within 48 hours.

†Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria

¥ Refers to VARC bleeding definitions.

The bleeding, AKIN and vascular access site and related complications definitions are adapted from Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 (VARC-2).

BARC, Bleeding Academic Research Consortium

RBC, red blood cell

Appendix D: Participant Information and Consent Form