Procyrion

Clinical Investigational Plan

Aortix Therapy for Perioperative Reduction of Kidney Injury (A PRIORI)

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Version	A
ClinicalTrials.gov Identifier	NCT04999163
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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

Revision History Table		
Rev.	**Description of Change**	**Effective Date**
A	Initial Release	16-Jan-2022

INVESTIGATOR STATEMENT

Study Product Name	Perioperative Reduction of Acute Kidney Injury
Clinical Investigation Plan Identifier	PVP054
Version	A
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:	

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1 INTRODUCTION AND RATIONALE

1.1 BACKGROUND

Medical conditions that require surgical interventions are common worldwide. In the United States alone, there were over 750,000 cardiac and major abdominal surgeries in 2017[1]. The stresses of these surgeries (e.g., prolonged operative time, hypotension, and low blood flow) can lead to complications with lasting effects. One common and serious complication is acute kidney injury (AKI)[2].

Perioperative AKI, marked by signs ranging from a mild decrease in glomerular filtration rate (GFR) to complete renal failure, affects up to 40% of surgical patients and is a leading cause of morbidity and mortality in patients undergoing major surgery. Even AKI that resolves completely is linked to increased risks for hemodialysis, chronic kidney disease, and death years after surgery[2–8].

The introduction of the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) consensus definition of AKI marked the start of recognizing the importance of less severe AKI[9]. RIFLE defines 3 stages of AKI based on at least a 50% change in serum creatinine (SCr) from baseline[10]. The recent KDIGO (Kidney Disease: Improving Global Outcomes) consensus guidelines expand the RIFLE criteria to include creatinine changes as small as 0.3 mg/dl[2,11].

AKI is more prevalent in patients in more serious condition and afflicts 55-60% of those admitted to a critical care unit[17,18]. A single-center cohort study of over 27,000 surgical patients found 37% of patients met the RIFLE criteria for AKI and those patients had a 9x increase in hospital mortality and accounted for 89% of all the post-surgery hospital deaths even though most of them had mild to moderate AKI only[15].

Even patients whose AKI resolves quickly are at increased risk of requiring hemodialysis, development of chronic kidney disease (CKD) and/or end stage kidney disease (ESKD), and premature death; this increased risk lingering for years after the initial insult[7,19]. In cardiac surgery patients, moderate AKI doubles length of stay (LOS), hospital cost, and 30-day readmission rates, with severe AKI tripling these same metrics. Hospital mortality is 5x greater for moderate AKI and 11x greater for severe AKI. In a study of more than 36,000 hospitalized patients with baseline GFR over 45 ml/min per 1.73 m^2, one-year mortality for patients who developed AKI (defined as ICD-9 584.xx) without myocardial infarction (defined as ICD-9 410.xx) was 30%. This is more than twice as high as the 14% one-year mortality for patients with myocardial infarction (and without AKI) and is worse than many forms of cancer[7].

Direct increase of hospital costs in the United States for surgical patients who develop AKI is over $2.5B per year[1,2,8]; secondary costs due to later complications and increased risk of CKD and ESKD (which cost the US $120B/year) are even higher[20].

Preoperative risk factors can help identify patients at higher risk of developing AKI. Chief among these are underlying chronic kidney disease and heart failure, along with diabetes, persistent atrial fibrillation and hypertension (among others)[21,22]. Several predictive models have been built

using these risks and other factors[12,15,23,24]. For example, an analysis of the 2018 National Inpatient Survey (NIS) data shows that abdominal and cardiac surgery patients with even one of the risk factors listed above have at least a 30% incidence for AKI (compared to 8% for patients with none of these risk factors[1].

The goal of preoperative risk stratification is to know when preventative measures should be used during surgery. The current challenge with this approach is that there are few preventative measures to be employed. Apart from the general goals of minimizing bypass and cross-clamp time and minimizing prolonged hypotension, hemodilution, transfusions, and embolic events, very few therapies have been conclusively shown to reduce the incidence of AKI or be protective to the kidneys[25].

Therapeutic options in the post-surgery period are similarly limited (e.g., avoidance of nephrotoxic agents and hyperglycemia, discontinuation of ACE inhibitors and ARBs, close monitoring of SCr and urine output, and invasive hemodynamic monitoring) and are farther removed from the time of the initial insult[11].

None of these treatment options address what is frequently the primary cause of AKI: renal ischemia and subsequent reperfusion injury driven by surgery induced hemodynamic perturbations, which are thought to play the largest role in the development of AKI. Studies of noncardiac surgery patients suggest that sustained maintenance of sufficient mean arterial pressure is the most important hemodynamic parameter to preserve in the perioperative period[26] .

Even when focused on hemodynamic maintenance, however, physicians are forced to choose between tools that work against one another. Volume expanders, fluids, and vasopressors can be used to raise mean arterial pressure, but these also reduce flow and increase central venous pressure. Vasodilators can promote flow, but they reduce central pressure[27].

A better approach may be to provide the kidneys with a “perfusion reserve” or “hemodynamic stabilization system” to act as a hemodynamic prophylaxis against AKI by ensuring the kidneys receive adequate pressure and flow during the surgical procedure.

Procyrion, Inc. (Procyrion) has developed a percutaneous Mechanical Circulatory Support (pMCS) system. The investigational device, the Aortix System, includes an electrically driven micro-pump with an integrated nitinol localization system. The 18F device is deployed trans-femorally to the descending thoracic aorta where its position is maintained by struts that expand to contact the aortic wall. Compared to other percutaneous MCS devices, Aortix has the advantages of not being preload dependent and being located between the heart and kidneys with no part of the system in the left ventricle or crossing the aortic valve.

Once implanted and activated, the Aortix Pump is designed to simultaneously improve renal artery pressure and flow. This “perfusion reserve” may insulate and protect the kidneys against AKI from hemodynamic shocks and generate a renal protective effect through augmented renal perfusion resulting in improved renal function. Aortix also reduces the workload of the heart, which may provide additional benefit during abdominal surgeries or in the immediate period when cardiac surgery patients are off cardiopulmonary bypass. When surgery is complete, the

device is retrieved in the surgical suite or in the catheterization lab, in a procedure that is essentially the reverse of deployment.

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. In an ovine microsphere embolization model of heart failure, cardiac afterload (-26%) and cardiac work (-39%) were significantly reduced while cardiac output (+14%) and ejection fraction (+28%) were significantly increased, as were key measures of renal function, GFR (+29%) and urine output (+100%)[28]. A separate acute study in a high dose esmolol porcine model of cardiac dysfunction shows how quickly renal artery blood pressure and flow change with pump activation (see Figure 1). The gradual decrease in flow (blue trace) after each step up is evidence of resumed autoregulation by the renal afferent arterioles.

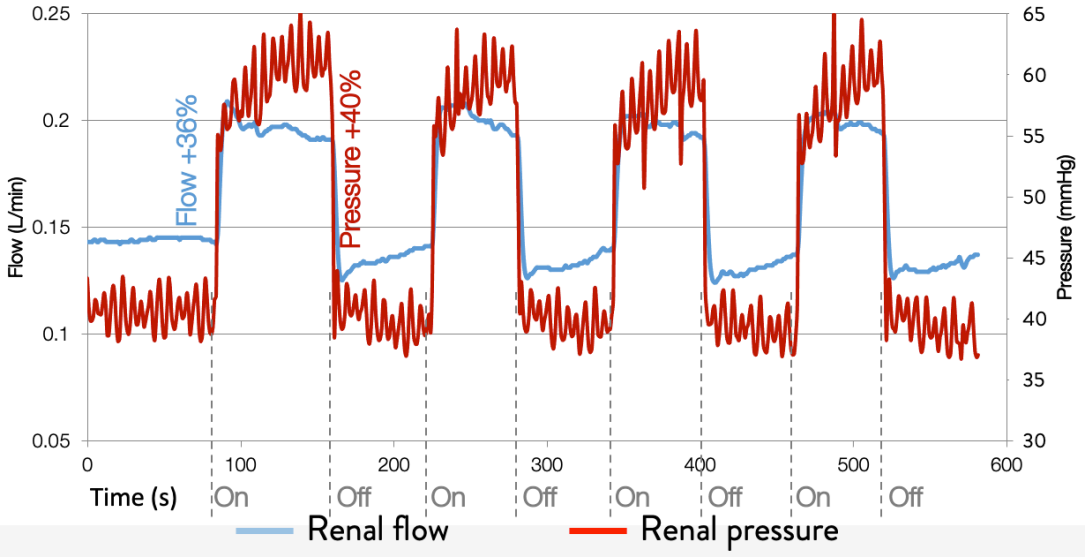


Figure 1: Renal Artery Pressure and Flow During On-Off Cycles of Aortix Operation

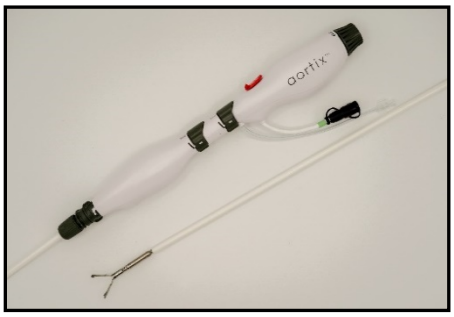
The Aortix System is currently under safety and effectiveness evaluation in the United States and Australia via a multisite pilot study of patients hospitalized with acute decompensated heart failure who are refractory to medical management with persistent clinical signs of congestion and worsening renal function.

Given the ongoing need to perform operations on high-risk patients and the need to perform lengthy complex surgical procedures, newer strategies are warranted to mitigate surgical risk. Despite advances in surgical techniques, AKI after surgery remains a challenge and newer therapies are needed to reduce the incidence of kidney injury. Along with the investigators, Procyrion proposes performing a small (N=20 patients receiving Aortix therapy) feasibility study to evaluate the impact of the Aortix System on AKI incidence and severity in patients

undergoing cardiac surgeries who are at increased risk of developing AKI. In addition, the study will collect data on a control group that does not receive the Aortix System.

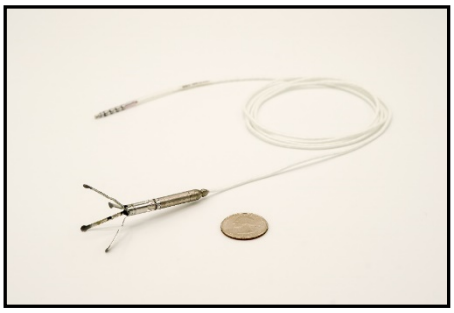
2 DEVICE DESCRIPTION

The Procyrion Aortix System comprises the Aortix Delivery System, the Aortix Pump, the Aortix Control System, and the Aortix Retrieval System. The Aortix System is investigational. A brief description of each component and a picture follow. Refer to the Aortix System Instructions for Use (PPL004) and Addendum 1 (PPL011) for detailed product specifications and instructions for use.



Aortix Delivery System and Introducer Set

The Aortix Delivery System (ADS) comprises the Aortix Pump positioned inside the Aortix Delivery Tool. The Introducer Set (IS) comprises a sheath and dilator. As described in the Instructions for Use, the Aortix Pump is introduced through the 18F ID / 21F OD sheath.

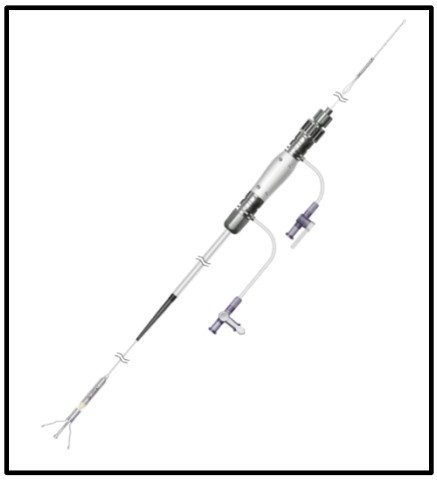


Aortix Pump

The Aortix Pump is packaged in the Aortix Delivery System. The Aortix pump is an impeller pump that is approximately 6.5cm long and 6mm (18F) in diameter (pump body) and is 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 at a nominal pump speed for 25 krpm. The Aortix Pump has an integral Power Lead (6F in diameter) that exits the arteriotomy and connects to the Aortix Control System. 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 reduction in myocardial work. Downstream of the pump, aortic pressure is higher, driving increases in renal perfusion (flow *and* pressure).

Aortix Control System

The Aortix Control System (ACS) comprises the Aortix Cradle and Aortix Controller. The Aortix Controller is connected to the Aortix Pump via an extension Lead, either through the Aortix Deployment Tool handle or through a Power Lead Adapter. The Aortix Controller 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 ACS version 1.1, 1.2 or 2.0 may be used.



Aortix Retrieval System

The Aortix Retrieval System (ARS) includes (amongst other components) an 18F ID/21F OD Sheath and Dilator. The ARS may be used if the pump remains implanted post-surgery. For the case where the pump is only used during surgery and the sheath remains in place, the only ARS component used is the Retrieval Handle. Either the ARS or the ARS (integrated) systems may be used.

2.1 Indication for Use

Aortix is indicated as a partial circulatory support device to increase renal perfusion and reduce the incidence of acute kidney injury (AKI) in patients undergoing cardiac surgeries who are at heightened risk of developing AKI.

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; the electronic Instructions for Use (eIFU) document is available exclusively for clinical investigation at: *www.procyrion.com/ifu*. 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 non-sterile and reusable 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 an electronic the Instructions for Use is provided.

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

2.3 STERILIZATION

The Aortix Delivery System (including the Aortix Pump), Introducer Set, and the Aortix Retrieval System are sterilized by Ethylene Oxide (EO) Sterilization. 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.

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 be required to account for and 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.

3 STUDY DESIGN

The study is a prospective, non-randomized feasibility study to evaluate the safety and performance of providing support with the Aortix System to patients at heightened risk of acute kidney injury (AKI) undergoing cardiovascular surgery. Patients who decline Aortix system implant or fail to meet anatomical requirements for Aortix implant will be followed in a the non-Aortix arm. Both arms will have the same visit schedule and data collection requirements except for data pertaining to the Aortix system. Data will be reported for both groups.

3.1 STUDY OBJECTIVES

3.1.1 Safety

1) Observe the nature, severity, and frequency of adverse events associated with the delivery and use of the Aortix System

3.1.2 Effectiveness:

1) Demonstrate a lack of deterioration in post-surgery kidney function
2) Reduce postoperative need for advanced renal supportive therapies such as dialysis or renal replacement therapy (RRT)
3) Reduce readmission rate secondary to postoperative AKI

3.2 STUDY ENDPOINTS

3.2.1 Primary Safety Endpoint

1) Rate of Occurrence of Serious Adverse Events related to the Aortix implant, retrieval, and therapy (rate will be calculated and reported) [timeframe: enrollment to 30 days post-surgery]

3.2.2 Primary Effectiveness Endpoints

1) Characterize the change in severity of AKI observed up to 72 hours post-surgery using the KDIGO criteria [timeframe: baseline to 72 hours post-surgery]
2) Characterize the rate of postoperative use of renal replacement therapy (RRT), ultrafiltration and/or dialysis [timeframe: Aortix placement to 30 days post-surgery]
3) Characterize the rate of 30-day post-surgery readmission due to worsening renal function (if discharged by day 30 post-surgery)

3.2.3 Other Data to be Characterized and Reported

1) Rate of all adverse events, including death over the course of the study
2) Characterize AKI stages as defined by the KDIGO criteria observed postoperatively
3) Characterize serum Creatinine changes over the course of the study
4) Characterize urine output pre- and post-surgery
5) All-cause 30-day post discharge readmissions (if discharged by day 30 post-surgery)
6) Characterize the rate of patients remaining hospitalized 7,14, and 30-days post-surgery.
7) Characterize the length of stay in the ICU/CCU and total duration of length of stay in the hospital post-surgery

3.3 STUDY POPULATION

Patients undergoing cardiac surgeries who are at high risk of developing AKI.

3.3.1 Inclusion Criteria

The patient must meet all of the following inclusion criteria:

1) Have the following risk factor(s) for AKI prior to surgery:
    a. Estimated glomerular filtration rate (eGFR) of ≥ 15 and < 30 ml/min/1.73m^2, **OR**

b. eGFR ≥ 30 and < 60 ml/min/1.73m^2 and **ONE** or more of the following:
    1. Diabetes (regardless of cause) with metabolic, renal, ophthalmic, neurologic, circulatory, or other complications
    2. Documented NYHA class III or IV heart failure within 1 year prior to enrollment
    3. Left ventricular ejection fraction < 35%
    4. Hypertension with comorbid heart or kidney disease
    5. Persistent Atrial Fibrillation

2) Planned (non-emergency) cardiac surgical procedure including, but not limited to coronary bypass surgery, surgical valve replacement or valve repair

3) Age >21 years, willing and able to provide written informed consent.

3.3.2 Exclusion Criteria

The patient must be excluded if they have any of the following:

1) An eGFR of <15 ml/min/1.73m^2 at enrollment
2) Cardiac surgical procedure that uses femoral artery cannulation for cardiopulmonary bypass
3) Current support with a durable LVAD, intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), or percutaneous ventricular assist devices (e.g., Impella or TandemHeart)
4) Patient has known hypo- or hyper-coagulable state such as disseminated intravascular coagulation or heparin induced thrombocytopenia (HIT)
5) Endovascular procedure with ilio-femoral access >12F within previous 30 days
6) Severe Bleeding Risk (any of the following):
    a. Previous intracranial bleed such that the patient cannot safely use anticoagulation per the study requirements
    b. Platelet count <75,000 cells/mm^3
    c. Uncorrectable bleeding diathesis or coagulopathy (e.g., INR ≥ 2 not due to anticoagulation therapy
7) Current endovascular stent graft in the descending aorta or either of the ilio-femoral vessels
8) Contraindicated Anatomy:
    a. Descending aortic anatomy that would prevent safe placement of the device [<18 mm or >31 mm 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

9) Known hypersensitivity or contraindication to study required medications (e.g., anticoagulation therapy) or device materials (e.g., history of severe reaction to nickel or nitinol)
10) Positive pregnancy test if of childbearing potential
11) Participation in any other clinical investigation that is likely to confound study results or affect the study

3.4 Study Duration

It is expected that up to 50 study patients will need to be recruited and enrolled in order to be able to identify and implant 20 patients. Patients who decline to receive the Aortix device or fail anatomical screening and are still planning to undergo surgery, will be offered enrollment in the non-treatment arm of the study. The number of these patients will be capped at 30. Each site should not exceed a 3:2 ratio in terms of non-treatment to treatment patients in order to not exceed the cap.

Patients will be enrolled over a period of approximately one year from time of site activation. The total duration of the patients' participation in the study will not exceed 30 days post the date of surgery.

3.5 Subject Withdrawal and Discontinuation

If a patient chooses to withdraw from the study prematurely, the date, time, and reason for withdrawal will be documented. 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 patient in question.

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.

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.

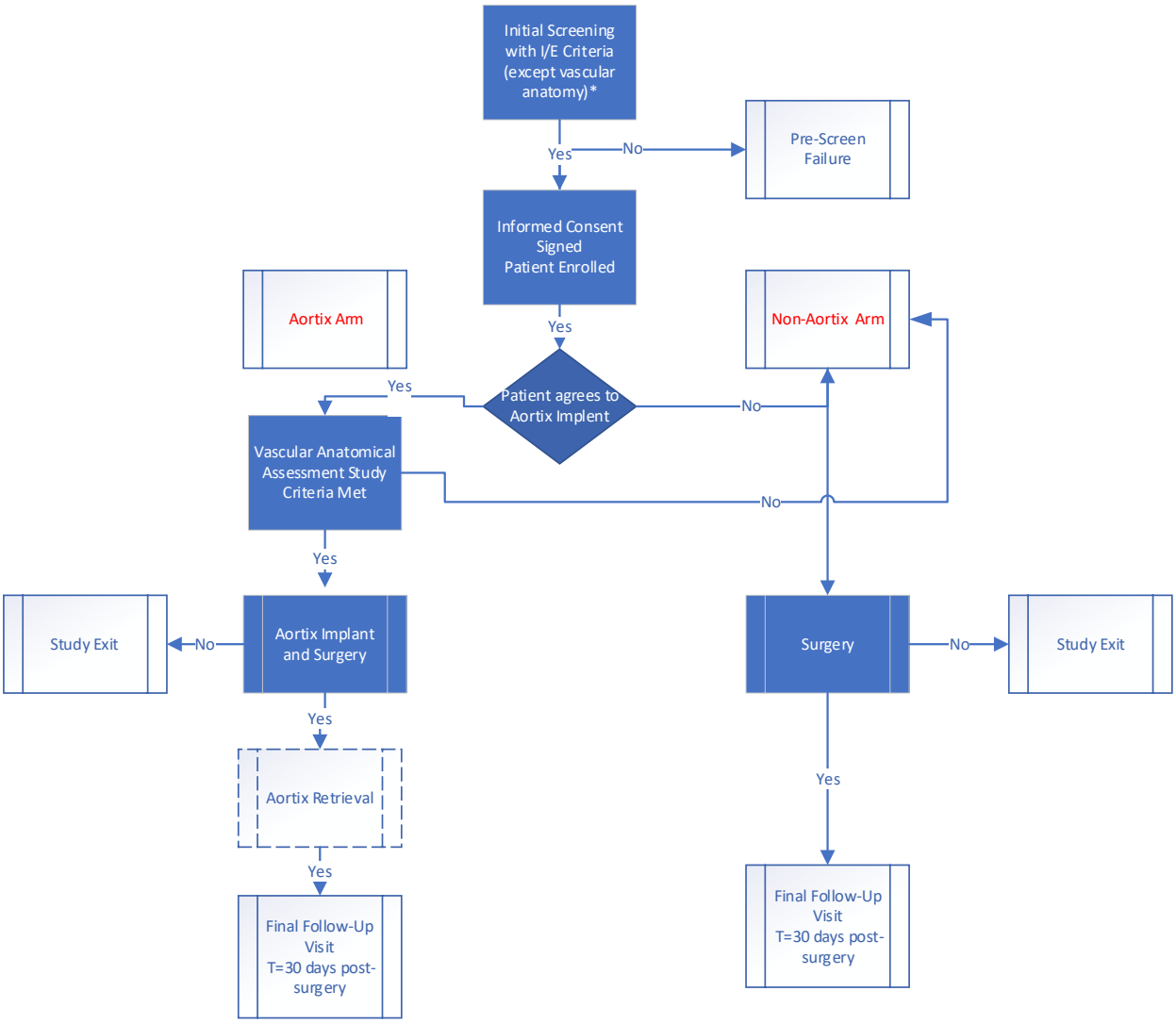
3.6 Subject Confidentiality

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 CRFs 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

4.1 Screening

Prior to consent, medical records will be reviewed to see if the inclusion and exclusion criteria addressed by available information are met. Patients who meet all eligibility criteria with available information will be approached for informed consent prior to final screening. Patients must sign informed consent before undergoing study-related tests including anatomical imaging assessments. Patients who decline the Aortix implant may choose to enroll in the non-treatment arm of the study. Patients who decline the Aortix implant do not need to meet exclusion criteria items 4, 6, 7 and 8. Additionally, patients who fail anatomical screening may also be enrolled in the non-treatment arm of the study. Figure 1 illustrates this process. If, after consent, the patient does not undergo the cardiac surgery, the subject will be withdrawn and exited from the study. Patients at a minimum must be consented, meet inclusion criteria and have a cardiac surgery to be included in the full data collection. A patient that undergoes study related assessments (e.g., anatomical imaging) but then does not undergo a surgery should be followed for 7 days (+/-2 days) for any adverse events related to the assessment.



*If patient refuses the Aortix device, but consents to be followed in the non-Aortix arm, then exclusion criteria 4, 6, 7 and 8 do not apply.

Figure 1: Screening Overview

4.2 ENROLLMENT

The patient is considered enrolled in the study when they sign the informed consent and before protocol-related imaging screening is initiated. Patients who decline implant and enroll directly in the non-treatment arm will not proceed to anatomical imaging.

Following informed consent, patients in the active treatment arm with planned implant will be screened to verify acceptable aortic and femoral anatomy (see exclusion criteria 7). Screening may use sufficiently recent previous imaging studies (less than 12 months old). It is recommended that if imaging studies associated with the upcoming surgical procedure are planned that they include the aorta in the area around the renal arteries and/or femoral arteries when possible. If such studies are not available, aortic screening method may be determined by the site and could include one or more of the following modalities: non-contrast CT, intravascular ultrasound (IVUS), or external arterial ultrasound. Magnetic Resonance Angiography (without contrast) or CO_2 angiography may also be considered. Ilio-femoral screening could be done by angiogram using the lowest possible contrast dose at the time of surgery. Aortic diameter may also be assessed without contrast at the time of surgery by snare expansion or similar method. Patients who do not have appropriate anatomy to proceed to implant may be enrolled in the non-treatment arm.

4.3 BASELINE MONITORING BEFORE SURGERY

Once the patient is enrolled, baseline monitoring will begin. The following activities must be performed (see schedule of procedures in Appendix A):

1. Medical history and physical exam, including height, weight (use standing scale) and ejection fraction
    - EF can be from an echocardiogram or a cardiac catheterization. Baseline EF should be the most recently recorded EF within the previous 6 months available in the medical record
2. Collect admission H&P (include relevant kidney health labs such as serum creatinine), de-identify and provide to sponsor
3. Provide information on current medications
4. Obtain blood for BNP and Serum Creatinine. See required study labs (per Appendix B)
5. Begin monitoring of urine output (ideally Foley catheter will be present) and fluid intake. Record fluid intake and output beginning at least 6 hours prior to the surgery. Note if the patient is admitted for the surgery less than 6 hours prior to the surgery, collection begins on admission.
6. Document use of any prior use of advanced renal supportive therapies such as dialysis or continuous renal replacement therapy (RRT)

4.4 DATA COLLECTION DURING SURGERY

During the surgical procedure, the following data should be collected:

1. Record vital signs during surgery
2. Record fluids in and urine output during surgery

4.5 Aortix Implant Procedure (for active Aortix treatment arm patients only)

Prior to implanting the pump, image vascular anatomy to ensure anatomic suitability for safe implantation as per IFU (PPL004), unless an imaging study is available from within the last 12months, and no clinically significant changes are suspected or likely, in which case a past study may be used to confirm anatomic suitability. Renal artery takeoffs from the aorta should be determined to assist in proper pump placement. Ultrasound or other imaging modality which shows vascular blood flow should be used after implanting and retrieval of the pump to verify the ilio-femoral artery structure and blood flow is not compromised (no vascular damage or clots).

The Aortix implant should occur in the operating theatre during the scheduled surgery post administration of heparin. Refer to the Aortix System Instructions for Use (PPL004) plus IFU Addendum 1 (PPL013) for all details of the Aortix Pump implant, deployment, monitoring, management, and retrieval technique.

Anticoagulation should be initiated prior to the deployment of Aortix Pump in accordance with Appendix C.

Fluoroscopy must be used to aid in device placement, and images of final device position are to be recorded with this modality. The fluoroscopic image of the final device position will be sent to the sponsor. If the Aortix Pump is not positioned or functioning satisfactorily, the device may be repositioned or replaced as appropriate.

During the placement of the Aortix pump, patients should be monitored for any adverse events. All adverse events should be documented and reported to Procyrion. Any components of the Aortix System that malfunction or are associated with an Adverse Event should be returned to the sponsor. Any device deficiencies should be reported.

4.6 Pump Speed

The default pump speed is 25 krpm (kilo revolutions per minute or 1 krpm =1,000 revolutions per minute). This may be adjusted based on clinical need. Any speed changes should be documented in the pump speed changes eCRF. If the pump is being removed at the conclusion of the surgery, the pump should be turned OFF immediately prior to removal.

For patients who continue support with the Aortix pump post-surgery, the pump speed should be gradually reduced prior to removal. The pump speed should be adjusted down in increments of 2-3 krpm to a minimum speed of 20krpm while monitoring the patient. This process should ideally be performed over a minimum timeframe of three hours, with a minimum of two hours to reduce the speed to 20 krpm and a minimum of one hour of observation of the patient at 20 krpm before removal. Only once in the cath lab/procedure room and ready for retrieval should the pump be turned OFF.

4.7 Pump Retrieval and Removal

After the scheduled surgery has been completed, the Aortix pump will be removed following the surgery in accordance with the procedure in the IFU (PPL004) and the IFU Addendum 1 (PPL013).

Alternatively, the treating physician may opt for the pump to remain in-situ post completion of the surgery. The removal procedure requires a fluoroscopy capable operating room or catherization lab. The target suggested therapy duration post-surgery is 48 hours. The Aortix pump will be removed in accordance with the procedure in the IFU (PPL004).

See Appendix C for guidance on anticoagulation therapy during 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.

After the pump is retrieved, it must be placed in the jar located in the Aortix Pump Return kit. The jar must be filled with Formalin collected from your site. The pump should remain in the Formalin for a minimum of 24 hours. The Formalin should then be disposed of and the pump returned in the jar. Please refer to the Return Kit instructions for further information on how to package the pump after retrieval.

4.8 Post-Surgery Follow Up and Data Collection

The data collection described below and summarized in Appendix A and Appendix B are required until the patient completes the study. The term "surgery" refers to the patient's cardiac surgery and not placement or removal of the Aortix pump.

4.8.1 Post-Surgery Patient Management:

Evaluate distal limb perfusion per institutional guidelines until four hours post removal of the Aortix pump. It is important to monitor perfusion to ensure there is no decreased perfusion to the lower extremities.

Cystatin C levels may be used to monitor for potential renal dysfunction. Monitor the patient's anticoagulation status per institution guidelines. This may include institutional guideline directed monitoring of haemostasias status with ROTEM or TEG point of care devices.

While the Aortix pump is implanted, patients should be monitored frequently for issues related to pump origin arterial thromboembolisms. The patient is to be monitored for access site bleeding.

4.8.2 Post-Surgery Data Collection:

4.8.2.1 Immediately Post-Surgery:

1. Record fluids in and urine output during surgery
2. Complete Operative Procedure CRF (e.g., surgery, incision and closure time, anesthesia time, vital signs during surgery, etc.)
3. Obtain operative note and cardiopulmonary bypass (CPB) record (if CPB used), de-identify and provide to sponsor
4. Document use of any advanced renal supportive therapies such as dialysis or continuous renal replacement therapy (RRT)

4.8.2.2 Twenty-Four Hours Post-Surgery (± 1 hour)

1. Monitor and record vital signs

4.8.2.3 72 Hours Post-Surgery (± 4 hours)

1. Record patient's weight (use standing scale[1])
2. Document the ejection fraction (EF), if available during the above required timeframe. EF can be from an echocardiogram or a cardiac catheterization. Document the most recent EF recorded post-surgery.

4.8.2.4 Every Twenty-Four Hours Post-Surgery (± 6 hours) until Day 7 Post-Surgery or Hospital Discharge (whichever comes first)

1. For patients with Aortix, continue to evaluate Aortix pump access site for bleeding or infection
2. Draw blood to monitor BNP and Serum Creatinine
3. Monitor and report any adverse events or deviations
4. Document medications used and medication changes
5. Record 24-hour urine output and fluid ins
6. Document use of any advanced renal supportive therapies such as dialysis or continuous renal replacement therapy (RRT)
7. Obtain post-operative notes daily, de-identify and provide to sponsor
8. Document any new diagnosis of postoperative Acute Kidney Injury
9. If patient remains hospitalized at day 7, document if prolonged admission is due to AKI (document as adverse event)

Prior to discharge, provide patient instructions for reporting any hospitalizations or device related adverse events. Provide an appointment for the study follow-up discharge visit.

4.8.2.5 Visit at Day 30 Post-Surgery (± 3 days)

1. Draw blood for monitoring of BNP and Serum Creatinine
2. Document and report any adverse events or deviations
3. If not discharged from index hospitalization by day 30 post-surgery, document if inability to discharge is due to AKI
4. Document and report any rehospitalizations including date and reason for hospitalization
5. Document use of any advanced renal supportive therapies such as dialysis or continuous renal replacement therapy (RRT)
6. Document days spent in ICU/CCU

4.9 SOURCE DOCUMENTS TO BE PROVIDED TO SPONSOR

The following, de-identified source documents should be provided to the sponsor. Make sure to include the subject ID with the source before providing to the sponsor.

1. Admission history and physical (H&P) (include relevant kidney health labs such as serum creatinine)
2. Operative note for the surgery
3. CPB record for the surgery

[1] If patient is unable to use a standing scale, delay assessment until patient is able to do so.

4. Post-operative notes daily for 7 days or until discharge (whichever is first)
5. Fluoroscopic images of the final pump position post-deployment and pre-retrieval (for Aortix patients only)
6. If any adverse events occurred, discharge summary, if available

5 STUDY TERMINATION

The study may be terminated by the Sponsor at any time with suitable notice to the Principal Investigator, the reviewing EC/IRB and appropriate regulatory agencies. Similarly, the Principal Investigator may withdraw from the study at any time provided patients are followed until study termination.

6 PROTOCOL DEVIATIONS

Every effort must be taken 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 CRF.

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

In the case of repeated or serious non-compliance, Procyrion reserved the right to disqualify the offending site.

7 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.

7.1 POTENTIAL BENEFITS

The Aortix Pump has been designed to improve kidney function and improve hemodynamics. While these benefits have been validated in preclinical studies, the benefits have yet to be validated in this population. It is possible the device may reduce the risk of perioperative kidney injury better than the current standard of care, possibly reducing the hospital length of stay and the need for dialysis. These potential benefits are not yet known and shall be evaluated in this study. The information gathered is expected to benefit patients at risk of developing perioperative kidney injury.

7.2 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, albeit the deployment location of the Aortix pump removes risk of mural thrombotic, or cerebral embolic events associated with MCS devices upstream from the carotid arteries. 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:

- Access site pain or discomfort
- 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
- Embolism
- Hemolysis
- Hematoma
- Hepatic Injury
- Immune reaction
- Infection
- Insertion Site Hematoma
- Limb Ischemia
- Need for Additional Intervention (Surgical or Non-Surgical)
- Neurological Event
- Nerve Injury
- Pump Thrombosis
- Renal Injury
- Sepsis
- Syncope
- Thrombocytopenia
- Thromboembolic Complication
- Thrombotic Vascular Complication
- Vascular Injury (non-Aortic)
- Vascular Steal
- Wound Dehiscence

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.

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.

7.3 Risk Mitigation

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

1. Limited Study Size: A limited number of patients will receive the Aortix Pump in this study to determine performance and safety.
2. Treatment Duration: The Aortix Pump is not a permanent implant and will only remain implanted during the scheduled surgery and at most for a limited time post-surgery.
3. 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 worsening renal function.
4. Site Selection: Study sites will have sufficient expertise and resources to manage the study.
5. 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.
6. Subject Screening: The study protocol includes appropriate precautions in patient selection. For example, patients with known anatomic incompatibilities or a significant bleeding risk are excluded.
7. Adverse Event Monitoring: Timely detection, treatment, and reporting of all adverse events.
8. Independent Safety Monitoring. Use of an external clinical events committee for safety monitoring with timely adjudication of adverse events.

8 Safety

8.1 Subject Death

If a patient dies during or after deployment or retrieval of the Aortix Pump and the death is believed to be related to the device or procedure, 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.

8.2 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 in 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.

For purposes of this study, adverse events considered by the investigator to be related to the Aortix device system or Aortix device procedure or that are due to worsening kidney function postoperatively must be reported. Postoperative adverse events associated with the main surgical procedure such as nausea, bleeding, constipation or the like, when not related to the Aortix system, or diminished kidney function are not required to be reported. If adverse events related to the surgery but not to Aortix are reported, they should be indicated on the eCRF as being "not related" to study procedures.

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:

- led to death
- led to serious deterioration in the health of the participant that resulted in:
  a. a life-threatening illness or injury, or
  b. a permanent impairment of a body structure or a body function, or
  c. prolonged hospitalization, or
  d. 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.

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:

Relatedness should be classified by the Investigator. The following definitions shall be used to classify relatedness:

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. Not related can be used if the event is unlikely to be related.

Related: The event could be attributed to the use of the investigational device or the investigational procedure. Related classification can be used if the event is felt to be likely or probably related.

8.3 Adverse Event Reporting Requirements

Adverse events should be reported to Procyrion on the Adverse Event Electronic Case Report Form (AE eCRF) and using one eCRF 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

9 STATISTICAL CONSIDERATIONS

For the primary purposes of this pilot study, each patient's data will be reviewed individually. The sample size of up to 20 implanted patients is based upon industry standards for early-stage studies of medical devices; the sample size is not statistically derived or powered to show any significant effect. This study is not designed to provide statistically significant outcomes. The study will provide data to be used for subsequent trial design and possible further development of the Aortix System.

10 ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

10.1 INFORMED CONSENT

A patient informed consent form (PICF) template will be provided. If necessary, updates to the template can be made while leaving in the required elements of the PICF. Prior to submission to the IRB/IEC, the investigator customized template must be reviewed and approved by the Sponsor. It is the investigator's responsibility to obtain IRB/EC approval of the updated version of the PICF prior to enrolling any patients into the study.

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.

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.

10.2 Investigator Responsibilities

The investigator is responsible for 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.
- Assisting in identification of potential patients for the study.

10.2.1 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: Maintain signed informed consent forms, copies of all completed CRFs and supporting documentation (laboratory reports, vascular scan reports, etc.), and records of exposure of each patient to the device (procedure note for example).

- Investigational Plan: Keep 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 following the required timelines.
- Ethics Committee (EC) / Institutional Review Board (IRB): Maintain 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: Keep copies of the signed Investigators' Agreements with the Investigators' Curriculum Vitae attached.
- Other: Save any pertinent correspondence and/or records that may be require by applicable laws and regulations

10.3 Sponsor Responsibilities

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

- Selecting and training qualified Investigators
- Providing Investigators and study sites with any new risk information in a timely manner
- Ensuring that site EC/IRB review and approval are obtained prior to any study related procedures and ensuring approvals 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 data monitoring to ensure compliance with the Investigational Plan and to ensure the site continues to be adequate for this study.

10.4 Study Monitoring

Procyrion will ensure appropriate sites and investigators are selected. 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. Occasional site visits will be conducted by an authorized Procyrion representative 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.

10.5 Clinical Events Committee (CEC)

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 physicians who are not participating in the clinical study.

The sponsor will ensure that adequate source documentation is gathered prior to bringing 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. Additionally, if upon review of the source documents, the CEC believes there is an adverse event that has not been reported, the CEC has the authority to request additional AE(s) be reported. 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.

10.6 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. All data requested on the CRF is considered required data unless otherwise specified as “if available.” Pertinent records in connection with this study shall be maintained. This would include patients’ charts, laboratory data, and any documents used to support data entered onto CRFs. Patient worksheets may be provided to collect data not commonly found in patients’ medical records.

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.

10.7 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.

APPENDIX A: SCHEDULES OF DATA COLLECTION

Category	Schedule of Data Collection for Patients with Aortix Removed at the Conclusion of Surgery (Aortix Arm)					
	Pre-Surgery Period (Baseline Monitoring)	**Surgery and Aortix Implant**	**Post-Surgery Monitoring (in Hospital)**			**Study Exit (Day 30 Post-Surgery)**
	Current hospitalization once	Once	24 Hours Post-Surgery (± 1 hour)	At 72 hours Post-Surgery (± 4 hours)	Daily starting at 24 Hours Post-Surgery until Hospital Discharge or Day 7, if still hospitalized (± 6 hours)	Study Exit Visit ± 3 Days
Informed Consent	X					
Anatomy Screening	X					
Med History and Physical Exam	X					
Collect Admission H&P	X					
Weight & Ejection Fraction (EF)	X			X*		
Vital Signs		X	X			
Medications Summary	X	X			X	
Fluid Intake and Urine Output	X	X			X	
Surgical Data with Operative Summary Report and CPB Record		X				
Post Operation Notes		X			X	
Review of AE's, renal replacement therapies	X	X			X	X
Aortix Deployment		X				
Fluoro Image of pump		X				
Required labs (see details App. B)	X		X		X	X
Re-hospitalization, LOS data						X

*Document the most recent EF recorded post-surgery (if available). Acceptable if it is out of the window.

Category	Schedule of Data Collection for Patients with Aortix Removed in a Separate Procedure Post-Surgery (Aortix Arm)						
	Pre-Surgery Period (Baseline Monitoring)	**Surgery and Aortix Implant**	**Aortix Retrieval Post-Surgery**	**Post-Surgery Monitoring (in Hospital)**			**Study Exit (Day 30 Post-Surgery)**
	Current hospitalization once	Once	Once	24 Hours Post-Surgery (± 1 hour)	At 72 hours Post-Surgery (± 4 hours)	Daily starting at 24 Hours Post-Surgery until Hospital Discharge or Day 7, if still hospitalized (± 6 hours)	Study Exit Visit ± 3 Days
Informed Consent	X						
Anatomy Screening	X						
Med History and Physical Exam	X						
Collect Admission H&P	X						
Weight and Ejection Fraction (EF)	X				X*		
Vital Signs		X		X			
Medications Summary	X	X				X	
Fluid Intake and Urine Output	X	X	X			X	
Surgical Data with Operative Summary Report and CPB Record		X	X				
Post-Operation Notes		X	X			X	
Review of AE's, renal replacement therapies	X	X	X			X	X
Aortix Retrieval			X				
Fluoro Image of pump		X	X				
Required labs (See details App. B)	X			X		X	X
Re-hospitalization, LOS data							X

*Document the most recent EF recorded post-surgery (if available). Out of window measurement acceptable (not a deviation) for EF.

Category	Schedule of Data Collection for Patients Who Do Not Receive the Aortix Pump (Non-Aortix Arm)					
	Pre-Surgery Period (Baseline Monitoring)	**Surgery**	**Post-Surgery Monitoring**			**Study Exit (Day 30 Post-Surgery)**
	Current hospitalization once	Once	24 Hours Post-Surgery (± 1 hour)	At 72 hours Post-Surgery (± 4 hours)	Daily starting at 24 Hours Post-Surgery until Hospital Discharge or Day 7, if still hospitalized (± 6 hours)	Study Exit Visit ± 3 Days
Informed Consent	X					
Anatomy Screening**	X					
Med History and Physical Exam	X					
Collect Admission H&P	X					
Weight and Ejection Fraction (EF)	X			X*		
Vital Signs		X	X			
Medications Summary	X	X			X	
Fluid Intake and Urine Output	X	X			X	
Surgical Data with Operative Summary Report and CPB Record		X				
Post Operation Notes		X			X	
Review of AE's, renal replacement therapies	X	X			X	X
Required labs (See details App. B)	X				X	X
Re-hospitalization, LOS data						X

*Document the most recent EF recorded post-surgery (if available). Acceptable if it is out of the window.

**If patient consents to and undergoes anatomical screening

APPENDIX B: DETAILED SCHEDULE OF BLOOD LABS

Lab Requirements for all Consented Patients			
Category	**Pre-Surgery Period (Baseline Monitoring)**	**Post-Surgery**	**Day 30 Post- Surgery**
	Once	Every 24 Hours Post Surgery through Day 7 (or discharge if earlier) (± 6 hours)	Once ± 3 days
BNP	X	X	X
Serum Creatinine	X	X	X

APPENDIX C: ANTICOAGULATION PROTOCOL GUIDANCE

Follow your institution's protocol for percutaneous MCS devices.

The following targets are recommended:

Device Implant:
Device implant takes place in the operating theatre between the initial, un-heparinized portion of the surgery and full heparinization. Once the initial portion of the surgery (including, for example, vessel harvesting and sternotomy as well as femoral access for Aortix deployment and placement of suture-mediated closure devices) is complete, Aortix deployment commences.

1. Once the Aortix Introducer Sheath is inserted into the femoral artery, administer unfractionated heparin (UFH) to a target ACT of 200 seconds.
2. After insertion of the sheath and until end of pump implantation procedure, ACT should be maintained at 200 seconds.
3. Once the sheath has been removed and intermediate hemostasis has been achieved (e.g., using the pre-placed suture-mediated closure devices), full heparinization for initiation of cardiopulmonary bypass (if used) may proceed.

Peri and Post-Operative Support Period:
During cardiopulmonary bypass (if used) the patient does not require any additional anticoagulation management beyond your institution's normal practices. Upon completion of surgery, the patient may have their anticoagulation reversed with protamine or similar to a target ACT of 180-200 seconds as per institution practice and treating physician's discretion.

Note: High inter- and intra-patient variability is common with patients receiving 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).

Post-surgery, as soon as the treating physician deems the patient to not be at risk of post-operative bleed and continuing up to retrieval of the Aortix device:

1. Titrate systemic heparin dose to achieve a goal aPTT of 45-60 seconds or a goal Anti-Xa UFH level of 0.3-0.7 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. Management of oral anti-platelet therapy is at the discretion of the treating physician based on surgical factors.
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 may be a viable alternative until device retrieval if post-operative bleeding risk is deemed low.

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

APPENDIX D: KDIGO STAGING OF AKI

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	≥3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) OR Initiation of renal replacement therapy OR In patients <18 years, eGFR <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Baseline is SCr level known or presumed to have occurred within the prior 7 days

Acute increases are within 48 hours

APPENDIX E: REFERENCES

1. HCUP National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP). Published online 2017. www.hcup-us.ahrq.gov/nisoverview.jsp

2. Bihorac A. Acute Kidney Injury in the Surgical Patient: Recognition and Attribution. *Nephron*. 2015;131(2):118-122. doi:10.1159/000439387

3. van Kuijk J-P, Flu W-J, Chonchol M, et al. Temporary Perioperative Decline of Renal Function Is an Independent Predictor for Chronic Kidney Disease. *Clin J Am Soc Nephro*. 2010;5(7):1198-1204. doi:10.2215/cjn.00020110

4. Hobson CE, Yavas S, Segal MS, et al. Acute Kidney Injury Is Associated With Increased Long-Term Mortality After Cardiothoracic Surgery. *Circulation*. 2009;119(18):2444-2453. doi:10.1161/circulationaha.108.800011

5. Bihorac A, Yavas S, Subbiah S, et al. Long-Term Risk of Mortality and Acute Kidney Injury During Hospitalization After Major Surgery. *Ann Surg*. 2009;249(5):851-858. doi:10.1097/sla.0b013e3181a40a0b

6. Ishani A, Nelson D, Clothier B, et al. The Magnitude of Acute Serum Creatinine Increase After Cardiac Surgery and the Risk of Chronic Kidney Disease, Progression of Kidney Disease, and Death. *Arch Intern Med*. 2011;171(3):226-233. doi:10.1001/archinternmed.2010.514

7. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and Long-Term Renal and Cardiovascular Outcomes in United States Veterans. *Clin J Am Soc Nephro*. 2014;9(3):448-456. doi:10.2215/cjn.02440213

8. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. *Ann Surg*. 2015;261(6):1207-1214. doi:10.1097/sla.0000000000000732

9. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet*. 2013;382(9887):170-179. doi:10.1016/s0140-6736(13)60647-9

10. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204. doi:10.1186/cc2872

11. Kellum, JA. Lameire NH, et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplement*. 2012;(2):1-138. doi:10.1038/kisup.212.1

12. Kheterpal S, Campbell DA, M H, al et. Development and Validation of an Acute Kidney Injury Risk Index for Patients Undergoing General Surgery. *Anesthesia*. 2009;(110):505-515.

13. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in Hospital Mortality Associated with Inpatient Surgery. *New Engl J Medicine*. 2009;361(14):1368-1375. doi:10.1056/nejmsa0903048

14. O'Neal et al. The Importance Of Continuous Monitoring Of Urine Flow In Critical Care Patients. *Critical Care*. 2016;(20):187.

15. Bihorac A, Brennan M, Ozrazgat-Baslanti T, et al. National Surgical Quality Improvement Program Underestimates the Risk Associated With Mild and Moderate Postoperative Acute Kidney Injury. *Crit Care Med*. 2013;41(11):2570-2583. doi:10.1097/ccm.0b013e31829860fc

16. Lewington AJP, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84(3):457-467. doi:10.1038/ki.2013.153

17. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intens Care Med*. 2015;41(8):1411-1423. doi:10.1007/s00134-015-3934-7

18. Mandelbaum T, Scott DJ, Lee J, et al. Outcome of critically ill patients with acute kidney injury using the Acute Kidney Injury Network Criteria. *Crit Care Med*. 2011;39(12):2659-2664. doi:10.1097/ccm.0b013e3182281f1b

19. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81(5):442-448. doi:10.1038/ki.2011.379

20. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*. 2019;73(3):A7-A8. doi:10.1053/j.ajkd.2019.01.001

21. Alshaikh HN, Katz NM, Gani F, et al. Financial Impact of Acute Kidney Injury After Cardiac Operations in the United States. *Ann Thorac Surg*. 2018;105(2):469-475. doi:10.1016/j.athoracsur.2017.10.053

22. Gumbert SD, Kork F, Jackson ML, et al. Perioperative Acute Kidney Injury. *Anesthesiology*. 2020;132(1):180-204. doi:10.1097/aln.0000000000002968

23. Borthwick E, Ferguson A. Perioperative acute kidney injury: risk factors, recognition, management, and outcomes. *Bmj*. 2010;341(jul05 1):c3365. doi:10.1136/bmj.c3365

24. Aitken E, Carruthers C, Gall L, Kerr L, Geddes C, Kingsmore D. Acute kidney injury: outcomes and quality of care. *Qjm Int J Medicine*. 2013;106(4):323-332. doi:10.1093/qjmed/hcs237

25. Kellum JA, Lameire N. For the KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17(1):204. doi:10.1186/cc11454

26. Nadim MK, Forni LG, Bihorac A, et al. Cardiac and Vascular Surgery–Associated Acute Kidney Injury: The 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. *J Am Heart Assoc*. 2018;7(11). doi:10.1161/jaha.118.008834

27. Squara P, Hollenberg S, Payen D. RECONSIDERING VASOPRESSORS FOR CARDIOGENIC SHOCK Everything should be made as simple as possible, but not simpler. *Chest*. 2019;156(2):392-401. doi:10.1016/j.chest.2019.03.020

28. Rio C del, Clifton W, Heuring J, et al. AORTIX™, A Novel Catheter-Based Intra-Vascular Assist Device, Provides Cardio-Renal Support While Improving Ventriculo-Arterial Coupling and Myocardial Demand in Sheep with Induced Chronic Ischemic Heart Failure. *J Am Coll Cardiol*. 2015;65(10):A800. doi:10.1016/s0735-1097(15)60800-2