CLINICAL INVESTIGATIONAL PLAN

Multi Center, Prospective, Non-Randomized, Single-Arm Trial Evaluating the Clinical Safety and Performance Of the HeartWare MVAD® System For the Treatment of Advanced Heart Failure

Investigational Product:	**MVAD® System**
CIP Number:	**HW-MVAD-01**
Version Number:	**7.0**
IDE Number:	**N/A**
Date:	**11 November 2014**

1.0 ADMINSTRATIVE INFORMATION

1.1 Sponsor Contacts

Medical, Clinical and Operational Support

Sponsor Name:	HeartWare, Inc.
Sponsors Responsible Medical Officer	[redacted]
Sponsor Telephone Number	+1 508 739 0842
Sponsor Fax Number	+1 508 739 0948
Manufacturer and Sponsor Address:	14400 NW 60th Avenue Miami Lakes, FL 33014 USA

1.2 European Authorized Representative

Authorized Representative Name:	[redacted]
Address:	MedPass International Limited Windsor House, Bretforton Evesham Worcs. WR11 7JJ, United Kingdom

1.3 Australian Authorized Representative

Authorized Representative Name:	[redacted]
Address:	HeartWare Pty Limited 68 Pitt Street Level 10 Sydney NSW 2000 Australia

1.4 CIP Administrative Information

CIP Number:	HW-MVAD-01
Revision Number:	7.0
CIP Date:	11 Nov 2014
IDE Number:	N/A
Investigational Product:	MVAD System

1.5 Amendment History

Date	Amendment Number	Amendment Type

1.6 Sponsor CIP Approval

Representatives of HeartWare

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this CIP and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Organization of Standardization (ISO)14155 2011- Clinical investigation of medical devices for human subjects – Good Clinical Practice

All applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

Sponsor Signatory: [redacted]

Name & Title

Name & Title

Name & Title

Name & Title

Name & Title

Name & Title

1.7 Investigator Agreement

I will provide copies of the clinical investigational plan (CIP) and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the investigational products and the conduct of the study.

I will use only the informed consent form approved by the sponsor and the Institutional Review Board/Independent Ethics Committee (IEC/EC) or its representative.

I also understand that this study will not be initiated without approval of the appropriate Institutional Review Committee, Competent Authority (CA) and that all administrative requirements of the governing body of the institution will be complied with fully.

I will obtain written informed consent from all participating subjects in accordance with requirements as specified in ISO 14155 2011- Clinical investigation of medical devices for human subjects -- Good Clinical Practice.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report without unjustified delay, all Serious Adverse Events (SAEs) and Device Deficiencies (DDs) that could have led to an Unanticipated Serious Adverse Device Effect (USADE).

I further agree that HeartWare and/or designee will have access to any original source documents from which electronic case report form (eCRF) information may have been generated.

I also agree to have control over all clinical supplies (including investigational products) provided by HeartWare and/or designee and collect, account and handle all clinical specimens in accordance with the CIP.

I further agree not to originate or use the name of HeartWare Inc. and/or MVAD, or any of its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this CIP, to any amendment hereto, or to the performance hereunder, without the prior written consent of HeartWare Inc.

I herewith declare that I agree with the CIP described in detail in this document and agree to conduct the study in accordance with the CIP and in compliance with Good Clinical Practice, and all applicable regulatory requirements.

Investigator Name (print) _____

Investigator Signature _____ Date _____

Name of Facility _____

Location of Facility (City) _____

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2.0 STUDY SUMMARY

Name of Sponsor(s): HeartWare Inc.	
Title of CIP: **Multi Center, Prospective, Non-Randomized, Single-Arm Trial Evaluating the Clinical Safety and Performance Of the HeartWare MVAD® System For the Treatment of Advanced Heart Failure.**	
Trial Number: HW-MVAD-01	
Number of Subjects: 60 subjects	**Number of Sites:** Minimum of 5 sites and a maximum of 10 sites in up to 5 countries
Trial Design: Multi-center, prospective, non-randomized, single-arm trial	
Primary Endpoint: The primary endpoint is survival at 6 months presented as a simple proportion (subjects alive on the MVAD pump divided by endpoint eligible subjects). Transplants, explants for recovery and exchanges (to a device other than the MVAD pump) prior to 6 month follow-up will be eligible for endpoint analysis (with survival status identified at the time of the procedure). Survival failure is associated with events (death) on the MVAD pump.	
Secondary endpoints: 1. Survival at 24 months presented as a simple proportion (defined like the primary endpoint) 2. Overall Survival (Time to Death) 3. Incidence of major bleeding, per INTERMACS definition 4. Incidence of all device failures and device malfunctions per INTERMACS definition 5. Incidence of major infection, per INTERMACS definition 6. Incidence of neurological dysfunction per INTERMACS definition 7. Health Status change, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol EQ-5D-5L 8. Functional status change, as measured by NYHA and 6-minute walk 9. Frequency and rates of adverse events (AEs) throughout VAD support per INTERMACS Definition 10. Length of operative time and initial hospital stay 11. Re-Hospitalizations (excluding planned procedures) 12. Transplantations 13. Explants	
Safety Assessments: Laboratory and clinical parameters will be followed to evaluate the safety and performance of the Miniaturized Ventricular Assist Device (MVAD) System; these include adverse event reporting and monitoring, routine clinical laboratory tests (hematology, biochemistry, and urinalysis), vital signs, hemodynamic, MVAD parameters, abbreviated neurological examinations/ questionnaires, review of concomitant medications and echocardiogram.	

Device: MVAD Pump

The MVAD Pump is an implantable ventricular assist device that requires the following major components to implant and operate it: Implantable Axial Flow Pump with Conduits, Controller, Monitor, Batteries, Battery Charger, Surgical Tools, Explant Plug and Pump Accessories.

Intended Use:

The MVAD System is intended for use in patients who are at risk of death from refractory end-stage heart failure. The MVAD System is designed for in-hospital and out-of-hospital settings. The MVAD System is contraindicated:

- For patients who cannot tolerate anticoagulation therapy

Period of Evaluation:

Estimated start date: Second Quarter 2015 (First Implant)

Estimated end date: Fourth Quarter 2015 (Last Implant) to Fourth Quarter 2017 (Last subject out)

Trial Design:

This multi-center, prospective, non-randomized, single-arm trial will investigate the safety and performance of the Miniaturized Ventricular Assist Device (MVAD) system over 24 months in subjects with advanced heart failure. The primary endpoint is survival at 6 months presented as a simple proportion (subjects alive on the MVAD pump divided by endpoint eligible subjects). Secondary endpoints include the incidence of bleeding, incidence of major infections (per INTERMACS definitions), time to death, incidence of all device failures and device malfunctions, Health Status improvement, and Functional status improvement. Safety measures will include the frequency and rates of adverse events, overall and for each specific event, which will be collected throughout VAD support.

This is a performance goal based trial concerning the primary endpoint and the first secondary endpoint. The primary endpoint is survival at 6 months (estimated to be 85%) based on a performance goal of 70%, with a one-sided significance level of 0.05. The secondary endpoint is survival at 24 months (estimated to be 70%) based on a performance goal of 52.5%, with a one-sided significance level of 0.05.

Background:

Heart failure is one of the leading causes of death in the developed world. Overall, 50% of heart failure patients are dead at 4 years.[1] It is estimated that 2-6% of the adults in the world suffer from heart failure with a higher prevalence in industrialized nations. There are up to 15 million cases in the European Union.[1]

Improvements in treatment and survival as well as expansion of the aging population have contributed to the rising incidence and prevalence of the disease. Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts this form of therapy to just over 3700 patients/year worldwide.[4]

Over the last decade, bridging to cardiac transplantation with implantable left ventricular assist device (LVAD) systems has gained wider clinical acceptance, and today LVADs are used to extend life expectancy for patients with advanced heart failure who deteriorate while awaiting a donor heart. Approximately 32% of the patients who receive heart transplants are bridged with ventricular assist devices.[4] There are currently several approved devices in the European Union and throughout the world being used to bridge candidates to cardiac transplantation. The use of permanent LVADs as an alternative to transplantation has also gained approval and acceptance. This permanent use is known as destination therapy. The MVAD Pump is an implantable continuous flow pump that was designed to provide flows up to 7 L/min in a small device that is both lightweight and simple to use. Due to its small size and mechanical simplicity, the MVAD system may provide benefits not currently available with existing technology that require abdominal pump pockets. Furthermore, the size of the MVAD Pump and intrapericardial positioning may be suitable for patients who cannot tolerate an abdominal surgical procedure.

Main Criteria for Inclusion:

1. Must be ≥18 years of age at consent
2. Subjects with advanced heart failure symptoms (Class IIIB or IV) who meet one of the following):
    a. on optimal medical management including dietary salt restriction and diuretics, for at least 45 out of the last 60 days and are failing to respond; or
    b. in Class III or Class IV heart failure for at least 14 days and dependent on intra-aortic balloon pump (IABP) and/or inotropes.
3. Left ventricular ejection fraction ≤25%.
4. Female subjects of childbearing potential must agree to use adequate contraceptive precautions (defined as oral contraceptives, intrauterine devices, surgical contraceptives or a combination of condom and spermicide) for the duration of the study.
5. The subject has signed the informed consent form.

Main Criteria for Exclusion:

1. Body Mass Index (BMI) > 47.
2. Body Surface Area (BSA) < 1.0 m^2.
3. Partial or full mechanical circulatory support within thirty days of implant.
4. Existence of any ongoing mechanical circulatory support (MCS) other than an intra-aortic balloon pump (IABP) or TandemHeart PTVA .
5. Prior cardiac transplant or cardiomyoplasty.
6. History of confirmed, untreated abdominal or thoracic aortic aneurysm (diameter > 5 cm).
7. Acute myocardial infarction within 14 days of implant as diagnosed by ST or T wave changes on the electrocardiogram (ECG), diagnostic biomarkers, ongoing pain and hemodynamic abnormalities.
8. On ventilator support for > 72 hours within the four days immediately prior to implant.
9. Pulmonary embolus within three weeks of implant as documented by computed tomography (CT) scan or nuclear scan.
10. Symptomatic cerebrovascular disease, stroke within 180 days of implant or > 80% stenosis of carotid or cranial vessels in the absence of confirmed collateral circulation
11. Uncorrected moderate to severe aortic insufficiency.
12. Severe right ventricular failure as defined by the anticipated need for extracorporeal membrane oxygenation (ECMO) at the time of screening.
13. Active, uncontrolled infection diagnosed by a combination of clinical symptoms and laboratory testing, including but not limited to, continued positive cultures, elevated temperature and white blood cell (WBC) count, hypotension, tachycardia, generalized malaise despite appropriate antibiotic, antiviral or antifungal treatment.
14. Uncorrected thrombocytopenia or generalized coagulopathy (e.g., platelet count < 75,000, International Normalized Ratio (INR) > 2.0 or Partial Thromboplastin Time (PTT) > 2.5 times control in the absence of anticoagulation therapy).
15. Intolerance to anticoagulant or antiplatelet therapies or any other peri- or postoperative therapy that the investigator may administer based upon the subject s health status.
16. Serum creatinine > 3.0 mg/dL within 72 hours of implant or requiring dialysis.
17. Specific liver enzymes [Aspartate Aminotransferase (AST) (SGOT), and Alanine Aminotransferase (ALT) (SGPT)] > 3 times upper limit of normal within 72 hours of implant.
18. A total bilirubin > 3 mg/dL within 72 hours of implant, or biopsy proven liver cirrhosis or portal hypertension.
19. Pulmonary vascular resistance (PVR) is demonstrated to be unresponsive to pharmacological manipulation.
20. Subjects with a mechanical heart valve.
21. Etiology of heart failure is due to, or associated with, uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis or restrictive cardiomyopathy.
22. History of severe COPD or severe restrictive lung disease (e.g. FEV1 < 50% predicted value).
23. Participation in any other trial involving investigational drugs or devices within 4 weeks prior

to screening and last visit of the trial.

24. Severe illness, other than heart disease, which would limit survival to < 3 years.
25. Peripheral vascular disease with rest pain or ischemic ulcers of the extremities.
26. Pregnancy and breast feeding.
27. Psychiatric disease, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the CIP and LVAD.
28. Subject unwilling or unable to comply with trial requirements.
29. Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the investigator.
30. Employees of the investigator or trial site, with direct involvement in this trial or other trials under the direction of the investigator or trial site, as well as family members or employees of the investigator.

Trial Procedures: Please refer Appendices 17.1.1 and 17.1.2: Time and Event Schedules

Course of the trial:

The trial will last up to 24 months for each subject and includes of a Screening Visit (Pre-implant) followed by Hospitalization period (Day 1-3) after Implantation of the MVAD Pump, leading into the visit at subject discharge, and Follow-Up Visits at Month 1, 3, 6, 12, 18 and 24.

Main Criteria for Evaluation and Analyses:

Subjects not eligible for endpoint analysis include lost to follow-up and withdrawals prior to endpoint. Transplants, explants for recovery and exchanges (to a device other than the MVAD Pump) prior to endpoint will be eligible for endpoint analysis with their survival status identified at the time of the procedure. Survival failure is associated with events (death) on the MVAD pump. Endpoint analyses will be performed at 6 months and 24 months.

Additional secondary endpoints will also be assessed at 6 months and 24 months. No formal statistical hypothesis tests will be conducted. Analyses for the additional secondary endpoints will involve Kaplan-Meier curves for time to event outcomes, descriptive statistics for quantitative outcomes, and count and frequency results for categorical outcomes.

Sample Size Justification and Statistical Considerations:

The primary endpoint is survival at 6 months presented as a simple proportion (binomial rate). The survival rate at 6 months is estimated to be 85%, based on HeartWare s experience with the HVAD. This estimated rate will be compared to a performance goal (70%). A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and a power greater than 80% (the lower bound of a one-sided 95% exact binomial confidence interval must exceed 70% for success). Three additional subjects (for a total of 60) will be implanted to address for possible attrition due to lost to follow-up or withdrawal.

The first secondary endpoint is survival at 24 months presented as a simple proportion (binomial rate). The survival rate at 24 months is estimated to be 70%, based on HeartWare s experience with the HVAD. This estimated rate will be compared to a performance goal (52.5%). A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and a power greater than 80% (the lower bound of a one-sided 95% exact binomial confidence interval must exceed 52.5% for success). Three additional subjects (for a total of 60) will be implanted to address for possible attrition due to lost to follow-up or withdrawal.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AC or DC	Alternating-Current or Direct-Current
ACC	American College of Cardiology
ADE	Adverse Device Effect
ACT	Activated Clotting Time
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
ASA	Acetylsalicylic Acid
BiVAD	Biventricular Assist Device
BMI	Body Mass Index
BPC	Blood Pressure Cuff
BSA	Body Surface Area (m2)
BTT	Bridge to Transplantation
cc	Cubic Centimeter (equal to a milliliter)
CA	Competent Authority
CFR	Code of Federal Regulations
CHF	Chronic Heart Failure
CIP	Clinical Investigational Plan
CK	Creatine Kinase
CK- MB	Creatine Kinase MB Isoenzyme
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C- Reactive Protein
CRT	Cardiac Resynchronization Therapy
CSS	Clinical Summary Score of KCCQ
CT	Computed Tomography
CVA	Cerebral Vascular Accident (stroke)
CVP	Central Venous Pressure
DD	Device Deficiency
dL	Deciliter

Abbreviation	Definition
DNR	Do Not Resuscitate
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EEC	European Economic Community
EEG	Electro Encephalogram
EQ-5D-5L	EuroQoL (European Quality of Life) 5-Dimensions and 5 levels (tool)
EU	European Union
FEV_1	Forced expiratory volume in one second
GCP	Good Clinical Practice
g	Gram
HEPA	High-Efficiency Particulate Arresting
HF	Heart Failure
HPA	High Pressure Area
hr	Hour
IABP	Intra-Aortic Balloon Pump
IBPM	Improved Blood Pressure Management
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethic Committee
IFU	Instructions For Use
INR	International Normalized Ratio
INTERMACS	InterAgency Registry for Mechanical Assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
ISO	International Organization for Standardization
ITT	Intent to Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire (tool)
kg	Kilogram
LCD	Liquid Chrystal Display
LDH	Lactate Dehydrogenase
LED	Light Emitting Diode
Li-Ion	Lithium ion
L/min	Liters per minute

Abbreviation	Definition
LOS	Length of Stay
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End- diastolic Diameter
LVEDV	Left Ventricular End- diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End- systolic Diameter
LVESV	Left Ventricular Endiastolic Volume
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MCSD	Mechanical Circulatory Support Device
MEDDEV	Medical Devices
m	Meter
Mg	Milligram
MI	Myocardial Infarction
mL	Milliliter
Mm	Millimeter
MRS	Modified Rankin Scale
N or n	Number of Subjects
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association (heart failure classification)
NP	Nurse Practitioner
OMM	Optimal Medical Management
OR	Operating Room
OSS	Overall Clinical Summary Score of KCCQ
PA	Physician Assistant
PCWP	Pulmonary Capillary Wedge Pressure
PG1	Performance Goal 1
PG2	Performance Goal 2
PI	Principal Investigator
PP	Per-Protocol
PRBC	Packed Red Blood Cells
Pt (or Pts)	Patient (or Patients)
PTT	Partial Thromboplastin Time (activated = aPTT)
PVO_2	Pulmonary Venous Oxygen Tension
PVR	Pulmonary Vascular Resistance
QoL	Quality of Life
RAP	Right Arterial Pressure

Abbreviation	Definition
RGA	Returned Goods Authorization
RHC	Right Heart Catheterization
RPM	Rotations per Minute
RV	Right Ventricle
RVAD	Right Ventricular Assist Device
RVEF	Right Ventricular Ejection Fraction
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SVO_2	Mixed Venous Oxygen Saturation
TIA	Transient Ischemic Attack
TTR	Time in Therapeutic Range
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VAD	Ventricular Assist Device
VO2 max	Maximal Rate of Oxygen Consumption
WBC	White Blood Cell

4.0 INTRODUCTION

4.1 Background and Rationale

Heart failure is one of the leading causes of death in the developed world. It is estimated that 2-6% of the adults in the world suffer from heart failure with a higher prevalence in industrialized nations. There are up to 15 million cases in the European Union,[1] near 300,000 cases in Australia and approximately 5.3 million cases diagnosed in the United States.[2, 3] Overall, 50% of patients with heart failure die within four years, while 40% of patients who are hospitalized due to acute heart failure are readmitted or die within one year.[1] Improvements in medical treatments and longer life expectancies have expanded the heart failure patient population, consequently increasing the prevalence of the disease. Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts this form of therapy to just over 3,700 patients/year worldwide, as reported to the International Society for Heart and Lung Transplantation (ISHLT) Transplant Registry.[4]

Over the last decade, bridging to cardiac transplantation with implantable left ventricular assist device (LVAD) systems has gained wider clinical acceptance, and today LVADs are used to extend life expectancy for patients with advanced heart failure who deteriorate while awaiting a donor heart. Approximately 32% of the patients who receive heart transplants are bridged with ventricular assist devices.[4] There are currently several approved devices in the European Union and throughout the world being used to bridge candidates to cardiac transplantation. The use of permanent LVADs as an alternative to transplantation has also gained approval and acceptance. This permanent use is known as destination therapy.

The HeartWare Miniaturized Ventricular Assist System includes an implantable continuous, axial flow pump (MVAD Pump) that was designed to provide flows up to 7 L/min in a small device that is both lightweight and simple to use. Due to its small size and mechanical simplicity, the MVAD System may provide benefits not currently available with existing technology that require abdominal pump pockets.

Furthermore, the size of the MVAD Pump may be suitable for patients who cannot tolerate an abdominal surgical procedure.

Previous Patient Experience

This trial will involve the first clinical use of the MVAD Pump.

However, many of the design aspects of the MVAD Pump were either derived from, or are improvements based on experiences gained from, the HeartWare HVAD. Some of these include integrated inflow, intrapericardial pump placement via a rigid tightening sewing ring, and a gel impregnated outflow graft. Many of the design, pump control algorithms, and alarm features of the MVAD Pump peripherals are the result of lessons learned from the HVAD controllers, chargers, power adapters and batteries. In addition, there has been clinical experience with an Intraventricular VAD manufactured by another company but the impeller design and suspension differ from the MVAD Pump. Positive in-vitro and in-vivo results with the MVAD pump are a substantial base justifying the conduct of a first clinical use of the MVAD pump in patients with refractory end-stage heart failure.

4.2 Name and Intended Use

The MVAD System is intended for use in patients who are at risk of death from refractory end-stage heart failure. The MVAD System is designed for in-hospital and out-of-hospital settings.

The MVAD System is contraindicated:

- For patients who cannot tolerate anticoagulation therapy

5.0 DEVICE DESCRIPTION

5.1 MVAD® System

5.1.1 MVAD® System Overview

The MVAD System consists of a small, wearless, continuous flow pump and associated surgical tools and implant accessories, peripheral components which control and power the system, and a monitor which allows for programming and monitoring of the system.

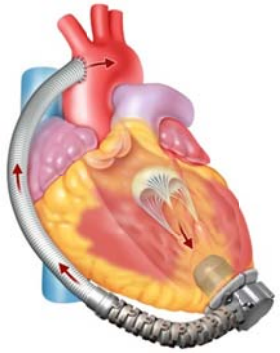
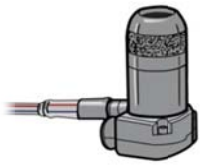
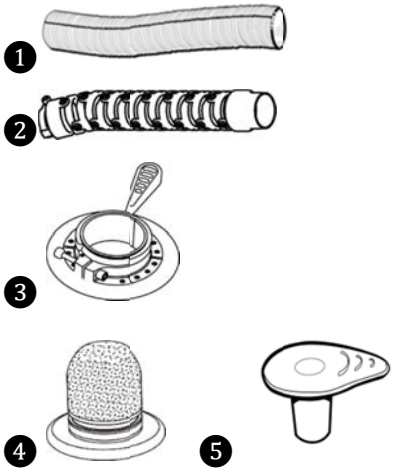
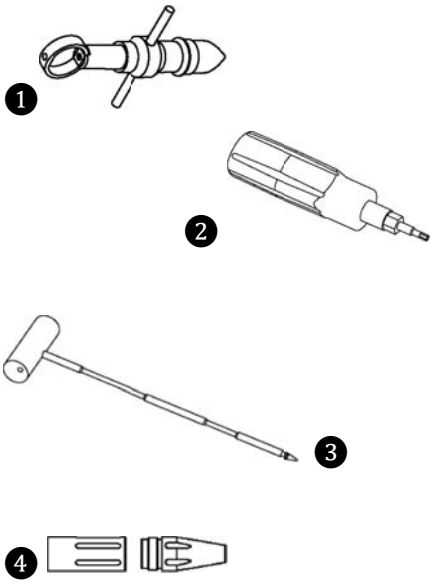


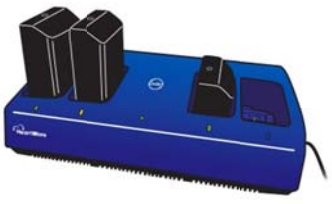
Figure 1: MVAD® Pump Placement

During implantation, the pump s integrated inflow cannula is inserted into the left ventricle and is secured to the myocardium using an adjustable sewing ring (Figure 1). A 10mm diameter, gel impregnated, polyester outflow graft connects the pump to a major artery. A strain relief fits over the outflow graft to prevent kinking and to secure the outflow graft to the pump housing. The percutaneous driveline connects the implanted pump to the Pal Controller and power sources. The driveline is wrapped with a woven polyester fabric to encourage tissue in-growth at the skin exit site. The pump size and intraventricular inflow cannula allow for pericardial placement, eliminating the need for an abdominal pocket.

5.1.2 MVAD® System Components

Component	Image	Description
MVAD® Pump		Small, wearless, continuous flow pump with integrated inflow cannula. Can generate up to 7 L/min of blood flow. Implanted in the pericardial space.
MVAD® Pump Implant/ Explant Accessories		Components required for VAD implantation/ explantation: ❶ HeartWare System Quick Connect Outflow Graft ❷ Strain Relief ❸ Gimbaled Sewing Ring with Zero Positioning Tool ❹ HeartWare Plug ❺ Inflow Cap **STERILE**: All HeartWare components used at implant including surgical tools are provided sterile.
MVAD® Pump Surgical Tools		Tools utilized during VAD implantation and/or explantation: ❶ Coring Tool ❷ Torque Wrench ❸ Tunneler ❹ Driveline Cap **STERILE**: All HeartWare components used at implant including surgical tools are

Component	Image	Description
		provided sterile.
Pal™ Driveline Extension Cable		The Pal Driveline Extension Cable connects the controller to the pump and allows a non-sterile controller to bridge the sterile field at implant. The Pal Driveline Extension Cable is intended to be used only in the operating room. **STERILE**: All HeartWare components used at implant, including the Pal Driveline Extension Cable, are provided sterile.
Pal™ Controller	 	Wearable, lightweight, and water-resistant (when connected to external battery/cap) microprocessor based device that operates the MVAD Pump. Provides audible, visual, and vibratory alerts, system status, and troubleshooting tips to the patient. Contains a built-in driveline cable that connects to pump driveline. Also has an internal, rechargeable, lithium ion battery that will run the pump for up to 45 minutes. Attaches to Pal Cap, Pal Batteries, and Pal AC/DC Adapters.

Component	Image	Description
Pal™ Cap		Small, black cover that attaches to the controller. Protects the battery connection from dust, dirt, and fluid ingress when the controller is only connected to the AC or DC adapter or when used on the backup controller.
Pal™ Batteries	 **Pal™ Single Battery**  **Pal™ Dual Battery**	Available in two sizes: Single and Dual. Each is a wearable, lightweight, and water resistant lithium ion rechargeable battery. The Single Battery provides approximately 5 hours of support and the Dual Battery provides approximately 10 hours of support at 5 L/min. The amount of battery time may increase or decrease significantly dependent upon the pump operating conditions. When disconnected, the battery capacity can be determined by pressing the Battery Capacity Display. Batteries are charged when the controller is plugged into an AC or DC outlet; they may also be charged via the battery charger.
WARNING! Other than when changing external power sources, a battery, AC adapter or DC adapter must be connected at all times.		
Pal™ Battery Charger		Charger used to simultaneously recharge and test up to four batteries (Single or Dual).

Component	Image	Description
Pal™ Controller AC Adapter		A portable power adapter used to power the controller and pump from a wall power source.
Pal™ Controller DC Adapter		A portable power adapter used to power the controller and pump from a vehicle.
Patient Accessories		Facilitate carrying and use of the primary and backup equipment. ❶ Pal Carry Bag ❷ Pal Night Bag ❸ Pal Accessories Bag ❹ HeartWare Shower Bag*
HeartWare® Monitor		Touchscreen tablet PC that enables adjustment of selected controller parameters. Displays both current and historical pump information as well as alarm conditions when connected to a controller. May be powered from its internal battery or from a wall outlet*. Data stored on the monitor can be downloaded via USB*.

*****HeartWare Shower Bag, HeartWare Monitor AC Adapter, USB Memory Stick are components of the commercially available HVAD System.

5.2 Principles of Operation

5.2.1 Background

Continuous flow pumps contain a rotating impeller that adds energy to the blood by converting mechanical kinetic energy into hydraulic energy. Impeller blades push the fluid through the pump using hydrodynamic and centrifugal forces. The net effect is to build up the fluid pressure, sometimes referred to as pump head (i.e., related to the differential pressure across the device) such that the fluid is moved from the inlet to the outlet of the pump. Pump head is the difference between the afterload (arterial pressure) and the preload (left ventricular pressure).

The MVAD Pump is a continuous flow pump utilizing a wearless, hybrid, suspension system that employs both passive magnetic and hydrodynamic forces. The MVAD Pump has a displaced volume of 20cc and weighs 67 grams (without the driveline). The pump s motor is located in the pump housing and it generates power to spin the impeller, the only moving part (Figure 2), resulting in up to 7L/min of blood flow at 75mmHg arterial pressure. The impeller is hydraulically suspended inside the inflow tube, centered by radial forces generated by thrust bearings. The magnetic interaction between the stator and the impeller is responsible for establishing the necessary force to help center the impeller during operation. Design of the motor stator geometry has been matched to the magnetic signatures of the impeller to achieve optimal motor efficiency while maintaining the desired axial stiffness.

Impeller rotation is achieved by a sensor- less brushless motor driver, which sequentially energizes the coils in the stator to produce the force necessary to rotate the impeller.

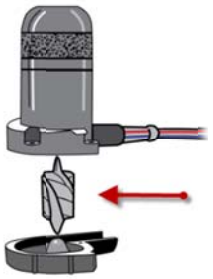


Figure 2: Exploded view of MVAD® Pump, Impeller (see arrow)

5.2.2 Blood Flow Characteristics

There are two flow paths through the MVAD Pump. In the primary flow path (Figure 3), blood enters the inflow cannula, moves through the impeller flow channels, and exits the pump through the outflow port into the outflow graft. In the secondary flow path (Figure 4) blood flows across the gap between the impeller and the inflow tube creating hydrodynamic thrust bearings.

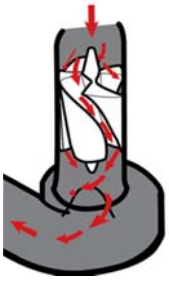


Figure 3: Primary flow path

Figure 4: Secondary flow path

The amount of flow the pump can generate is dependent upon the diameter of the impeller, the geometry of the impeller blades, housing design, motor capacity, rotational speed, and pressure differential across the pump.

The MVAD System estimates blood flow rate using MVAD Pump characteristics, including motor speed, current and patient hematocrit (HCT). To obtain the most accurate estimate of blood flow, the patient s hematocrit must be entered into the HeartWare Monitor.

The ideal rotational speed is dependent on left ventricular preload. If the speed is set too high and the MVAD Pump attempts to pump more blood than is available, ventricular suction may occur. This may cause arrhythmias or damage the myocardium and/or septum. Additionally, hemolysis may develop if ventricular collapse occurs or if the pump inflow becomes occluded.

The controller motor speed is set by the clinician and ranges from 8000 to 18000 RPM. The appropriate speed should be determined based on the patient condition. MVAD Pump speeds below 13000 RPM or above 16000 RPM should be used with caution.

5.2.3 Physiological Control Algorithms

Control algorithms provide clinicians with information on device performance and blood flow estimation. The MVAD System has four physiologic control algorithms: Flow Estimation, Suction Detection and Response, qPulse™ Cycle, and Pump Pressure. Two of these algorithms qPulse and Suction Detection and Response have settings that may be defined by the user.

Operation of the Flow Estimation, Suction Detection and Response, and Pump Pressure algorithms vary depending on the set speed. These three algorithms are not

operational at all speeds. The qPulse Cycle algorithm can operate at any speed setting. Figure 5 shows the ranges of speeds at which each algorithm is operational.

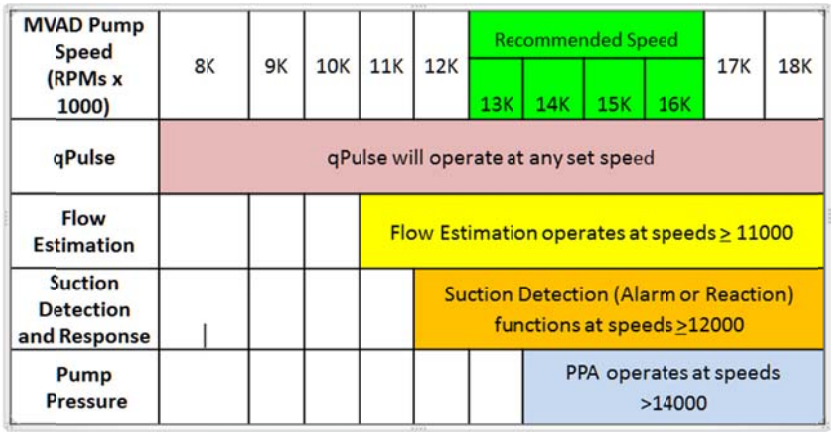


Figure 5: Ranges of Set Speeds Where the Algorithms Operate

5.2.4 Flow Estimation

MVAD Pump estimated blood flow is calculated using motor speed, current and patient s hematocrit (HCT). The correlation between flow and current is not linear over the full operating MVAD Pump flow range, which affects the accuracy of the flow estimation. DO NOT rely only on the flow estimation alone to assess cardiac output. Inaccurate assessment of perfusion based on pump flow alone may lead to less than optimal treatment. The clinician shall rely on conventional methods to assess cardiac output and to guide patient and device management.

Flow estimation operates at speeds of ≥ 11000 RPM. The flow estimation will display as --- when speeds are set at < 11000 RPMs, when the flow is not being calculated due to operation outside of the expected ranges or during brief averaging periods associated with algorithm related speed changes.

The patient s HCT should be updated in the monitor if it increases or decreases by 5% or more to optimize flow estimation. The default HCT setting is 30%.

5.2.5 Suction Detection & Response

A suction condition can occur as a consequence of ventricular collapse or inflow occlusion. Ventricular collapse occurs when a continuous flow VAD attempts to pump more blood from the left ventricle than is available. Left ventricular collapse can be the result of clinical events affecting left ventricular preload including hypovolemia (bleeding), right heart failure, arrhythmia, pulmonary hypertension or pulmonary embolus. An inflow occlusion occurs when the inflow cannula is obstructed by the interventricular septum or left ventricular free wall. Temporary inflow obstruction can occur as a result of surgical positioning, patient position, thrombus, or during straining (Valsalva maneuver).

The MVAD System Suction Detection and Response algorithm functions by monitoring VAD parameters for changes indicative of sudden decreases in flow rate. Suction Detection and Response (alarm or reaction) is only available at speeds ≥ 12000 RPM. There are three states to the algorithm selected by the Suction Detection and Response setting: [**Off**], [**Alarm**], and [**Auto**]. The Suction Detection and Response setting is selected by the clinician based on each patient s hemodynamics and clinical status. The default setting is [**Alarm**].

When the Suction Detection and Response algorithm is set on [**Alarm**], alarms will alert the user when a suction condition is suspected. There will be no automatic changes to the MVAD Pump operation.

When the Suction Detection Response algorithm is set on [**Auto**], no alarm will sound but the Suction Detection and Response algorithm will automatically decrease the speed followed by a slow ramping increase in speed back to the set speed. Once the speed returns to the set speed, a re-assessment of the suction condition is made. If the suction condition has resolved, the algorithm will shut off. If the suction condition is still present, the next sequence is initiated with a greater decrease in speed followed by a slow ramping increase in speed back to the set speed. This cycle will continue as long as there is a suction condition. If the suction event persists for one hour, a Non-Critical alarm will be triggered.

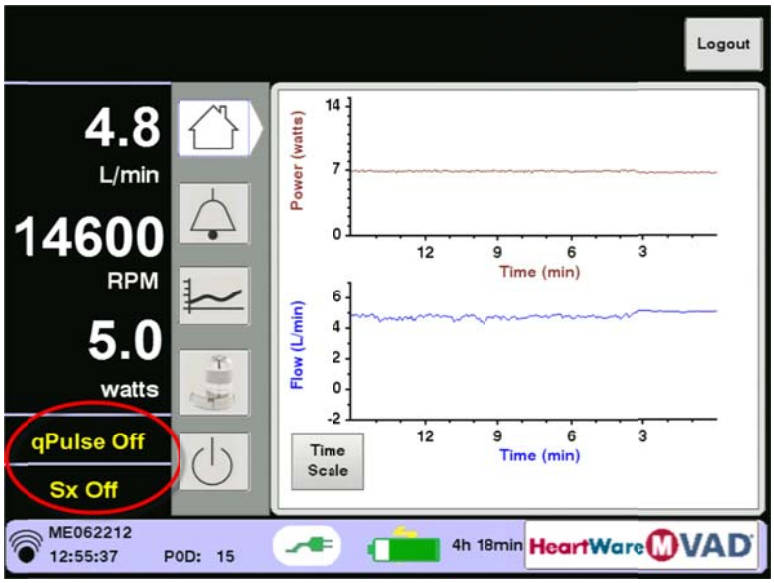


Figure 6: Monitor Home Screen showing status of qPulse and Suction Detection and Response Algorithms

The Suction Detection and Response algorithm can only be enabled from the System screen of the HeartWare Monitor. Therefore, only the clinician has access to control the state of this algorithm. When the setting for the algorithm is [**Off**], there is no alarm

during a ventricular suction condition. The suction setting will be displayed on the lower left corner of the monitor screen, as [**Sx Off**] or [**Sx Alarm**].

The Suction Detection and Response [**Alarm**] or [**Auto**] mode must NOT be turned on if the patient is in a suction condition. If the mode is turned on during a suction condition, the [**Alarm]** or **[Auto]** message will be displayed on the monitor and the Suction Detection and Response alarm will be enabled but will be inaccurate due to the fact that normal baseline parameters could not be established during a suction condition. The algorithm attempts to establish a baseline detection level to distinguish abnormal conditions. Therefore, suction detection and response should not be set during a suction event.

If a Suction Detection and Response alarm is triggered, the clinician should evaluate whether the alarm was triggered by a transient, reversible condition which corrects itself or whether the alarm is more serious and requires intervention. Transient alarms often occur at certain times during the day and/or under particular circumstances such as bending over or lying on one side. They usually resolve quickly without problems. If the Suction Detection and Response alarm is persistent and there are clinical symptoms of decreased blood flow such as dizziness or hypotension, or if a [**Low Flow**] alarm is active, then the patient should be evaluated. This can be accomplished by visualizing the left ventricle with echocardiography. Next, the clinician should attempt to identify and treat the underlying cause of the suction event. If the cause for the suction event cannot be determined or if the cause is refractory to treatment, the clinician should manually adjust the speed to resolve the suction condition under echocardiographic guidance.

5.2.6 qPulse™ Cycle

The qPulse Cycle algorithm was designed to mimic normal cardiac physiology by allowing the left ventricle to fill sufficiently to promote ventricular ejection. As a result of increased ventricular filling and pressure, the aortic valve opens, the aortic root is better washed and there may be increased pulsatility. The qPulse Cycle accomplishes this by decreasing pump speed below the set speed followed by a return to the set speed (Figure 7). The cycle is repeated intermittently as shown in Figure 7. The qPulse Cycle can be activated at any speed, however, activation at speeds below 14000 RPM should be done with caution since this may result in decreased or retrograde flow. The qPulse Cycle may be enabled or disabled by the clinician via the HeartWare Monitor. The qPulse Cycle has four possible settings: [**Off**], [**Low**], [**Medium**] and [**High**]. The default setting is [**Off**]. The qPulse Cycle setting is selected by the clinician based on each patient s hemodynamics and clinical status. If the qPulse Cycle is used, it is recommended that it be initiated once the patient is hemodynamically stable.[20, 21, 22]

qPulse™ Cycle	% Speed Drop	Interval-Down (Seconds)	Interval-Up (Seconds)	Operation
Low	**15%**	**5**	**30**	
Medium	**15%**	**5**	**10**	
High	**20%**	**5**	**10**	

Figure 7: qPulse™ Cycle

5.2.7 Pump Pressure Algorithm

The MVAD Pump has a hybrid system which utilizes both magnetic and hydrodynamic forces to levitate the impeller. The free floating impeller is surrounded by a cushion of blood, which along with magnetic forces keeps the impeller centered in the inflow tube of the pump. As a result of this free floating design the impeller can move within the inflow tube. While movement of the impeller is usually minimal it can be influenced by increases in pressure within the pump. A high pressure condition can develop when the pump is operating at speeds above 14000 RPM in conjunction with low flow across the impeller. Under these high pressure conditions the impeller may come in contact with the mechanical stop. The mechanical stop is built into the pump housing. It was designed to prevent the impeller from moving too far up the inflow tube. The Pump Pressure Algorithm is intended to prevent and resolve high pressure conditions that could lead to the impeller coming in contact with the mechanical stop.

The Pump Pressure Algorithm monitors the estimated flows, speeds, and MVAD System parameters for conditions indicative of high pressure. The Pump Pressure Algorithm can be either [**Enabled**] or [**Off**]; the default setting is [**Enabled**]. The Pump Pressure Algorithm should always be enabled.

When a high pressure/low flow condition is detected, a Non-Critical [**Pressure**] alarm will be activated which will direct the patient to Call the clinician for instructions. The [**Pressure**] alarm can be muted for one hour. At the same time, the controller will automatically decrease the pump speed from the current set speed to a predetermined lower speed. The pump will be maintained at this speed until the estimated flow reaches a pre-determined flow recovery value indicating the pressure condition has cleared. After clearing, the controller will attempt to resume operation at the original set speed via a series of speed increases. If at any time during these attempts the original set speed is reached, the algorithm will return to a monitoring only status. However, if the original set speed is not reached after two unsuccessful speed recovery attempts, the algorithm will pause for 15 minutes before any further attempts are made. If the pressure condition is not resolved after approximately two hours, then the speed will remain at the last known speed where a pressure condition was not detected. No additional attempts will be made to return to the original set speed.

5.3 HeartWare® Monitor

5.3.1 Monitor Overview

The monitor (Figure 8) is a touchscreen tablet PC that uses proprietary software to display system performance and that enables adjustment of selected controller parameters. When connected to a controller, the monitor receives continuous pump and power status information from the controller and displays both real-time and historical pump information. The monitor also displays alarm conditions. Data stored on the monitor can be downloaded via a USB drive. The monitor is powered from a wall outlet using an AC adapter but also possesses an internal battery to allow for up to 45 minutes of untethered operation during patient transport. Keep the monitor s battery charged by connecting the monitor AC adapter to an electrical outlet at all times even while in storage. It takes approximately four hours to charge a depleted monitor battery.

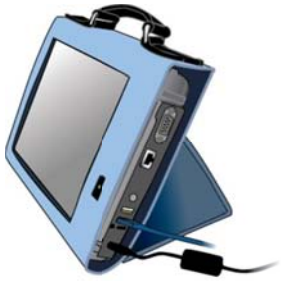


Figure 8: The HeartWare® Monitor

5.4 PAL™ Controller

The Pal Controller (Figure 9) is a wearable, water-resistant, ergonomically designed microprocessor-based device [Dimensions = 9.7 x 5.0 x 8.9 cm, Weight = 0.43 kg], worn by the patient that monitors and controls MVAD System operation. The controller attaches to the percutaneous pump cable. It sends power and operating signals to the pump and collects information from it. The controller monitors pump status and issues alerts to the patient using vibratory, visual, and audible alarms. The controller transmits alarm and pump operating information to the monitor. Pump status, battery capacity and time remaining, alarm conditions and troubleshooting tips are displayed on the controller screen.

The controller utilizes power from an external power source: an external battery, wall outlet (with AC adapter) or car outlet (with DC adapter). An internal, non-replaceable, rechargeable lithium ion battery inside the controller is used to power the controller and pump when changing external power sources. If all power sources fail, an additional internal backup battery will alert the user to change the controller.

Software Parameters, Ranges & Factory Default Settings are shown below.

Software Parameters, Ranges & Factory Default Settings			
Parameter	**Range**	**Resolution**	**Factory Default**
MVAD Pump Speed	8000 to 18000 RPM	200 RPM	13000
[**Low Flow**] Alarm	1.0 to 7.0 L/min	0.1 L/min	1.0 L/min
[**High Power**] alarm Limit	1.0 to 25 watts	0.1 watt	16.0 watts
[Suction] Detection and Response	Off, Alarm, Auto	N/A	Alarm
[**qPulse™**] Cycle	Off, Low, Medium, High	N/A	Off
Pump [**Pressure**] Algorithm	Off, Enabled	N/A	Enabled
Hematocrit	20-50%	1%	30%

The Pal Cap should be connected to the controller when a battery is not attached to protect it from dust, dirt, and fluid ingress.

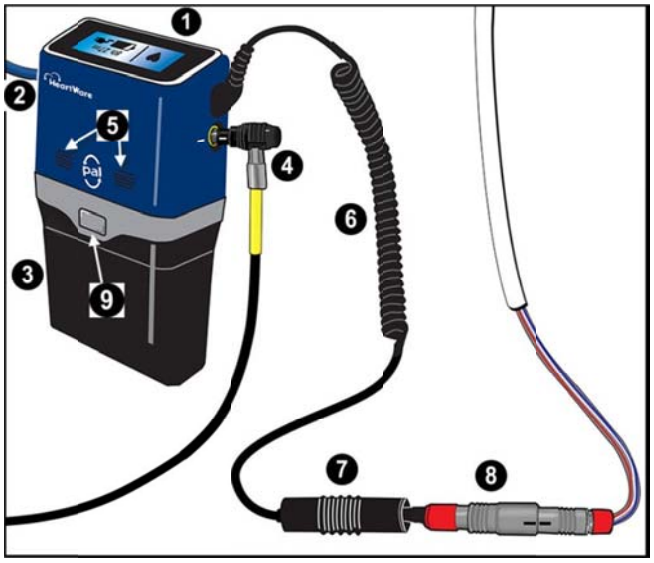


Figure 9: Pal™ Controller

1 – Touchscreen display
2 – Data port
3 – Pal™ Battery (Single)
4 – Power connector
5 – Speakers
6 – Controller cable
7 – Driveline cover
8 – Driveline connector
9 – Battery release button

5.4.1 Controller Features & Connectors

Touchscreen display: The Pal Controller user interface consists of an LCD touchscreen. System health is available on the primary (Home) screen with secondary screens containing alarm, pump parameter, and alarm information. The LCD background color will change from blue to yellow or red if there is a Non-Critical or Critical alarm, respectively. Non-Critical alarms can be silenced via the touchscreen.

Controller Cable: The Pal Controller has its own cable that connects to the pump driveline that passes through the patient s skin. The controller cable has a reinforced strain relief, as well as a curly coil to absorb strain and tension put on the cable. The connector on the controller cable is red to match the connector on the pump driveline. The connector should be covered with the driveline cover to protect it from dust, dirt, and fluid.

Internal Controller Battery: The Pal Controller has an internal battery that can power the system for up to 45 minutes. It is intended to provide power when the patient is changing the external power source. The internal battery is recharged whenever there is an external power source attached to the controller. For more information, see Section 5.4.2 Pal Controller Internal Battery.

Controller connectors: All connectors are color-coded to make connections easier **(YELLOW** = power**, RED** = pump, **BLUE** = data). When alignment markers are shown on the connector, they should be aligned before making the connection.

- **Power adapter connector:** The AC or DC adapter plugs into the color-coded yellow power port to bring power from a wall outlet or car DC power outlet to the controller.
- **Battery connector:** The external battery connector is located on the bottom of the controller. When the Pal Battery is latched onto the controller, the connection is complete. When the battery is not connected (and the controller is powered by AC or DC power), the controller cap should be used to protect the connection.
- **Data port:** The monitor data cable plugs into the color-coded blue data port on the controller to relay data from the controller and to send instructions from the monitor to the controller.
- **Driveline connector:** The color-coded red controller connector attaches to the color-coded red driveline connector. The driveline sends power from the controller to the pump.

Speakers: There are two (2) speakers on the front of the Pal Controller to sound the alarms.

Battery Release button: Allows for removal of the external battery or Pal Cap from the controller when pushed.

Pal™ Cap: Cover that should be placed on the controller whenever a battery is not attached (e.g., when the controller is powered by AC or DC power). Its purpose is to protect the power connections from dust, dirt, and fluid.

5.4.2 Pal™ Controller Internal Battery

The controller internal battery contains lithium ion cells that power MVAD Pump and controller for up to 45 minutes. The controller s internal battery is intended to provide power while changing from one external power source to another (battery, AC adapter, or DC adapter). The controller should always be connected to an external power source (except when changing batteries or switching to a power adapter). The internal battery in the Pal Controller is a backup power source and should never be used as the only source of power for the controller. The internal battery works together with the external power source to provide safe operation with no interruption in pumping even while power sources are being changed.

The controller internal battery is recharged whenever there is an external power source attached to the controller. The amount of time the internal battery has remaining is displayed on the Controller Status on the Information screens. It takes approximately 90 minutes of charge time to charge the internal battery.

When the external power source is removed or when the external battery has no power remaining, the controller internal battery will automatically begin to provide power to the pump. Whenever the internal battery s power is put to use, the [**Connect Power**] alarm will sound, beginning at a low volume and getting louder if the alarm is not resolved. This alarm may be silenced (depending on internal battery time remaining) by pressing on the controller screen. This should provide time to connect an external power source (battery, AC adapter or DC adapter) to the controller before the alarm sounds again.

If external power is not connected after 30 minutes of running on the controller internal battery -- or when the internal battery has only 15 minutes of power remaining -- a Critical [**Connect Power**] alarm will sound.

The [**Connect Power**] alarm will clear as soon as an external power source (battery, AC adapter, or DC adapter) has been connected. When power is restored, the controller internal battery will immediately begin to recharge.

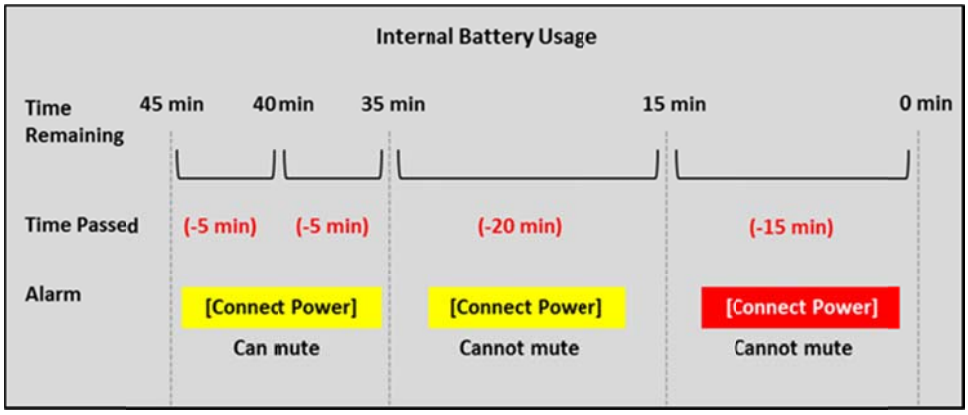


Figure 10: Internal Battery Usage chart

5.4.3 Power Sources for the Pal™ Controller

Except when changing power sources, the controller should be attached to an external power source. The AC adapter (see Section 5.7.1 AC Adapter) is used to connect to a wall outlet. The DC adapter (see Section 5.7.2 DC Adapter) is used to plug into a vehicle DC power outlet. While relaxing or sleeping, patients should use power from an electrical outlet because it provides power for an unlimited period of time. The DC adapter is used when traveling in a vehicle. When patients are active, the external battery (see Section 5.5 Pal Batteries) provides a mobile power source. An internal battery is also available for up to 45 minutes of power - when changing batteries as well as for emergencies.

Patients should have spare, fully-charged batteries available at all times. When battery power is low, the controller displays the message, [**Change Battery**]. The patient should change the battery or connect an adapter to charge the battery as soon as possible after receiving this message.

5.5 PAL™ Batteries

For safe operation, the controller requires an external power source in addition to the controller internal battery. While active, patients will typically use an external battery as the primary power source. The battery should be changed when the controller initiates a [**Change Battery**] alarm. Fully-charged spare batteries should be available at all times.

The battery is available in two sizes: Single and Dual. Each is a wearable, lightweight, and water resistant lithium ion rechargeable battery. At 5 L/min, the Single Battery provides approximately 5 hours of support and the Dual Battery provides approximately 10 hours of support. The amount of battery time may increase or decrease significantly dependent upon the pump operating conditions. The battery capacity display on the controller provides accurate battery capacity and time remaining to the user. The battery requires no user calibration and experiences a 20% capacity fade after as many as 500 charge/discharge cycles.

When the battery is disconnected from the controller, battery capacity can be determined by pressing the Battery Capacity Display on the battery.

Batteries charge when attached to a controller connected to an AC or DC adapter or when inserted into the Pal Battery Charger. The capacity of each battery (in hours) is based on controller and MVAD Pump power consumption and the number of battery charge and discharge cycles. It takes approximately three hours to charge a Single Battery and five hours to charge a Dual Battery, depending on degree of battery depletion. If the controller internal battery is also depleted, it will always charge first, and will increase the total charging time for the batteries; therefore, total time could be up to 4.5 hours for the Single Battery and up to 6.5 hours for the Dual Battery.

5.6 PAL™ Battery Charger

The battery charger (Figure 11) can charge up to four batteries at a time.

A green indicator light in the center of the charger confirms that the charger is properly connected to electrical power. Each battery slides into a bay to connect to the battery charger. Each bay has an indicator light to show the battery charging status. It takes approximately three hours to charge a Single Battery and five hours to charge a Dual Battery, depending on the degree of battery depletion. It is safe to leave the batteries in the charger and the charger plugged into a wall outlet at all times.

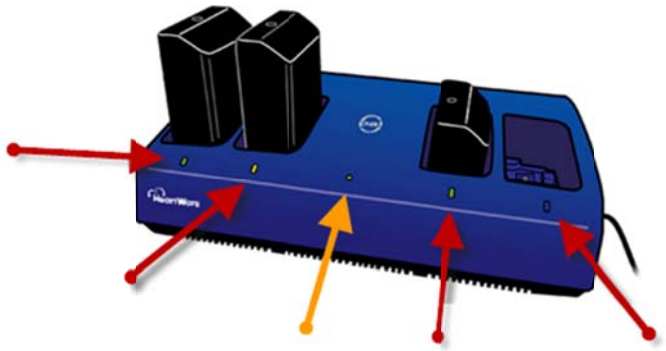


Figure 11: Pal™ Battery Charger (Red Arrows indicate Battery Charging Status Lights; Orange Arrow indicates Power Indicator Light)

Battery Charging Status Light	What it Means
Green	Battery is fully charged and ready for use.
Yellow	Battery being charged; NOT ready for use.
<Flashing> Yellow	Battery NOT charging. Check battery connections. If connections are intact, switch to another battery slot. If problem persists, return battery to HeartWare.
Red	Battery too cold or too hot; waiting to charge.
<Flashing> Red	Defective battery. Do NOT use. Mark battery and return to HeartWare.

5.7 PAL™ Controller AC Adapter or DC Adapter

5.7.1 AC Adapter

The AC adapter (Figure 12) connects the controller to a wall electrical outlet. When the AC adapter is properly connected to power, a blue indicator light will be displayed on the adapter. When connected to the controller via the YELLOW port, it supplies power to the controller and pump and charges both the controller internal and external batteries. If the controller is connected to the AC power source when both batteries are depleted, the internal battery will charge first. After the internal battery is completely charged, the external battery will charge.

When using the AC or DC adapter with no external battery attached, be sure to always place the Pal Cap on the Pal Controller.

Before connecting the AC adapter to the controller, verify proper connection of the power cord to the adapter (Figure 12) and electrical outlet.

Figure 12: AC adapter & Power cord connection

5.7.2 DC Adapter

The DC adapter (Figure 13) is used to provide power to the controller and pump from a vehicle power port. When connected to a running vehicle, it will power the controller and charge both the internal and external battery. The charge sequence for both batteries is the same as that of the AC adapter. When the DC adapter is properly connected to power, a blue indicator light will be displayed on the adapter.

Figure 13: DC adapter

5.8 Device Accountability

The MVAD Pump and components are investigational devices. The Investigator is responsible for ensuring that only study participants utilize the MVAD Pump, and all MVAD Systems must be stored in a location that is accessible only by authorized personnel. The disposition of all MVAD components must be maintained by serial number or lot number and must be accounted for in the Device Accountability Log. All unused product will be returned to HeartWare.

6.0 STUDY OBJECTIVES AND ENDPOINT MEASURES (ENDPOINTS)

6.1 Study Objectives

This multi-center, prospective, non-randomized, single-arm trial will investigate the safety and performance of the HeartWare Miniaturized Ventricular Assist Device (MVAD Pump) system over 24 months in subjects with advanced heart failure. Secondary endpoints include the incidence of bleeding, incidence of major infections (per INTERMACS definitions), time to death, incidence of all device failures and device malfunctions, health status improvement, and functional status improvement. Safety measures will include the frequency and rates of adverse events, both overall and for each specific event, which will be collected throughout MVAD Pump support.

This is a performance goal based trial concerning the primary endpoint and the first secondary endpoint. The primary endpoint is survival at 6 months (estimated to be 85%) based on a performance goal of 70%, with a one-sided significance level of 0.05. The initial Clinical Study Report will be submitted with the 6 month data and will be submitted for CE Mark. The secondary endpoint is survival at 24 months (estimated to be 70%) based on a performance goal of 52.5%, with a one-sided significance level of 0.05. These data will be submitted for long term use labeling.

6.2 Estimated Period of Trial

6.2.1 Time schedule

Enrollment of subjects is expected to start in the second quarter of 2015 (First Implant) and each subject will be in the trial for up to 24 month (including Screening and Follow-up phases).

6.2.2 End of trial

Enrollment of subjects is expected to be completed in the fourth quarter of 2015 (Last Implant) and the overall end of trial is defined as the day of the last visit performed on the last subject. The last Follow-up visit of the last subject is expected to take place by the fourth quarter of 2017.

6.3 Primary Endpoint

The primary endpoint is survival at 6 months presented as a simple proportion (subjects alive on the MVAD pump divided by endpoint eligible subjects). Transplants, explants for recovery and exchanges (to a device other than the MVAD Pump) prior to 6 month follow-up will be eligible for endpoint analysis (with survival status identified at the time of the procedure). Survival failure is associated with events (death) on the MVAD Pump.

6.4 Secondary Endpoints

1. Survival at 24 months presented as a simple proportion (defined like the primary endpoint)
2. Overall Survival (Time to Death)
3. Incidence of major bleeding, per INTERMACS definition
4. Incidence of all device failures and device malfunctions per INTERMACS definition
5. Incidence of major infection, per INTERMACS definition
6. Incidence of neurological dysfunction per INTERMACS definition
7. Health Status change, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol EQ-5D-5L
8. Functional status change, as measured by NYHA and 6-minute walk
9. Frequency and rates of adverse events(AEs) throughout VAD support per INTERMACS Definition
10. Length of operative time and initial hospital stay
11. Re-Hospitalizations(excluding planned procedures)
12. Transplantations
13. Explants

7.0 STUDY DESIGN

7.1 Number of Clinical Sites and Subjects

The trial will be conducted at a minimum of 5 sites and a maximum often (10) sites in up to 5 countries, including Germany, Austria, France, United Kingdom (UK), and Australia.

Screening will be continued until 60 subjects are implanted.

It is anticipated that each site will enroll up to 10 subjects but at least 1 subject each. No site will enroll more than 10 subjects into the study without prior written approval from HeartWare.

7.2 Subject Participation and Study Duration

Subjects will participate for 24 months.

All subjects will be followed for 6 months to the primary endpoint, and will continue until assessment at 24 months for the key secondary endpoint.

The study is anticipated to start in the Second Quarter 2015 (First Implant) and enrollment is estimated to be complete by Fourth Quarter 2015 (Last Implant) to Fourth Quarter 2017 (Last subject last visit).

7.3 Site Selection Criteria

Factors determining whether centers will be selected include the number and kinds (e.g. continuous flow) of VAD implants per year, the infrastructure necessary to perform this trial, in particular having the core surgical and cardiology VAD teams and an established research group structure. The center s interest in participating in the trial, their academic history and geographic location will all be taken into consideration. In addition, sites need to adhere to all trial-related requirements, to Good Clinical Practice (GCP), ISO 14155 2011 and to all applicable regulatory rules and regulations.

8.0 PATIENT POPULATION, SELECTION AND WITHDRAWAL

8.1 Characterization of Study Population

The study population will be selected from patients with American Heart Association (AHA) Stage D/NYHA Class IIIB/IV heart failure who have failed optimal medical management. Candidates will be selected for the study regardless of gender, race or ethnicity.

Prior to enrollment, candidates must meet all the inclusion criteria, and none of the exclusion criteria.

8.1.1 AHA Stage D, NYHA Class IIIB/IV Heart Failure

The distinction between NYHA Class III versus IV heart failure is primarily based upon the presence or absence of symptoms of failure at rest. A Class III patient experiences dyspnea with activities of daily living or walking short distances (20 100 m). Class IIIB patients may not be able to walk >300 meters, and experience some symptoms at rest. Physical measures such as PVO_2 , neuro-hormonal levels and LVEF do not provide sufficient resolution to differentiate a later stage Class IIIB patient from a Class IV, although tools such as the Seattle Heart Failure Score appear to be better for stratifying risk of death in patients defined as IIIB or IV. However, a formerly stable NYHA IIIB patient may transition to Class IV by the gradual development of symptoms at rest or by failure of optimal medical management. In the former case, transitional symptoms would be the development of paroxysmal nocturnal dyspnea, increasing orthopnea, reduction in tolerance to exercise and the occurrence of symptoms at rest, all of this occurring on previously stable and optimal medical management.

8.1.2 Definition of Optimal Medical Management (OMM)

Optimal medical management is defined as dietary salt restriction and *maximal tolerable therapy* with:

- Angiotensin Converting Enzyme (ACE) Inhibitors (or Angiotensin Receptor Blockers (ARBs))
- Diuretics
- Beta Blockers
- Aldosterone Antagonists

Many patients will also receive cardiac glycosides and hydralazine/nitrates. In addition, therapy with Cardiac Resynchronization Therapy (CRT), use of anti-arrhythmic agents and an Implantable Cardiac Defibrillator (ICD) may be expected in many Stage D/NYHA Class IIIB/IV patients.

Intermittent or continuous therapy with inotropic agents may be required or have been used in this patient population. Enrollment, however, does not require concurrent intravenous inotropes, provided criteria for Stage D/NYHA Class IIIB/IV are met.

Failure of optimal medical management[1, 5, 6] is defined as:

- Development of symptoms at rest and reduction in exercise tolerance in previously stable IIIB patients who have received maximally tolerable doses of the four major categories of drugs and are not candidates for, or improved by, CRT.
- Development of drug intolerance in a previously stable IIIB patient due to hypersensitivity (e.g. ACE inhibitors or ARBs), hypotension (e.g. ACE inhibitors, ARBs or beta blockers) or renal impairment (e.g. ACE inhibitors, aldosterone antagonists) resulting in development of some symptoms at rest despite alternative drug therapy.
- Occurrence of pulmonary congestion, ascites or refractory peripheral edema despite maximal tolerable medical therapy in Class IV patients.
- Necessity for intermittent or continuous IV inotropes, intra-aortic balloon pump or hospitalization for heart failure in either Class IIIB or IV patients who have failed maximal tolerable medical therapy or who developed sensitivity to any of the classes of drugs.

8.2 Inclusion Criteria

1. Must be ≥18 years of age at consent
2. Subjects with advanced heart failure symptoms (Class IIIB or IV) who meet one of the following):
    a. on optimal medical management including dietary salt restriction and diuretics, for at least 45 out of the last 60 days and are failing to respond; or
    b. in Class III or Class IV heart failure for at least 14 days and dependent on intra-aortic balloon pump (IABP) and/or inotropes.
3. Left ventricular ejection fraction ≤25%.
4. Female subjects of childbearing potential must agree to use adequate contraceptive precautions (defined as oral contraceptives, intrauterine devices, surgical contraceptives or a combination of condom and spermicide) for the duration of the study.
5. The subject has signed the informed consent form (ICF).

8.3 Exclusion Criteria

1. Body Mass Index (BMI) > 47.
2. Body Surface Area (BSA) < 1.0 m^2.
3. Partial or full mechanical circulatory support within thirty days of implant.
4. Existence of any ongoing mechanical circulatory support (MCS) other than an intra-aortic balloon pump (IABP) or TandemHeart PTVA .
5. Prior cardiac transplant or cardiomyoplasty.
6. History of confirmed, untreated abdominal or thoracic aortic aneurysm >5 cm.
7. Acute myocardial infarction within 14 days of implant as diagnosed by ST or T wave changes on ECG, diagnostic biomarkers, ongoing pain and hemodynamic abnormalities.
8. On ventilator support for > 72 hours within the four days immediately prior to implant.
9. Pulmonary embolus within three weeks of implant as documented by computed tomography (CT) scan or nuclear scan.
10. Symptomatic cerebrovascular disease, stroke within 180 days of implant or >80% stenosis of carotid or cranial vessels in the absence of confirmed collateral circulation.
11. Uncorrected moderate to severe aortic insufficiency.
12. Severe right ventricular failure as defined by the anticipated need for extracorporeal membrane oxygenation (ECMO) or BiVAD at the time of screening.

13. Active, uncontrolled infection diagnosed by a combination of clinical symptoms and laboratory testing, including but not limited to, continued positive cultures, elevated temperature and white blood cell (WBC) count, hypotension, tachycardia, generalized malaise despite appropriate antibiotic, antiviral or antifungal treatment.
14. Uncorrected thrombocytopenia or generalized coagulopathy (e.g., platelet count <75,000, INR >2.0 or PTT >2.5 times control in the absence of anticoagulation therapy).
15. Intolerance to anticoagulant or antiplatelet therapies or any other peri- or postoperative therapy that the investigator may administer based upon the subject s health status.
16. Serum creatinine >3.0 mg/dL within 72 hours of implant or requiring dialysis.
17. Specific liver enzymes [AST (SGOT), and ALT (SGPT)] >3 times upper limit of normal within 72 hours of implant.
18. A total bilirubin >3 mg/dL within 72 hours of implant, or biopsy proven liver cirrhosis or portal hypertension.
19. Pulmonary vascular resistance (PVR) is demonstrated to be unresponsive to pharmacological manipulation.
20. Subjects with a mechanical heart valve.
21. Etiology of heart failure is due to, or associated with, uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis or restrictive cardiomyopathy.
22. History of severe chronic obstructive pulmonary disease (COPD) or severe restrictive lung disease (e.g. forced expiratory volume in one second (FEV1) < 50% predicted value).
23. Participation in any other trial involving investigational drugs or devices within 4 weeks prior to screening and last visit of the trial.
24. Severe illness, other than heart disease, which would limit survival to <3 years.
25. Peripheral vascular disease with rest pain or ischemic ulcers of the extremities.
26. Pregnancy and breastfeeding.
27. Psychiatric disease, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the CIP and LVAD.
28. Subject unwilling or unable to comply with trial requirements.
29. Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the investigator.
30. Employees of the investigator or trial site, with direct involvement in this trial or other trials under the direction of the investigator or trial site, as well as family members or employees of the Investigator.

8.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be noted using the following categories. For screen failure subjects, refer to Section 9.4.2.

1. Lost to follow-up. The subject did not return to the clinic and at least three attempts to contact the subject were unsuccessful. All attempts to contact the subject must be documented.
2. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded).
3. Study termination. The sponsor, Independent Ethic Committee (IEC), or regulatory agency terminates the study.
4. Other. NOTE: The specific reasons should be recorded in the eCRF.

8.5 Procedure for Discontinuation or Withdrawal of a Subject

A subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject s participation be discontinued, the primary reason for termination must be recorded in the eCRF. In addition, efforts should be made to perform all procedures scheduled for the Month 6, 12 and 18 visit if discontinuation is prior to that visit, or the Month 24 visit if discontinuation is after Month 18 but before Month 24. Discontinued or withdrawn subjects will not be replaced.

8.6 Subject Follow- up after trial completion or early termination

After completion of the last study visit the subject will continue to participate in the site specific VAD Follow- up program and may have the possibility to be included in a registry or follow- up trial.

9.0 STUDY PROCEDURES, DEVICE EXPLANT AND STUDY EVALUATIONS

9.1 Study Procedures

The following sections describe the procedures to be completed throughout the conduct of the study. Subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is described here in Section 9 and also in Appendices 17.1.1 and 17.1.2.Every attempt should be made to perform evaluations at the designated time points. However, for visits conducted at Month 1, 3 there is a window of ± 7 days for visits at Month 6, 24 there is a window of + 14 days and for visits at Month 12, 18 there is a window of – 14 days.

9.1.1 Informed Consent Procedure

Before enrolling the subject in the trial, i.e., before any trial-related examination is performed, a written ICF must be obtained. Each potential participant shall be informed of the aim of the trial and what participation entails. They shall be supplied with an Information Sheet summarizing the details of the trial. Ample time should be given to the subjects to consider their participation. Agreement to participate in the trial is to be confirmed by the subject and the principal investigator (or authorized designee) by signing and dating the consent form. Documentation of this procedure is required in the medical record.

Standard of care assessments obtained within the 30 days prior to consent for screening may be used: 1) to confirm eligibility; and 2) for screening measurements, if the subject meets eligibility criteria and signs the ICF. Echocardiograms obtained within the 6 months prior to ICF may be used for screening measurements.

Vulnerable populations will not be included in this trial.

9.1.2 Point of contact

A point of contact of where to obtain additional information on the trial, on the rights of the subject and whom to contact in the event of trial-related injury will be provided to each subject. This information will be specified in the ICF.

9.1.3 Informing the subject's general practitioner

In certain applicable countries, and in cases where the subject is typically treated by a general practitioner or other equivalent health care provider, then with the subject s agreement this health care provider is to be informed of the subject s participation in the trial at enrollment. The provider should be informed of the title of the trial, date of enrollment into the trial, and the dates of the outstanding visits. The communication with the general practitioner should be documented in the subject s medical record.

9.1.4 Demographics, Medical History, and Physical Examination

9.1.4.1 Demography

Demographic data that will be collected and identified by a non-identifying number on the eCRF include sex, year of birth, gender, weight, height, race and ethnicity*. Subject BMI and BSA will also be recorded.

* per country specific regulation

9.1.4.2 Cardiovascular/ Medical history & Hospitalization

Medical history will be collected and recorded for all subjects enrolled in the trial. This includes diagnosis, general medical history and cardiovascular history as follows:

- General medical history
- Primary cardiac diagnosis
- Previous cardiac surgery
- Current mechanical support (ECMO, balloon pump)
- Previous mechanical circulation support
- Etiology of Heart Failure
- Duration of Heart Failure
- Number of hospitalizations in past year for cardiac
- Smoking

With co-morbidities to be identified as

- Diabetes (diet, oral, insulin)
- COPD
- Previous neurological event
- Carotid artery disease
- Peripheral vascular disease
- Arterial Fibrillation
- NYHA class

Childhood illnesses, unless considered to be relevant to the etiology of heart failure, do not need to be documented.

9.1.5 Hemodynamic parameters/ Vital Signs & Improved Blood Pressure Management Plan (IBPM)

9.1.5.1 Hemodynamic parameters/ Vital Signs

Hemodynamic parameters will include the following, which will be captured at screening/ pre-implant, day 1-3, and month 1, 3, 6, 12, 18, 24, and re-hospitalization (where applicable):

	Screening	Day 1-3 post implant	Month 1, 3, 6, 12, 18, 24
Heart Rate/ Rhythm	x	x	x
Respiratory Rate	x	x	x
Temperature	x	x	x
Systolic blood pressure	x	x	x[1]
Diastolic blood pressure	x	x	x[1]
Mean Arterial Blood Pressure (MAP)[3]	x	x	x[1]
Doppler - Pressure	x	x	x[1]
Central venous pressure[2]	x		
SVO_2	x	x*	x*
Right atrial pressure[2]	x		
Systolic pulmonary artery pressure[2]	x		
Diastolic pulmonary artery pressure[2]	x		
Mean pulmonary artery pressure[3]	x		
PCWP	x		
Cardiac Index	x		
Cardiac output	x		
PVR [3]	x		

*if available

[1] follow IBPM program (Section 9.1.5.2) as applicable

[2] After screening only to be collected in case of late Right Heart Failure

[3] Auto calculatedEvery effort should be made to obtain hemodynamic assessments per the Time and Event Schedules (Appendix 17.1.1). However, some parameters are available only during right heart catheterization (RHC) monitoring, while others are not available due to RHC monitoring. In addition, some parameters may not be available in some subjects who have a VAD implanted. A hemodynamic parameter that is not available due to RHC monitoring or implant status is not considered to be protocol deviation. However, the ability/inability to obtain hemodynamics due to presence of a RHC will be documented in the eCRF, as needed.

9.1.5.2 IBPM, Mean Arterial Blood Pressure (MAP) Assessment Procedure and Documentation

General

From the Instructions For Use (IFU), the recommended MAP target for subjects supported by the MVAD System is ≤ 85 mmHg (as tolerated) for subjects using an automated cuff method and ≤ 90 mm Hg for subjects who use the Doppler/cuff method.

While both device approaches yield MAP values within approximately 5 mm Hg of arterial line measurements, the Doppler/cuff method appears to give slightly higher values in non-pulsatile patients and a small adjustment is provided.

Following discharge from the index hospitalization, all subjects are required to adhere to an IBPM plan, in addition to receiving standard follow up care. Prior to discharge, subjects/caregivers will be trained to take blood pressures and record values (Automated cuff or cuff/Doppler) in a Blood Pressure (BP) diary.

Following discharge, the blood pressure will be obtained twice a day for at least the first 3 months and continue until the subject is medically stable with blood pressure within the recommended values (defined as MAP measurements ≤ 85/90 mmHg) and as medically appropriate for the subject.

Stability (defined as MAP measurements ≤ 85/90 mmHg) and compliance with the IBPM plan will be assessed by HeartWare based on Time in Therapeutic Range analysis (TTR) at monthly intervals for the first 3 months post-discharge, although it is understood that blood pressure is volatile and continuous monitoring is an essential element of improved blood pressure management.

After continuous monitoring for the first 3 months post initial discharge regardless of re-hospitalizations, stable subjects will have quarterly (3 month) TTRs performed to assess compliance. For subjects who have not met the stability definition, monthly monitoring will continue for another 3 month period. This will be repeated as often as necessary until subjects are stable.

All blood pressure measurements, including those recorded in the patient diary as well as any intervention such as medication changes to maintain the blood pressure within the therapeutically recommended ranges will be documented in the eCRF.

Method of Measurement

HeartWare will provide a blood pressure cuff and Doppler device for all enrolled MVAD subjects. It is anticipated that cuffs of different sizes will be required and a selection of cuffs of different size will be provided to sites.

The protocol for blood pressure measurements is similar to that currently used in the current HeartWare US ENDURANCE Supplemental Trial. It is simple, reproducible and requires only that subjects be divided into 2 groups: those that have a palpable radial pulse and those who do not. For subjects with a palpable radial pulse, a standard

method of blood pressure measurement will be employed, namely an automated cuff. The specific methodology is listed below:

1. If the subject has a palpable radial pulse (approximately 40% of subjects), a Blood Pressure Cuff (BPC) will be used to obtain blood pressure measurements (systolic and diastolic) and MAP calculated as follows:
   MAP = (Systolic Blood Pressure + [2 x Diastolic Blood Pressure])/3
2. If the subject has no palpable radial pulse, a Doppler and BPC will be used and the opening pressure will be reported as MAP.

Measurement of mean arterial pressure is the goal and it is understood that cuff/Doppler pressures are expected to be 5 8 mm Hg higher than MAP measured by the automated cuff method. To adjust for this difference, the upper limit for MAP will be set at ≤ 90 mm Hg for cuff/Doppler subjects.

Sites will input raw blood pressure data (systolic, diastolic or Doppler pressures) into the eCRF and automated calculations will be performed within the database.

Index Hospitalization

All subjects will be provided with a blood pressure monitoring device (Doppler and blood pressure cuff, if blood pressure cannot be measured with a cuff alone) at implant. As soon as subjects are ambulatory, training will begin on blood pressure devices.

Prior to Discharge

Subjects implanted with the MVAD pump and caregivers must demonstrate competence to take accurate blood pressure measurements. Subjects/caregivers will be educated about the specific blood pressure values that are within the target range and will also be provided with instructions regarding out-of-range blood pressure values and when to contact the Investigator/Site VAD Team (see below). The subjects and caregivers training and competency will be documented as in Appendix 17.8.3 and 17.8.4 and in the eCRF.

A patient diary will be provided to the subject, along with the Investigator/Site Team contact information.

After Discharge

Specific instructions will be given to maintain MAP ≤ 85/90 mm Hg throughout the trial. At discharge, all subjects will be provided with a blood pressure cuff and Doppler device. Both the subject and caregiver will be trained on the use of the cuff and the cuff/Doppler combination. It is required to record blood pressure twice daily (time of day may be chosen by subject but must be done consistently) in the diary, starting the day after discharge. For subjects who have a radial pulse, systolic and diastolic blood pressures will be obtained. For subjects who do not have a radial pulse, the Doppler opening pressure will be obtained. The blood pressure data will be submitted weekly to

the site via FAX, email or telephone for the duration of the IBPM and subjects must immediately report any of the following for medical advice:

1. A *cuff systolic* reading exceeds 130 mm Hg or *cuff diastolic* exceeds 95 mm Hg on 2 successive days. If this happens, the subject or caregiver will notify the site immediately.
2. For cuff/Doppler readings, if the opening pressure (MAP) exceeds 100 mm Hg on 2 successive days, the subject or caregiver will notify the site immediately.
3. A MAP of ≤ 60 or systolic BP of ≤ 100 with clinical symptoms of hypotension (dizzy, orthostasis, etc.) will trigger notification of the site with subsequent adjustment of medications.

All blood pressure measurements recorded in the diary will be entered into the database within 48 hours of receipt of the patient diary. When stable after the first 3 months, blood pressure measurements may be obtained during regular VAD clinic visits.

For subjects/caregivers who are unable to obtain reliable MAP measurements, the subject needs to return to the site on a regular basis.

The blood pressure measurements must be recorded in the patient diary regardless of the discharge facility (home, rehabilitation or other health care facilities), or re-hospitalizations due to adverse events, for at least the first 3 months post initial discharge.

It is recommended that each study center document their study IBPM data collection procedures and their implementation.

9.1.6 Documentation of Concomitant Medications

Administration of antihypertensive medications (e.g., beta blockers, ACE inhibitors), angiotensin II receptor blockers, nitrates (including nitric oxide), inotropes, anticoagulants (e.g. coumadin, heparin), anti-arrhythmics, antiplatelet medications (e.g. aspirin, clopidogrel bisulfate), antibiotics and diuretics at all study visits between screening and month 24, and at Explant (where applicable) will be recorded in the eCRF.
In addition anticoagulant and antihypertensive medications will continuously be recorded throughout the study.
Information collected may include:

- Drug
- Dose
- Route of administration
- Frequency
- Start/ Stop Date

Any Concomitant Medications taken prior, up to onset and to treat an Adverse Event will be collected at the time of each event, including any specific medications pertaining to the anticoagulation guidelines for thromboembolism, stroke and/or VAD thrombosis.

9.1.7 Echocardiogram/ qPulse™

Parameters measured via Echocardiogram will include the following captured at screening/ pre-implant*, and month 1, 3, 6, 12, 18, 24.

*Echocardiograms obtained within the 6 months prior to ICF may be used for screening measurements.	**Unit**	**Screening/ Pre-implant***	**Month 1, 3, 6, 12, 18, 24**
qPulse setting		NA	x
Set Speed (rpm)	rpm	NA	x
Pump Flow (l/min)	l/min	NA	x
Pump Power	watt	NA	x
Aortic valve opening Y/N	Yes/ No	x	x
Aortic valve opening/min	min	x	x
Aortic valve opening duration	ms	x	x
Aortic Insufficiency	None/ Mild/ Moderate/ Severe	x	x
Commissural fusion	Yes/ No	x	x
LVEF	%	x	x
LVEDD	cm	x	x
LVESD	cm	x	x
LVEDV	ml	x	x
LVESV	ml	x	X

* qPulse settings NA for screening

Additional Parameter to be measured :	**Pre-implant, Month 1, 3, 6, 12, 18, 24**
Aortic regurgitation	x
Mitral regurgitation	x
Tricuspid regurgitation	x
LA dimension(Diameter)	x
LV wall thickness	x
Presence of LV Thrombus	x

- When hemodynamically stable turn qPulse on with the MEDIUM setting
- If the aortic valve is not opening on the MEDIUM setting then consider switching to the HIGH setting
- If the aortic valve is opening every cardiac cycle and not only during the low rpm portion of the qPulse cycle then consider switching to the LOW qPulse setting.

9.1.8 NYHA classification/ INTERMACS Patient Profile

AHA and NYHA classification guidelines can be found in Appendix 17.2. Determination of NYHA classification will be performed by an independent assessor (defined as a physician or qualified physician assistant (PA), registered nurse (RN) or nurse practitioner (NP) not directly involved with this clinical trial). NYHA will be captured at screening/ pre-implant and month 1, 3, 6, 12, 18, 24.

The site s same independent assessor will also assess the subject according to the INTERMACS Patient Profile at screening/pre-implant (refer to Appendix 17.3).

The name of the assessor will be recorded on the eCRF and in the medical files.

9.1.9 NIH Stroke Scale/ Modified Rankin Scale

National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) (refer to Appendix 17.4), when feasible, will be obtained at screening/ pre-implant and month 1, 3, 6, 12, 18, 24, by a trained individual. In addition to screening/ pre-implant assessment, NIH Stroke Scale is required in the event of a stroke. After a stroke, a follow-up NIH Stroke Scale is required at 12 weeks (+/-7 days), and 24 weeks (+/-7 days) after the event to document any deficits.

9.1.10 Six minute walk

Subjects will complete a six minute walk test at screening/ pre-implant and month 1, 3, 6, 12, 18, 24. If the Subject is unable or unwilling to perform the six-minute walk test, the distance recorded should be left blank. Instructions for the procedure are found in Appendix 17.5.

9.1.11 Quality of life Questionnaire (EuroQol EQ-5D-5L)

The EQ-5D-5L (refer to Appendix 17.6), an assessment of general well-being, will also be utilized. Pre-implant assessment will be performed at screening/ pre-implant (when feasible) and month 1, 3, 6, 12, 18, 24.

9.1.12 Kansas City Cardiomyopathy Questionnaire (KCCQ)

This study will use the KCCQ (refer to Appendix 17.7), a disease specific 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge and quality of life. Subjects will complete the KCCQ at screening/ pre-implant and month 1, 3, 6, 12, 18, 24.

9.1.13 Implant Data

The surgical implant data will be collected and will include:

Date of implant
Surgical Technique
Cardiopulmonary bypass (time on bypass)
Aortic Cross Clamp time (if applicable)
Concomitant cardiac procedure(s)
Ability to close chest
Presence of intraventricular thrombus
Driveline location
Start/ Stop time of surgery
Time leaving the OR
Transfusion Details
MVAD parameters at arrival at ICU

9.1.14 MVAD® Pump Parameters

Flow (L/min), Speed (RPM), Power (Watts), will be recorded at arrival in the ICU and then daily for the first 3 days post-implant, and then at months 1, 3, 6, 12, 18, and 24, and daily during re-hospitalization if possible.

Post discharge, the subject will be required to record MVAD pump parameters daily in the patient diary until the subject s blood pressure is stable as defined in Section 9.1.5.2.

9.1.15 MVAD® Pump Log Files

The Pal™ Controller monitors and captures alarm, trend and event data in the log files. Log files will be downloaded and send to HeartWare at discharge and during the clinic visits at month 1, 3, 6, 12, 18, and 24, as well as any time an issue occurs.

After every visit the three separate files (data, alarm and events) will be emailed to mvadlogsintl@heartware.com following download.

Instructions for the procedure are found in Appendix 17.12.

9.1.16 Safety Laboratory Investigations

Laboratory samples will be taken at Screening within 72 hours prior to MVAD Pump implantation and at time points stipulated in Appendix 17.1.1. All samples will be collected in accordance with acceptable laboratory procedures.

Hematology	**Biochemistry**	**Urine Pregnancy Test** (Screening only)
Hemoglobin	Creatinine	
Hematocrit	Blood Urea Nitrogen	
Leucocytes	Total Protein	
Red Blood Cell Count	Albumin	
Platelets	Total Bilirubin	
aPTT	LDH	
INR	SGOT (AST)	
Plasma free Hemoglobin	SGPT (ALT)	
ACT (periprocedural at implant only)	CRP	

The local laboratory will perform laboratory tests for hematology, and serum chemistries. Appropriate accreditation for all laboratories as well as the reference ranges for each of the laboratory parameters measured with a description of the methods to be used in the study must be provided to HeartWare Inc. prior to initiation of the study. Changes in the reference ranges or in the methodology during the trial are to be communicated to the Clinical Research Associate.

The results of laboratory tests will be returned to the investigator, who is responsible for filing and reviewing these results together with the data in the eCRF. The investigator is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for each laboratory used.

The total amount of blood per subject for laboratory tests will be approximately 100 mL.

9.1.17 Hospital LOS (Length of Stay)

At discharge and after every Re- Hospitalization, LOS will be collected for the following:

LOS overall
LOS ICU
LOS General Ward

Additional subject related health economic data will be collected throughout the trial to perform a health economics analysis for publication and/or presentation.

9.1.18 Subject training

9.1.18.1 Discharge Training

Prior to subject discharge to an out of hospital residence, subject and companion training to manage the MVAD System including responding to LED displays and power changes, will be completed and documented.

Training Requirements

- The subject and companion/caregiver must demonstrate comprehension of key points as assessed by the Investigator s team (refer to Appendices17.8.1 and 17.8.2).
- Comprehension will be demonstrated by knowledge of proper equipment use, diagnostic and emergency alarms with appropriate responses, MVAD System troubleshooting and knowledge of when and how to implement emergency procedures and reporting of significant adverse events.
- When the wounds have healed, the subjects will be allowed to wash their incisions with mild soap and water. Occupational and Physical Therapists will instruct the subject and caregiver on the techniques and equipment necessary for a sponge bath. Safety and a sense of well-kept personal hygiene will be emphasized. Examples of commercially available soaps and bathing aids will be discussed. Subjects will be instructed to keep the Controller, Batteries and Connectors protected from water and to keep the Controller and Batteries inside the Shower Bag when washing. The subjects will be trained to keep the exit site as dry as possible to avoid infection.
- The subject and companion/caregiver will be trained on the routine daily exit site/driveline care as described in the driveline care section of the Infection Control Guidelines (refer to Appendix 17.10).

Additional Discharge Requirements

- The subject must agree to return to the implanting hospital as designated by the Investigator for medical evaluations. The subject must also agree to participate in telephone discussions, as required, with the Investigator s clinical

staff to monitor his/her out of hospital status including any adverse events and alarm conditions.

- The subject must agree to have the specified backup equipment accessible at all times.
- The subject must agree to report suspected device malfunctions.
- The subject must agree to return to the clinical study site, as determined by the Investigator, for any device malfunction or clinical event necessitating evaluation or treatment.

Only subjects discharged from a hospital, rehabilitation or extended care facility to their legal place of residence or the home of a caregiver will be considered discharged to home.
Once surgical wounds have healed, subjects may shower if they have received permission from their physician. The subject is required to use the HeartWare Shower Bag. To ensure safe and appropriate use, all subjects and caregivers should be trained to the instructions, recommendations and warning as outlined in the patient manual.

9.1.18.2 IBPM Training
Prior to discharge the subject and the subject s caregiver will additionally receive training regarding the IBPM plan as described in Section 9.1.5.2 and Appendices17.8.3 and 17.8.4. A blood pressure cuff (BPC) /Doppler along with a diary will be provided to the subject. Subjects and the subject s companion/caregiver will be trained to take SBP/DBP and/or MAP measurements with the BPC or BPC/Doppler. Subjects and caregivers must demonstrate competence in obtaining accurate blood pressure measurements. Subjects/caregivers will be educated about the specific blood pressure values that are within the target range and provided with instructions regarding out-of-range blood pressure values and when to contact the Investigator/Site VAD Team.

Subject and companion/caregiver training requirements include:

- Comprehension and agreement to comply with blood pressure management plan requirements, including obtaining all MAP measurements as required and immediately recording all values in the subject diary, contacting Investigator s team as instructed, and adhering to diet and medication regimen.
- Demonstration of proper use of the BPC or BPC/Doppler.
- Agreement to bring the BPC or BPC/Doppler and diary to all study visits.

Subjects/caregivers who are unable to obtain reliable SBP/DBP and /or MAP measurements need to return to the site on a most frequent basis.

9.1.19 Out of Hospital Assessment

While out of hospital, subjects will be instructed to call the Investigator or Investigator s staff when they have any new alarm messages that instruct the subject to call the site or for any critical alarms.

9.1.20 MVAD® Pump Exit Site/Driveline Care

Data on exit site / driveline care will be collected at discharge (for the period of hospitalization after implant) and at month 1, 3, 6, 12, 18, 24. Information collected will include:

- Frequency of dressing change and by whom
- Agents used for cleaning
- Type of dressing used
- Device used to stabilized the driveline
- Location of the driveline velour

9.1.21 Re-hospitalization

Situations may arise which require subjects to be readmitted to the hospital. The details must be completed in the eCRF for each re-hospitalization (including Reason and Duration). A discharge summary may be requested by HeartWare.

If a subject is re-hospitalized while still actively on the IBPM Plan they will be instructed to bring their equipment and patient diary to the hospital. The VAD Team will be instructed to continue record the subject s blood pressure in the BP diary according to the IBPM plan during the re-hospitalization.

9.2 Device Explant

In the event that the MVAD Pump is explanted (i.e. death, transplant, recovery, device exchange) observations should be documented in the eCRF. A discharge summary may be requested by HeartWare.

At explant, the MVAD Pump and the incision sites should be inspected for:

- Pump condition prior to explant,
- Pericardial
- Sewing Ring condition,
- Outflow Conduit condition and position,
- Driveline status,
- Blood pump housing condition.

Any identified unusual findings are to be reported on the eCRF. Photographs can be taken of the MVAD Pump, cannula, driveline, or any anomaly at the explant.

The MVAD Pump should be briefly rinsed with saline then placed in formaldehyde for at least 2 days. After removal from the formaldehyde allow the pump to thoroughly dry and package as directed for return.

HeartWare will provide an Explant Kit that is designed for transportation of used health care products. Packaging instructions will be included in each Explant Kit.

In case the HeartWare Plug is used to seal the cored ventricle upon pump removal for recovery, the following Anticoagulation regimens are recommended:

- Warfarin for 3 months post plug insertion. Maintain INR at 1.8 to 2.0.
- Low dose ASA for 3 months and then re-evaluate

Anticoagulation regimens after implant of the HeartWare Plug have not been evaluated in clinical studies.

The MVAD® Pump should NOT be disassembled by the center.

See the Instructions for Use for the MVAD® Pump explant procedure.

9.2.1 Device Retrieval

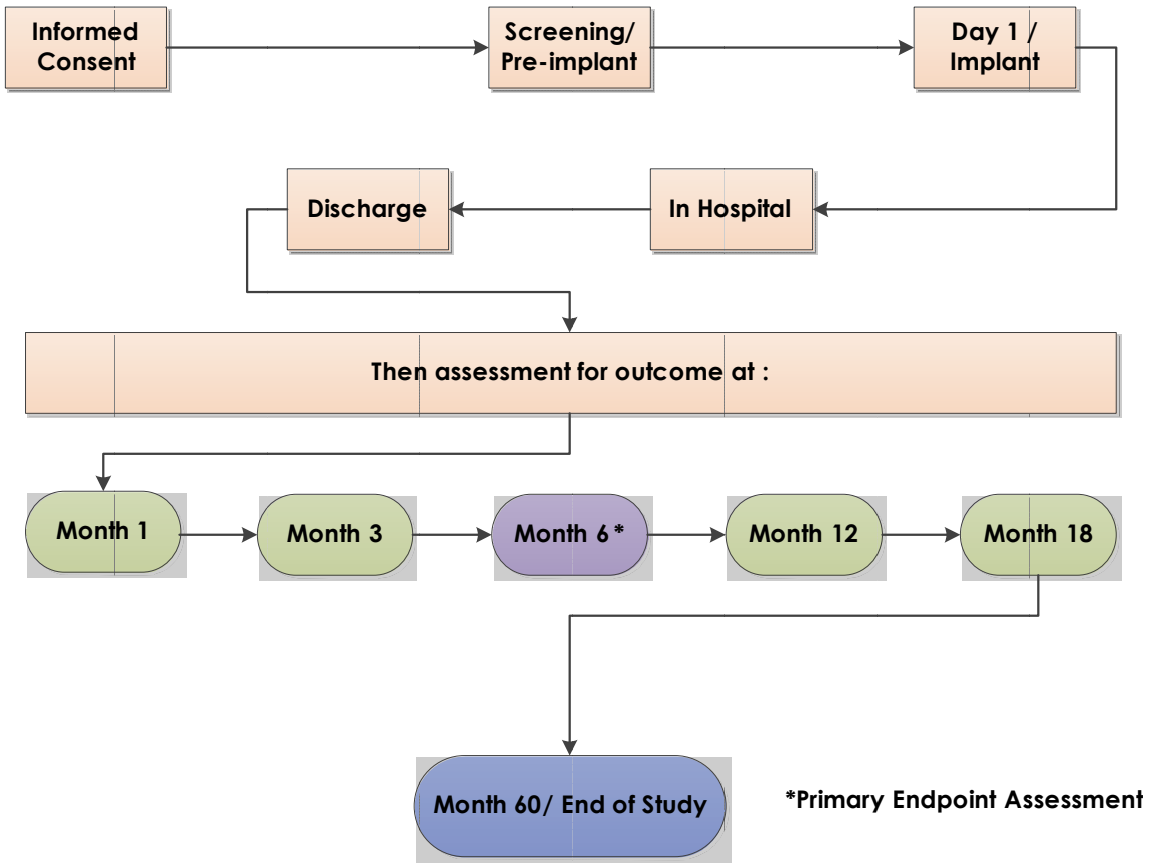
Upon MVAD Pump explantation, all MVAD Pumps should be returned to HeartWare for analysis. Devices must be returned in a MVAD Explant Kit. A Return Goods Authorization (RGA) number must be obtained from HeartWare prior to shipment of the MVAD . All explanted devices should be shipped as instructed to:

HeartWare, Inc.
Product Quality Department
14400 NW 60th Ave.
Miami Lakes, FL 33014, USA

9.3 Post- Study Clinical Follow- up

Subjects, who have safely completed the study through Month 24, will move into a Clinical Follow- up Study. Subjects will have the possibility to move into a follow- up visit schedule every 6 month where vital signs, Quality of Life and adverse events will be assessed.

9.4 Schedule of Observations and Procedures



9.4.1 Screening

Prior to MVAD Pump implantation, subject study eligibility will be determined at the completion of the screening process. Subjects will be screened against entry criteria, and if confirmed to meet all requirements for enrollment and sign/date the current IEC approved consent, will be eligible for implant and enrollment into the study. The screening log will be maintained per Section 9.4.2

Written ICF must be obtained from all potential study candidates prior to MVAD Pump implantation.

Written ICF must be provided by the subject prior to any study procedures being conducted, including screening labs or tests of any kind. Subjects will be screened against the inclusion and exclusion criteria and, if confirmed to meet all requirements, will then be enrolled into the study.

9.4.2 Screening Failure and Documentation

Subjects who do not meet the inclusion criteria or subjects who meet an exclusion criterion and are not enrolled into the study are considered screening failures. Information on screening failure subjects will be captured on a Screening Failure log and will include demographic information and the primary reasons for screen failure Screen Failures will not be recorded in the eCRF.

9.4.3 Enrollment

Subjects, who are screened and meet all the inclusion criteria, and none of the exclusion criteria, are eligible to be enrolled into the trial.

Once a subject has given consent to be enrolled, enrollment into the trial should be done within 72-hours of completion of the screening process. Exceptions may be expected for those subjects who develop a temporary complication that precludes surgery.

The following procedures will be performed at the Screening/ Pre-implant Visit:

- Date of Assessment
- Obtain signed and dated written ICF
- Evaluate suitability for participation according to inclusion and exclusion criteria
- Record Demographics
- Record cardiovascular / medical history & Hospitalizations
- Perform Echocardiogram
- Measure vital signs
- Measure Hemodynamic parameters
- Record concomitant medications taken by the subject
- Collect blood samples for laboratory testing
- Collect Urine pregnancy test on female subjects of childbearing potential
- Perform NYHA Classification/ INTERMACS Patient Profile
- Perform 6- Minute Walk Test
- Administer NIH Stroke Scale/ MRS
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Document any adverse events reported from date of signature of the ICF

9.4.4 Implant

Implants may be performed via a median sternotomy or lateral thoracotomy. In all cases a cardiopulmonary bypass is required. Implant procedures are described in detail in section 15 of the IFU which will be provided to each site at study start.

It is critical that accountability of the device is maintained for research records. Federal regulations require that the lots / ID number of the device and any accompanying surgical instruments, controllers or accessories are appropriately noted and tracked (please also see Section 5.8).

9.4.5 In Hospital

During the in hospital stay the subject will be assessed between days 1- 3.

- Date of Assessment
- Measure vital signs
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing (day 3 only)
- Document Implant Data
- Collect MVAD Pump parameter
- Record concomitant medications taken by the subject
- Document any adverse events reported

Any subject request for: 1) a do not resuscitate order (DNR), 2) device removal 3) device termination or 4) refusal to undergo device replacement, when indicated will be recorded.
Any operation that occurs after LVAD implant should be reported on the eCRF.

9.4.6 Hospital Discharge

Prior to discharge from hospital the subject and companion must be trained on managing the MVAD Pump which has been implanted as well as on the IBPM plan in Section 9.1.5.2. Subjects will be evaluated and prepared for discharge per the standard practice at each individual center.

Prior to discharge the following will be performed and documented:

- Date of Assessment
- Perform Subject Training (Discharge & IBPM)
- Record concomitant medications taken by the subject
- Document any adverse events reported
- Document LOS
- Document MVAD Pump Exit site/Driveline Care
- Download MVAD Pump log files

9.4.7 Month 1 and 3

The following information will be recorded for follow-up visits at Month 1 and 3.

- Date of Assessment
- Measure vital signs
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing
- Collect MVAD Pump parameters
- Perform Echocardiogram
- Perform 6- Minute Walk Test
- Perform NYHA Classification
- Administer NIH Stroke Scale/ MRS
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Record concomitant medications taken by the subject
- Document any adverse events reported
- Document Re-Hospitalization with LOS (if any)
- Document MVAD Pump Exit site/Driveline Care
- Check patient diary
- Download MVAD Pump log files

9.4.8 Months 6, 12, 18, 24

The following information will be recorded for follow-up visits at Months 6, 12, 18 and 24.

- Date of Assessment
- Measure vital signs
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing
- Collect MVAD Pump parameters
- Perform NYHA Classification
- Perform 6- Minute Walk Test
- Perform Echocardiogram
- Administer NIH Stroke Scale/ MRS
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Record concomitant medications taken by the subject
- Document any adverse events reported
- Document Re-Hospitalization with LOS (if any)
- Document MVAD Pump Exit site/Driveline Care
- Check patient diary (if applicable)
- Download MVAD Pump log files

9.4.9 Explant of MVAD® Pump

The rationale for explantation of the MVAD Pump will be recorded on the eCRF. Reasons for explantation may include:

- Heart Recovery
- Heart Transplantation
- MVAD Pump Exchange
- Mortality or
- Alternative Device Implant

9.4.10 Post-Explant Continuing Subject Follow-Up

The date of visit will be documented (if available) at 1 month (– 7 days), 6 months (– 30 days) and 12 month (– 30 days) after transplantation or MVAD Pump explant (includes exchange to a different MCSD).This visit will assess the survival status of the subject.

Refer to Appendix 17.1.2 for details

9.5 Subject Death

In the event of a subject death, details are to be documented in the eCRF. If an autopsy is conducted, a copy of the final autopsy report should be submitted to HeartWare or designee. The primary objective of the autopsy is to determine the cause of death, complications and other relevant findings.

10.0 ADVERSE EVENTS

From the time the ICF is signed, at each evaluation of a subject enrolled in the trial, the investigator or site staff determines whether any adverse events (AE) have occurred, and determines their relationship to the study devices or procedures. All adverse events, study device malfunctions and other product issues must be recorded in the appropriate eCRF section(s).

All adverse events will be collected until a subject s participation in the trial is considered complete.

In the event of an explant for transplant or recovery, adverse events will be collected until the induction of anesthesia for explant.
In the event the device is turned off in lieu of surgical explant, adverse events will be collected until the time the device is turned off.
In the event of an explant for an exchange for another HeartWare MVAD system, the subject will remain in the study post device exchange and adverse events will be collected throughout the subject s participation in this trial.
In the event of an explant for exchange for a non HeartWare MVAD system, adverse events will be collected until the induction of anesthesia for exchange.

Adverse events may be volunteered spontaneously by the subject, or discovered as a result of general, non-leading questioning. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it. The investigator must submit to sponsor (or designee) any USADEs, and SAEs occurring during the study **within 24 hours** after being notified of the event and provides additional information, if required by sponsor.

All AEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations necessary to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Investigators are not obligated to actively seek AEs in former study participants. However, if the investigator learns of any AE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the investigator should promptly notify HeartWare.

10.1 Definitions and documentation of adverse events

10.1.1 Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or the comparator. This includes events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational medical device.

10.1.2 Serious Adverse Event (SAE):

Adverse event that:

- Led to a death,
- Led to a serious deterioration in health that either:
  - resulted in a life-threatening illness or injury, or
  - resulted in a permanent impairment of a body structure or a body function, or
  - required in-subject hospitalization or prolongation of existing hospitalization, or
  - resulted in medical or surgical intervention to prevent life threatening illness or
  - Injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

10.1.3 Device or Procedure related

10.1.3.1 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

10.1.3.2 Device deficiency (DD)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error, and inadequate labeling.

10.1.3.3 Serious Adverse Device Effect (SADE)

A serious adverse device effect is one that has resulted in any of the consequences characteristic of a serious adverse event.

10.1.3.4 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current Risk Management section of the Investigator s Brochure and Instructions for Use.

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the VAD, that was not previously identified in nature, severity, or degree of incidence in the CIP or Instructions for Use, or any other unanticipated serious problem associated with the study device that relates to the rights, safety, or welfare of subjects.

An unanticipated event is one where the nature or intensity is not consistent with the information in the current Risk Management section of the Investigator s Brochure and the Instructions for Use.

Furthermore, reports which add significant information on specificity or severity of a known, already documented adverse effect constitute unanticipated events. For example, an event more specific or more severe than described in the Investigator s Brochure would be considered unexpected .

Unanticipation will be assessed by a Medical Monitor and reviewed by HeartWare.

10.1.4 Anticipated/ Expected Adverse Events:

An anticipated/ expected event by its nature, incidence, severity or outcome has been previously identified in the risk analysis report, and is included into the table in section 10.1.4.1.

Anticipated Adverse Events include those that are reasonably expected to occur in association with the use of a ventricular assist device and any cardiac surgery and are a result of implanting an investigational medical device.

10.1.4.1 The anticipated/ expected adverse events that will be collected are:

Potential Event	Incidence Events per Pt Year	Mitigation/Treatment	Possible Device Related*
Air Embolism	< 0.05	Training, Labeling and Conventional therapy**	Yes
Driveline Perforation	< 0.05	Training, Labeling and Conventional therapy**	Yes
Erosions and other Tissue Damage	< 0.05	Training, Labeling and Conventional therapy**	Yes
Hypertension	< 0.05	Subject Selection and Conventional therapy**	Yes
Myocardial Infarction	< 0.05	Subject Selection and Conventional therapy**	Yes
Sensitivity to Aspirin	< 0.05	Subject Selection and Conventional therapy**	No
Wound Dehiscence	< 0.05	Subject Selection and Conventional therapy**	Yes
Device Malfunction	< 0.05	Design, Training, Labeling and Conventional therapy**	Yes
Driveline Wire Damage	< 0.05	Design, Training, Labeling and Conventional therapy**	Yes
Interference with/from Other Devices	< 0.05	Design, Training, Labeling and Conventional therapy**	Yes
Psychiatric Episodes	< 0.05	Subject Selection and Conventional therapy**	Yes
Worsening Heart Failure	< 0.05	Subject Selection and Conventional therapy**	Yes
Hemolysis	0.06	Design, Training, Labeling and Conventional therapy**	Yes
Device Thrombosis	0.1	Subject Selection and Conventional therapy**	Yes
Aortic Insufficiency	0.1	Subject Selection and Conventional therapy**	Yes
Pericardial Effusion/Tamponade	0.12	Subject Selection and Conventional therapy**	Yes

Potential Event	Incidence Events per Pt Year	Mitigation/Treatment	Possible Device Related*
Pleural effusion	0.12	Subject Selection and Conventional therapy**	Yes
Stroke (Ischemic and hemorrhagic)	0.15	Subject Selection and Conventional therapy**	Yes
Multi-organ Failure	0.15	Subject Selection and Conventional therapy**	Yes
Neurologic Dysfunction (excluding stroke)	0.15	Subject Selection and Conventional therapy**	Yes
Hepatic Dysfunction	0.04	Subject Selection and Conventional therapy**	Yes
Renal Dysfunction	0.12	Subject Selection and Conventional therapy**	Yes
GI Bleeding/AV malformations	0.25	Subject Selection and Conventional therapy**	Yes
Right Ventricular Failure	0.32	Subject Selection and Conventional therapy**	Yes
Sepsis	0.34	Subject Selection and Conventional therapy**	Yes
Re-operation	0.35	Subject Selection and Conventional therapy**	Yes
Driveline Infection	0.4	Design, Training, Labeling and Conventional therapy**	Yes
Respiratory Dysfunction	0.5	Subject Selection and Conventional therapy**	Yes
Cardiac Arrhythmias	0.5	Subject Selection and Conventional therapy**	Yes
Local Infection	0.6	Subject Selection and Conventional therapy**	Yes
Bleeding, Perioperative or Late	1.5	Subject Selection and Conventional therapy**	Yes
Death	0.25	Subject Selection and Conventional therapy**	Yes

10.2 Assessment of Causality

The likely relationship of each adverse event to the investigational medical device will be assessed according to the definitions below:

10.2.1 Not related

Is defined as an AE which is not related to the use of the investigational medical device.

10.2.2 Possibly related

Is defined as an AE which might be due to the use of the investigational device. An alternative explanation (e.g., concomitant drug(s), concomitant disease(s)) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

10.2.3 Related

Data demonstrating clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the investigational medical device, which cannot be explained by concurrent disease or other factors.)

10.3 Adverse Event Reporting Requirements

10.3.1 Investigator Reporting Requirements

10.3.1.1 AE Reporting

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and in the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.
All events will be classified per INTERMACS definitions. - The date of the event, seriousness criteria and outcome should also be recorded.

Definitions for all INTERMACS-defined adverse events and AEs can be found in Appendix 17.9.

In addition, laboratory and clinical parameters will be followed to evaluate the safety and performance of the MVAD system; these include adverse event reporting and monitoring, routine clinical laboratory tests (hematology, biochemistry, and urinalysis), vital signs, hemodynamic, MVAD pump parameters, abbreviated neurological examinations/ questionnaires, review of concomitant medications and echocardiogram.

10.3.1.2 MVAD® Pump Malfunctions

Any suspected MVAD System malfunction will be recorded on the CRF. The pump(s) or component(s) will be returned to HeartWare for evaluation by quality control engineers. Additionally, following explant or autopsy, the MVAD Pump or any part of the system shall be returned to HeartWare for analysis. Instructions for returning the MVAD Components are included in Section 9.2.1.

10.3.1.3 Timelines

- **SAE Reporting**

The Investigator will complete the Adverse Event Form of the CRF **within 24 hours** of discovery for all SAEs, furthermore the CRF pages should be completed that are relevant for the understanding of the course of the event. The Investigator is obligated to provide information for SAEs as requested by the Medical Monitor in addition to the information listed on the Adverse Event Form in the CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible.

- **Unanticipated Serious Adverse Device Events**

Investigators must notify HeartWare (or designee) **within 24 hours** of discovering any Unanticipated Serious Adverse Device Event (USADE). USADEs must be documented on the appropriate CRF.

HeartWare is required to expedite to worldwide regulatory authorities USADE reports in line with the relevant legislations.

All investigators will receive a safety letter notifying them of relevant USADE reports. In accordance with all relevant legislations, HeartWare (or designee) will notify the relevant Ethics Committees as applicable.

10.3.2 Regulatory Reporting Requirements

HeartWare Inc. is required to expedite to worldwide regulatory authorities reports of AEs and device deficiencies as applicable for each region and in line with the relevant legislation including MDDEV 2.7/3 under Directives 90/385/EEC and 93/42/EEC.

All investigators will receive a safety letter notifying them of relevant reports. In accordance with the applicable national regulations, HeartWare or designee will notify the relevant IECs of applicable reports as individual notifications or through a periodic line listing as defined in the region s applicable Safety Plan.

HeartWare designee will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

10.3.3 Contacting HeartWare Regarding Safety

Contacts for SAE/ USADE receipt can be found at Sponsor/Medical Monitor Contact Information page in the Site File.

10.3.4 Study/ Implant Card

If the subjects are not under 24 hour supervision of the investigator or his/her staff they (or their designee, if appropriate) must be provided with a "study/ implant card" indicating the name of the investigational product, the study number, the investigator's name and a 24 hour emergency contact number.

11.0 DEVICE AND SUBJECT MANAGEMENT

11.1 Pre-Implant Device Management

The MVAD System and the external components will be stored under the control of the Principal Investigator and in close proximity to the operating room. Two complete sets of implant equipment, each containing one MVAD Pump and two Controllers, will be available to support the implant and provide backup capability. Trained hospital personnel will periodically check and document Controllers, Batteries, Battery Charger and Monitors for functionality.

Refer to the MVAD System Instructions for Use for detailed equipment set-up procedures. The Controller shall be run through a set up procedure to prepare the system for operation. When all components of the system are prepared, verify that all required connections for the system have been made and the system is ready for operation.

11.2 Implant Procedure

Refer to the Instructions for Use for the implant procedure, which describes MVAD Pump placement in the pericardial space, cannulation techniques and tunneling of the percutaneous lead.

11.3 Postoperative Subject Management

All investigative sites have extensive experience rehabilitating, discharging and following medically managed heart failure, heart transplant and VAD subjects. The methods used to rehabilitate subjects will vary by center and by the rehabilitation centers with which the implanting sites have relationships. Postoperative subject management guidelines providing general concepts managing right heart failure, hypertension blood pressure, device speed and flow, and physical rehabilitation are detailed in the Instructions for Use. In summary, postoperative subject management should include:

- Minimizing the risk of infection
- Minimizing the risk of bleeding
- Optimizing anticoagulation therapy
- Treatment of hypertension
- Management of blood pressure
- Management of device speed and flow
- Close surveillance of signs of right heart failure and treatment when appropriate
- A structured rehabilitation program to exercise and increase muscle strength and mass

11.4 Infection Control

It is recommended that centers follow the Infection Control Guidelines provided in Appendix 17.10.

11.5 Anticoagulation Guidelines

11.5.1 Pre Implant

Prior to a VAD implantation, many subjects with refractory heart failure have abnormal coagulation due to abnormal liver function and chronic use of anticoagulation. Prolonged INR can be associated with significant postoperative bleeding. The INR, PTT, and platelet count should be performed prior to MVAD Pump implantation. The return of each of these parameters to a normal range prior to MVAD Pump implantation is an important goal.

11.5.2 Post Implant

Subjects on the MVAD Pump should be properly anticoagulated to decrease the possibility of thromboembolism. Anticoagulation guidelines including recommendations for INR target range and for ASA sensitivity testing are included in Appendix 17.11.

11.6 Blood Pressure Management

Blood pressure should be specifically managed and tailored to maintain MAP (Mean Arterial Pressure) as tolerated at ≤ 85/90 mm Hg. Please refer to Section 9.1.5.2 for details.

All subjects will follow the IBPM plan as described in Section 9.1.5.2.

11.7 Device Speed and Flow

Post Implant the speed and flows should be ramped slowly during the first few weeks (e.g. 30 days) to avoid excessive hemodynamic forces that may damage fragile blood vessels that have undergone remodeling secondary to the lower pressures and reduced flow associated with medically-treated heart failure. There is no obvious need to exceed a cardiac index of 2.6 L/min/m^2 until subjects have fully recovered from the implant surgery and physical needs improve. A cardiac index of 2.6 L/min/m^2 is the lower limit of normal for a healthy adult.

11.8 Criteria for Return or Readmission to Hospital

Subjects must return and/or be readmitted to the hospital for any of the following conditions:

- The occurrence of any MVAD Pump malfunctions or alarm conditions that cannot be immediately diagnosed and corrected in the field.
- Medical emergency (e.g., cardiac arrest, MVAD Pump stops, loss of consciousness).
- Medical conditions (e.g., new onset infection, neurological complication) or other conditions as determined by the physician.
- Loss of power to the residence that is expected to last a period of time equivalent to or in excess of one-half the available battery support time.

12.0 STATISTICAL CONSIDERATIONS

12.1 General Statistical Considerations

All data collected in this study will be documented using summary tables and subject data listings. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented.

Demographic data, including gender, race, age and body surface area (BSA), and baseline assessments (e.g., chronic heart failure (CHF) etiology, cardiovascular history, current hospital admission) will be summarized using frequencies and percentages, or descriptive statistics, as applicable.

Survival will be calculated as actual survival and as estimated survival using the Kaplan-Meier product limit estimate.

Subjects not eligible for endpoint analysis include lost to follow-up and withdrawals prior to endpoint. Subject ineligibility is unexpected, and this protocol addresses it with a planned occurrence rate well under 5%. Transplants, explants for recovery and exchanges (to a device other than the MVAD pump) prior to endpoint will be eligible for endpoint analysis with survival status identified at the time of the procedure. Survival failure is associated with events (death) on the MVAD pump. Endpoint analyses will be performed at 6 months and 24 months.

Any deviations from the planned statistical analyses will be reported with proper justification as a protocol deviation.

Patient-years and follow-up time are based on database-driven known time on MVAD pump support (including post-exchange time). If a subject is on MVAD pump support at last known follow-up and a later date of death exists, the date of death must be considered the last follow-up for that subject. The subject is known to be alive and assumed to be on MVAD pump support up to the date of death.

Statistical analysis will be performed using SAS version 9.1 or higher.

12.2 Analysis Populations

The Intent-to-Treat (ITT) subject population will include all enrolled subjects intended to receive the MVAD pump at the time of skin incision.

The Per-Protocol (PP) subject population will include all ITT subjects who were implanted with the MVAD pump .

The primary analysis population is the ITT population. All primary and secondary analyses will be performed on the ITT and PP populations.

12.3 Primary Endpoint and Hypothesis

The primary endpoint is survival at 6 months presented as a simple proportion (subjects alive on the MVAD pump divided by endpoint eligible subjects). Transplants, explants for recovery and exchanges (to a device other than the MVAD Pump) prior to 6 month follow-up will be eligible for endpoint analysis (with survival status identified at the time of the procedure). Survival failure is associated with events (death) on the MVAD Pump. The survival incidence at 6 months is estimated to be 85%, based on HeartWare s experience with the HVAD. This estimate will be compared to a performance goal (PG_1). The null and alternative hypotheses are provided below:

H_0: $\pi_{MVAD1} \leq PG_1$

H_A: $\pi_{MVAD1} > PG_1$

π_{MVAD1} is the estimated proportion of survival in the treatment group. The performance goal at 6 months is 70%. Success is achieved if the lower bound of the one-sided 95% exact binomial confidence interval exceeds the performance goal.

A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and power greater than 80% (sample size determined using SAS 9.2). Three additional subjects (for a total of 60) will be enrolled to address for possible attrition due to lost to follow-up or withdrawal.

12.4 Secondary Endpoint and Hypothesis

The first secondary endpoint is survival at 24 months presented as a simple proportion (defined like the primary endpoint). The survival incidence at 24 months is estimated to be 70%, based on HeartWare s experience with the HVAD. This estimate will be compared to a performance goal (PG_2). The null and alternative hypotheses are provided below:

H_0: $\pi_{MVAD2} \leq PG_2$

H_A: $\pi_{MVAD2} > PG_2$

π_{MVAD2} is the estimated proportion of survival in the treatment group. The performance goal at 24 months is 52.5%. Success is achieved if the lower bound of the one-sided 95% exact binomial confidence interval exceeds the performance goal.

A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and power greater than 80% (sample size determined using SAS 9.2). Three additional subjects (for a total of 60) will be enrolled to address for possible attrition due to lost to follow-up or withdrawal.

12.5 Analysis Sites

The study will be conducted such that: 1) the same protocol will be used at each study site; 2) site investigators and personnel will receive uniform training; and 3) central data management, and monitoring will be applied with equal rigor at all sites. The diversity of hospital and clinical practice settings will add to the scientific validity and generalizability of the findings. Subjects will be pooled across sites for analysis of study endpoints.

Site effects will be considered for the primary endpoint using site as a blocking variable. Sites with at least 8 subjects will retain their identities. Smaller sites will be ranked in decreasing order of size and cumulatively pooled until pooled sites of no less than 8 are achieved.

12.6 Other Secondary Endpoints

Other secondary endpoints will also be assessed at 6, 12, 18 months and 24 months. No formal statistical hypothesis tests will be conducted. Analyses for additional secondary endpoints will involve Kaplan-Meier curves for time to event outcomes, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for quantitative outcomes, and count and frequency results for categorical outcomes. The additional endpoints include:

- Overall Survival (Time to Death)
- Incidence of major bleeding, per INTERMACS definition
- Incidence of all device failures and device malfunctions per INTERMACS definition
- Incidence of major infection, per INTERMACS definition
- Incidence of neurological dysfunction per INTERMACS definition
- Health Status change, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol EQ-5D-5L
- Functional status change, as measured by NYHA and 6-minute walk
- Frequency and rates of adverse events (AEs)throughout VAD support per INTERMACS Definition
- Length of operative time and initial hospital stay
- Re-hospitalizations(excluding planned procedures)
- Transplantations
- Explants

For the Kaplan-Meier analysis (Secondary Endpoint: Overall Survival), transplants, explants for recovery, exchanges (to a device other than the MVAD Pump) prior to endpoint, and any withdrawal or lost to follow-up will be censored, and death will be the defining event.

12.7 Adverse Events and Other Safety Analyses

Adverse events and other safety analyses will also be assessed at 6 months and 24 months. No formal statistical hypothesis tests will be conducted. Analyses will involve Kaplan-Meier curves for time to event outcomes, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for quantitative outcomes, and count and frequency results for categorical outcomes.

12.8 Study Retention and Handling of Missing and Incomplete Data

Every effort will be made to collect all data points in the study. HeartWare plans to minimize the amount of missing data in the treatment group by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators. Primary and secondary analyses will be performed on all available data.

It is anticipated that there will be little or no missing data that would impact the ability to assess the primary endpoint. If there are any subjects for whom the primary endpoint cannot be assessed, then a supplemental analysis (sensitivity analysis) of the primary endpoint will be performed with missing values imputed as failures.

For the 6-minute walk assessment, data imputation will be considered. Subjects medically unable to perform the assessment will have a value of zero imputed.

13.0 BENEFIT AND RISK ANALYSIS

13.1 Potential Benefit

It is estimated that 2-6% of the adults in the world suffer from heart failure with a higher prevalence in industrialized nations. There are approximately 5.5 million diagnosed cases in the United States[11] with 550,000 new cases identified each year and up to 14 million cases in the European Union.[12] Improvements in treatment and survival as well as increases in life expectancy have contributed to the rising incidence of the disease. The 1-year mortality rate in patients newly diagnosed with NYHA class IV HF is approximately 25%. Improvements in treatment and survival as well as expansion of the aging population have contributed to the rising incidence and prevalence of the disease.

The vast majority of heart failure patients are treated with conventional pharmacological therapy and intra cardiac defibrillators. Of these 15% to 25% would benefit from biventricular pacing.[13] NYHA Class IV patients who are refractory to conventional therapies including medications, intra-cardiac defibrillators, pacemakers, angioplasties and surgical repairs usually need their damaged hearts replaced by cardiac transplants[14] or supported with left ventricular assist devices (LVADs) .[15] Cardiac transplantation is currently the most effective therapy for advanced refractory heart failure. However, the lack of available donor organs restricts cardiac transplantation to just over 3,700 patients/year worldwide.[2]

Over the last decade, bridging to cardiac transplantation with implantable LVAD systems has gained wider clinical acceptance and today LVADs are used to relieve the symptoms of advanced heart failure and extend the life expectancy for both bridge to transplant and destination therapy patients. The Miniature Ventricular Assist System (MVAD) is an implantable pump that was designed to provide flows up to 7 L/min in a small device that is both lightweight and simple to use. Due to its small size and mechanical simplicity, the MVAD pump may provide benefits not currently available with existing technology.
The potential benefit to the subject participating in this study is the implantation of a blood pump that is less obtrusive. The potential benefits include:

Potential Benefits	**MVAD System Features**
Device reliability and durability	• Simple, passive impeller suspension system • No sensors • No valves • No contacting mechanical parts
Less invasive procedure	• Small (20 cc volume, 67 gram weight). Pump allows for pericardial placement • Integrated inflow conduit simplifies implant • No need for abdominal pocket may expedite implant time • A less invasive procedure may be associated with less morbidity, faster rehabilitation, earlier hospital discharge and improved survival.

Reduced bleeding	• Sealed outflow conduit
	  • Adjustable sewing ring with inflow tube clamp
	  • Less thoracic dissection
	• No abdominal dissection or drains

Reduced infection	• Pericardial placement • Less implanted prosthetic material • 3.5mm flexible driveline
Able to support a wider range of patient sizes	• Size of MVAD Pump may be suitable for patients with a BSA $\leq$ 1.2 m^2 who would otherwise not be candidates for implantable VAD support • Support patients who cannot tolerate an abdominal pump pocket
Able to provide left, right or biventricular support	• Size of MVAD Pump allows concurrent intrapericardial placement in the LV and RV

13.2 Risk Analysis

Placement of any implantable LVAD is a procedure that usually requires a median sternotomy, general anesthesia, a ventilator and cardiopulmonary bypass. These surgical procedures are associated with numerous risks including death. Risks associated with then implant procedure and use of the device may include, but are not limited to the following. Other than death, the adverse events are listed in alphabetical order:

- Death
- Arterial non CNS thromboembolism
  - Air Embolism
  - Embolization of sintered spheres
  - Embolization of tissue adherent to inflow at time of pump removal
  - Peripheral Thromboembolism
- Bleeding,
  - Major Bleeding (Bleeding requiring transfusion)
  - GI Bleeding
- Cardiac Arrhythmias
  - Supraventricular Arrhythmia
  - Ventricular Arrhythmia
  - ICD shock
- Device Malfunction
  - Battery failure
  - Controller failure
  - Driveline Wire damage
  - Electrostatic Discharge (ESD) damage to device
  - Injury from Device Exposure to Therapeutic ionizing Radiation
  - Injury from Device Exposure to Therapeutic Levels of Ultrasound Energy
  - Injury from High Electrical Power Sources
  - Interference with/from other devices
  - Pump Thrombosis
- Myocardial Infarction
- Neurological Dysfunction
  - Transient Ischemic (TIA) Stroke
    Ischemic Cerebral Accident (ICVA)
    Hemorrhagic Cerebral Accident (HCVA)
- Pericardial Fluid Collection
  - Pericardial Effusion
  - Tamponade
- Psychiatric Episode
  - Suicide
- Renal dysfunction
- Respiratory Failure
- Right Heart Failure
- Venous Thromboembolism Event
  - Deep Vein Thrombosis
  - Pulmonary Embolism
- Wound dehiscence
- Other
  - Aortic Insufficiency
  - Cardiopulmonary Arrest
  - Dizziness
  - Multi Organ Failure
  - Platelet Dysfunction
  - Sensitivity to Aspirin
  - Surgical Complications
    Arterio-venous fistulae
    Organ damage during driveline tunneling
    Pain
    Re-operation
  - Syncope

• Hemolysis • Hepatic Dysfunction • Hypertension • Major Infection – Driveline Infection – Internal Pump Component, Inflow or Outflow Tract Infection – Localized Non-device Infection – Sepsis	– Tissue Erosion and other tissue damage • Worsening Heart Failure

There have been reports of LVADs interfering with the telemetry of some ICDs and pacemakers which led to the inability to access data or adjust software parameters.[16-17] Other reports detail LVAD related interference with lead wires that are in close proximity to the VAD resulting in unnecessary ICD firings.[18] Design and testing of the MVAD System have attempted to address these issues and reduce their incidence and severity to as low as reasonably possible. Interactions with any other therapy are not anticipated. No other interactions are expected between the HeartWare MVAD and conventional therapies.

This study involves only standard of care procedures and does not differ from typical LVAD implantation and follow-up care. Therefore, the clinical study requirements pose no additional risk to the subject. There are no foreseeable, additional risks associated with implantation of the beyond those historically associated with implantable LVAD systems. HeartWare believes it has used its best efforts to foresee hardships and potential adverse events of either in-hospital or home use of the MVAD System. The MVAD System will comply with the testing requirements in conformance with European and United States standards.

During the Investigator Meeting and Site initiation Visit HeartWare Clinical Specialist will provide training to investigators and clinical personnel on the MVAD System, surgical implant procedure and subject management. HeartWare personnel will be available to support MVAD implants and for MVAD troubleshooting. In addition, subjects and companions will undergo an extensive MVAD system hospital training program prior to hospital discharge.

In the event of unforeseen or increased risks to subjects, suspension or termination of the clinical study shall be considered.

The potential risks associated with the MVAD System have been evaluated (per the MVAD System Clinical Risk Benefit Analysis) with residual risks found to be acceptable per the MVAD System Risk Analysis Report. Within the range for potential risks, the benefit of MVAD support for a subject with a need for mechanical circulatory support exceeds the risk.

14.0 ETHICAL ASPECTS

14.1 Ethical Considerations

This trial is to be conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ISO 14155 2011, ICH GCP and applicable regulatory requirement(s).

The Investigator is responsible for ensuring that the clinical trial is performed in accordance with the CIP, current ISO 14155 2011, ICH guidelines on GCP, and applicable regulatory requirements.

Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of the trial subjects are protected.

The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician. Each individual involved in conducting the trial should be qualified by education, training and experience to perform his or her respective task(s).

The trial can only start at the Investigator s site when the relevant IECs have given signed and dated approval of the CIP, written ICFs and other written information to be provided to the subjects (e.g., questionnaires).

14.2 Subject Information and Consent

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled. However, the Investigator should try to exclude an adverse event as the reason for withdrawing voluntarily.

With the help of the Information Sheet, the subject will be informed about the device and anticipated effects, and the reason, design and implication of the trial. The subject must give consent to participate prior to enrollment in the trial. This consent must be given in writing or orally in the subject s native non-technical language that is understandable to the subject if witnessed by a third party due to the subject s condition if allowed for by local legislation. The witness must sign the consent form. The person who conducted the ICF discussion must also sign. With consent, the subject will confirm that his participation is voluntary and that they will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

Prior to participation in the trial, the subject, should receive a copy of the signed and dated written ICF and any other pertinent written information.

The ICF and Information Sheet must include all elements required by law, local regulations ISO 14155 2011, and ICH GCP guidelines, and CA requirements as well as trial specific items.

The subject must be informed that it may be necessary for the analysis of certain data that their name will remain visible whilst the analysis is performed. The results of the analysis will be processed so that the confidentiality of the subject is maintained.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in the trial. The Investigator should not include themselves, their relatives, and members of their clinical team or their relatives in the trial. Ample time must be allowed for the subject to make his or her decision, and to make further enquiries about the trial.

The signed and dated consent form will be kept by the Investigator.

Should new information become available during the course of the trial that may be relevant to the subject s consent, the Information Sheet will be revised. The revised version will be submitted for IEC approval before use. The subject must be informed as soon as possible if new information becomes available that may be relevant to the subject s willingness to continue participation in the trial. The communication of this information should be documented. The subject should receive a copy of any updates to the signed and dated written ICF or other pertinent written information.

14.3 Independent Ethic Committee

Independent Ethic Committee (IEC) will safeguard the rights, safety, and well-being of all trial subjects. This study will be undertaken only after full approval of the CIP, addenda, and Informed Consent Forms (ICFs) have been obtained from a local IEC and a copy of this approval has been received by HeartWare.

The IEC must be informed of all subsequent CIP amendments issued by the sponsor.

Reports on, and reviews of, the study and its progress will be submitted to the IEC by the investigator at intervals stipulated in their guidelines.

14.3.1 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate and timely reports on this investigation to HeartWare Clinical Affairs or designee.

Responsibilities for Preparing and/or Submitting Reports

Type of Report	Submit to	Time of Notification to HeartWare	Time of Notification to IEC
Suspected Device Malfunction or problem	HeartWare, IEC	Within 5 working days of knowledge	As required
Device Failure	HeartWare, IEC	Within 72 hours of knowledge	As required
Unanticipated Adverse Device Event	HeartWare, IEC	Within 24 hours of knowledge	Within 10 days
Subject death during study	HeartWare, IEC	Within 24 hours of knowledge	As required
Subject withdrawal	HeartWare, IEC	Within 72 hours of knowledge	As required
Withdrawal of IEC approval	HeartWare	Within 72 hours of knowledge	Not Applicable
Serious deviations from the CIP	HeartWare, IEC	Within 5 working days	As required
ICF not obtained	HeartWare, IEC	Within 5 working days	As required
Progress Reports	HeartWare, IEC	At least annually	At least annually
Final summary report	HeartWare, IEC	≤6 months of study completion	≤6 months of study completion
Other information as requested by HeartWare, IEC and/or regulatory bodies	As appropriate	As requested	As requested

14.4 Insurance

Insurance for the subjects participating in this trial which will provide compensation to subjects for clinical investigation related injuries will be arranged by HeartWare.

A copy of the insurance certificate will be held in the central or the country specific parts of the Trial Master File at HeartWare.

The insurance regulations will be handed over to the subjects upon request.

14.5 Regulatory Affairs

This trial will be carried out in compliance with legal regulations. Before initiating the trial HeartWare and/or the Investigator, if required by the applicable regulatory requirement(s), will submit any required application(s) to the appropriate authorities for review, acceptance, and/or permission to begin the trial. A copy of the submission will be held in the central files.

The Investigator will be informed by HeartWare when new information about the Device and adverse events due to the Device becomes available.

14.6 Investigators and Trial Administrative Structure

14.6.1 Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the CIP, Declaration of Helsinki, ISO14155 2011, ICH GCP Guidelines, and any country laws, as applicable.

If the trial is conducted by a team of individuals at the trial site, the Investigator is the responsible leader of the team and may be called the Principal Investigator.

A Sub-Investigator (e.g., associates, residents, research fellows) is any individual member of the clinical trial team designated and supervised by the principal Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

The Investigator must maintain a signed list of appropriately qualified persons to whom they have delegated significant trial-related duties which must be specified. A copy is held in the site files at HeartWare and the CRO.

Trial-related medical decisions are the responsibility of a qualified physician (the Investigator or delegate).

Curricula vitae and/or other relevant documents confirming the qualifications of the Investigator and Sub-Investigators are required by HeartWare/the CRO. Any previous training in the principles of GCP or experience obtained from work with clinical trials and subject care should be described in the curriculum vitae. When personnel changes are made, the relevant documentation must be updated before a new member of the team can perform critical and/or significant trial-related activities.

The Investigator has to comply with the local legal requirements concerning reporting of information relevant for the trial conduct.

The standard requirements for IEC review, ICF, subject data protection, investigator agreements and financial disclosures will apply.

14.6.1.1 Investigator Agreement

Prior to study initiation, the Investigator must sign an Investigator Agreement (HeartWare to provide Investigator Agreement template to sites). The Investigator Agreement identifies the Investigator s legal and ethical commitments with respect to the conduct of the clinical study as defined in Practice ISO14155 2011.

In addition, responsibility for insurance or indemnity to cover any liability of the Investigator which may arise directly or indirectly from his participation in the trial will be specified in a contract between the Investigator and HeartWare.

14.6.1.2 Financial Disclosure

A Financial Disclosure Form must be reviewed and signed by the Investigator and sub-investigator(s) prior to study initiation. HeartWare or designee will provide Financial Disclosure Form to sites. Updates to financial disclosure will be made during the course of the study and for 1 year following completion of the study. The Financial Disclosure form is required to record the Investigator s and Sub-Investigator s financial interests in HeartWare, which may be a potential source of bias in the outcome of the clinical study.

14.6.1.3 CIP Deviations and Medical Emergencies

The Investigator will not deviate from the CIP without the prior written approval of HeartWare except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject s risk or affect the validity of the study. In addition HeartWare will not allow any deviations/waiver from the Inclusion and Exclusion Criteria.

In medical emergencies, prior written approval for CIP deviations will not be required, but HeartWare personnel must be notified via telephone within 24 hours of occurrence.

If there are any circumstances during the clinical trial which can affect the safety of the subjects, users or third person, HeartWare and the investigator will take all necessary security measures immediately to protect the subjects, users and third persons against direct or indirect risk. HeartWare and the investigator have to inform the CA and the responsible IEC immediately about these new circumstances and the measures taken.

However in case of any deviation for a scheduled assessment e.g. out of window assessment, missing laboratory sample, and prior approval from HeartWare is required in advance for changes in or deviations from the CIP.

14.6.2 HeartWare (Sponsor)

HeartWare accepts the responsibilities of the Sponsor.

14.6.3 Contract Research Organization

A CRO (commercial, academic or other) may be employed by HeartWare to perform 1 or more of its trial-related duties and functions. The extent of the delegation must be specified in a contract between the involved parties. The CRO should implement quality assurance and quality control but HeartWare will have the right to supervise the implementation of the methods for quality assurance and quality control.

14.6.4 HeartWare (Clinical Specialists)

HeartWare s Clinical Specialists are involved in many trial-related duties and functions in cooperation with HeartWare Clinical Operations. Their tasks include but are not limited to:

- Training the Investigator and site staff in the use of the MVAD Pump which includes Implantation and device operation and management
- Ongoing education
- Implant support
- On Call clinical and technical support
- Assist with subject training
- Device inventory and replacement
- Complaints

This will be specified case by case before actions for the trial are taken and documented in the trial documentation.

15.0 DOCUMENTATION OF TRIAL DATA

15.1 Case Report Forms

An Electronic Data Capture (EDC) system will be utilized to collect all subject data during the course of the study. Data must be entered into eCRFs in English. The eCRFs are to be completed within 72 hours of the subject's visit, with the exception of results from tests performed outside the investigator's office, so that they always reflect the latest observations on the subjects participating in the study. A predetermined/designated individual(s) will be responsible for completion of the Electronic Case Report Forms (eCRFs). The PI will ultimately be responsible for the review, completion and accuracy of data entered into the eCRF.

Completed eCRFs will be verified by a Sponsor monitor at the site at regular intervals throughout the study. The Investigator will allow the monitor and the regulatory bodies (Competent Authorities (CAs)) to review the study files, subject CRFs, medical records and other study-related documents.

15.2 Data Management

15.2.1 Data Management

Data Management will be coordinated by HeartWare or their assigned designee.

15.2.2 eCRFs

During data entry in the eCRF, queries will be directly issued to clarify missing data, inconsistencies and incorrect values. After completion of the eCRF, further queries will be issued to the Investigator to clarify (e.g., inconsistencies resulting out of the medical and manual review). Resolutions of queries will be made by the Investigator or the trial site s designated persons. The query is answered directly in the eCRF system and the original value is changed, if necessary.

15.2.3 Coding

Medication names will be coded using the World Health Organization Drug Dictionary. INTERMACS OTHER Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The version most currently implemented when the first subject is enrolled will be used through the study. Coding will be reviewed by a Drug Safety Medical Advisor.

15.2.4 Patient Blood Pressure Diary

Subject s blood pressure Measurements are to be recorded via a paper diary. The subjects will receive a Subject Diary at discharge and will be instructed on how to use it. The data collected will transcript into the eCRF by the site

15.2.5 Source data

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents which comprise clinical documentation, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments and data and records arising from other departments such as the pharmacy, laboratory and medico-technical departments).

Clinical documentation relevant to the trial includes all records in any form including, but not limited to:

- Medical history/physical condition of the subject before enrollment sufficient to verify
- CIP entry criteria
- Dated and signed notes for specific results of procedures and exams
- Laboratory reports
- Information related to adverse events
- Notes on subject s condition with device implanted and when explanted
- Stroke Scale and Quality of Life studies
- Discharge Summaries/Procedure reports
- Autopsy reports

All clinical documentation and data arising from the trial are to be kept by the Investigator who has to provide direct access for trial-related monitoring, audits, IEC/EC review, and regulatory inspection.

In certain circumstances data may only be recorded in the trial specific CRF and not in other documents. When this occurs, the CRF is considered to be the source document.

At the end of the trial, the Investigator will receive a certified copy of all data captured for their subjects, in human readable form, on a read-only CD-ROM. Data captured of all subjects will be sent to the sponsor in human readable form, on a read-only CD-ROM for archiving.

15.3 Data Review

All eCRFs will be reviewed for completeness and clarity. Missing data will be investigated by the monitor and clarified by study personnel as necessary. HeartWare may request additional documentation such as physician procedure notes or written summaries relating to adverse events or procedures. HeartWare will be responsible for the quality control of the database and confirming the overall integrity of the data.

15.4 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of CIP procedures with the investigator and associated personnel prior to the study and periodic monitoring visits by the sponsor. eCRFs will be reviewed for accuracy and completeness by the sponsor during on-site monitoring visits and after their return to HeartWare and any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

15.5 Database lock

When all data are received, all data checks and quality control checks have been performed, and a final data review meeting has been held, the trial database is considered clean and can be locked.

16.0 ADMINISTRATIVE REQUIREMENTS

16.1 Monitoring of the Study

HeartWare contracted a CRO (Theorem) who will perform on-site monitoring visits as frequently as necessary. Visits are usually made at intervals of at least four to twelve weeks. The dates of the visits will be recorded by the monitor in a study center visit log to be kept at the site. The first post initiation visit will usually be made as soon as possible after enrollment has begun. At these visits the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper ICF procedures, adherence to CIP procedures, adequate reporting and follow-up of AEs, administration of concomitant medication and device receipt/ return records. Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

16.2 Independent Data Review and Event Adjudication

To meet the trial s ethical responsibility to its subjects, results will be monitored by two independent groups that have no formal involvement with the subjects or the investigation, as follows:

1. DSMB- Data Safety Monitoring Board.
2. CEC- Clinical Events Committee.

The members of these committees shall function independently of HeartWare and the CRO.

16.2.1 DSMB and CEC Composition

These two committees will include a Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC). Each committee will be composed of at least three or more members (at least two physicians from the fields of cardiology and cardiac surgery) who are not directly involved in the conduct of the trial.

16.2.2 DSMB

The DSMB will review the study at key points during the conduct.

The first DSMB safety review will take place after the first 10 subjects have been implanted followed by a periodic safety review of study data every six months from the date of the first MVAD Pump implant. Members will be provided data summaries (listings) from the clinical study in a blinded fashion without site or physician identification. Based on the safety data, the DSMB may recommend that the trial be

modified or stopped. No formal statistical rule will be defined for stopping the trial for safety reasons.

The DSMB process (including their ability to stop an ongoing study due to safety concerns) is documented in the study specific DSMB Charter.

16.2.3 CEC

The CEC will adjudicate events including device malfunctions dynamically. All unanticipated serious adverse device effects and INTERMACS-defined events will be adjudicated by the CEC using the INTERMACS-specific definition. Each event will be adjudicated by an independent CEC committee (at least 3 reviewers) with the final adjudicated result being a consensus of the committee.

The CEC process is documented in the study specific CEC Charter.

16.3 Quality System, Audit and Inspection

16.3.1 Quality system

HeartWare is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures. HeartWare/the CRO is responsible for ensuring that all parties involved with the trial agree to direct access to all trial-related sites, source data and documents, and reports for the purposes of monitoring and auditing by HeartWare/the CRO, and inspection by domestic and foreign regulatory authorities.

The documentation of the trial should be adequate for reconstruction of the course of events (audit trail).

16.3.2 Audit

An audit is the systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data recorded, analyzed and accurately reported according to the CIP, HeartWare/the CRO s Standard Operating Procedures, GCP and applicable regulatory requirements.

The Investigator will permit an appointed person by the Quality Assurance Unit of HeartWare/the CRO to audit the facilities and documentation at agreed times. Auditors are independent of the clinical trial and its performance.

16.3.3 Inspection

Inspection is the act by regulatory authorities of conducting an official review of the documents, facilities, records and other resources that are deemed by the authorities to be related to the clinical trial and that may be located at the trial site, at HeartWare, at the CRO, or at other facilities deemed appropriate by the regulatory authorities. The Investigator is obliged to cooperate with any inspection.

16.4 Maintenance of Study Documentation

The Investigator must maintain the following documents throughout the study:

- CIP
- IEC Approvals and Correspondence
- IEC Approved ICF
- Correspondence with HeartWare
- Electronic Signature Authorization Form Device Accountability
- Investigator Agreements
- Curriculum Vitae
- Financial Disclosure Forms
- Telephone Logs
- Screening Logs
- eCRFs
- Monitoring Visit Log
- Laboratory Accreditation and Normal Values
- Site Delegation and Responsibility log
- Source Documents supporting information on eCRFs
- Any other study specific documents

16.5 Subject Data Protection

Subjects will be identified on the eCRF by a subject identification number. The investigator will maintain a confidential subject identification list separate from investigational files to link medical records and subject identification numbers.

All information and data sent to HeartWare or their authorized representative, concerning subjects or their participation in this study, will be considered confidential. All data used in analysis and reports will be used without identifiable reference to the subject. At all times throughout the study, confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access.

All subjects consented for this study will be informed and must agree to the use and disclosure of their study information by the institution and investigators to HeartWare, their agents and representatives, the Competent Authorities (CAs) or other government agencies or review boards.

16.6 CIP Modifications

Changes to the CIP during the trial will be documented as amendments. The amended CIP will be signed by the relevant personnel at HeartWare, and by the Investigator(s).

Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant IECs and, where necessary, to the relevant CAs.

The Investigator should not implement any deviation from, or changes to the CIP, without agreement by HeartWare and the CRO and prior review and documented approval/favorable opinion of the appropriate IEC and, if legally required, CAs, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the trial.

If an amendment substantially alters the trial design, increases the potential risk to the subjects or affects the treatment of the subject, then the Information Sheet must be revised and submitted to the relevant IEC and, where necessary, to the relevant CAs, for review and approval. When a subject is currently undergoing trial procedures and is affected by the amendment, then the subject must be asked to consent again using the new Information Sheet. The new Information Sheet must be used to obtain consent from new subjects before enrollment.

16.7 Compliance/ Investigational Site Termination

16.7.1 Compliance

Compliance is the adherence to all trial-related requirements, to Good Clinical Practice (GCP) and to regulatory rules and regulations.

16.7.2 Investigational Site Termination

An initiative for center closure or study termination can be taken at any time either by the sponsor or by the investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. HeartWare reserves the right to terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete case report forms
- Failure to obtain ICF
- Failure to report SAEs and USADs
- Loss of or unaccountable investigational device inventory
- Repeated CIP violations
- Failure of investigator to comply with training or Instructions for Use
- Failure to screen and/or enroll an adequate number of subjects
- Insufficient subject and caregiver/Companion training

16.8 Record Retention

HeartWare and all participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed ICFs, eCRFs, study documentation (listed above) and source documents for at least 15 years from the date of the manufacture of the last product in agreement with EU directive 90/385/EEC, Annex 6, section 4, and in agreement with the local regulations. HeartWare should be contacted if the Principal Investigator plans to leave or otherwise absent themselves from the investigational site.

In the event of a CA audit, the Investigator must allow CA access to the study records for inspection and copying. The Investigator must inform HeartWare of any CA audit and provide HeartWare with a copy of any Observations.

The trial master file, the eCRFs, and other material supplied for the performance will be retained by HeartWare according to applicable regulations and laws.

16.9 Site Training

Sites will be trained by HeartWare on the device usage and on implant technique as appropriate. Training on GCP, CIP required procedures and data collection will be provided by the vendor(s).

16.10 Confidentiality of trial results

The results of this trial are confidential and are not to be transmitted to a third party in any form or fashion. All persons involved in the trial are bound by this confidentiality clause.

16.11 Publication policy

The sponsor and the investigators are committed to the publication of the results of this study. The results of the trial will be submitted for publication in an international peer-reviewed heart failure or cardiothoracic surgical journal. Draft manuscripts of publications will be prepared in co-operation between HeartWare and the Coordinating Investigator/Investigator(s). Joint publications are only possible if all parties agree. All editorial decisions will be made jointly by HeartWare and the Coordinating Investigator/Investigator(s).

HeartWare reserves the right to review any publication pertaining to the trial before it is submitted for publication. Neither party has the right to prohibit publication unless publication can be shown to affect possible patent rights or regulatory submission requirements.

In case of discrepancies with other contracts, the provisions of the CIP shall prevail.

16.12 Final report

An interim report (after 6 month) and a final report, integrating medical and statistical aspects, will be prepared. This will be authorized by the relevant personnel of HeartWare, and the Coordinating Investigator on behalf of the Investigators. The Investigator(s) will be provided with a copy of the summary of the final report. HeartWare will provide the CA and IEC with the complete clinical trial report within 1 year after the end of the trial or on request, where required.

16.13 Organization/ Site personnel

It may be necessary to define additional site personnel (e.g., doctors, nurses, technicians) who have a special responsibility for the performance of portions of the trial at a site under the auspices of the Investigator. The information regarding all site personnel taking part in the trial will be documented and stored in the Investigator s site file.

17.0 APPENDICES

17.1 Time and Event Schedules

17.1.1 Screening to Month 24

Event / Assessment	Screening/ Pre-implant 72 hours before Implant	Day 1-3/ During initial Hospitalization	Discharge	Month 1, 3 +/-7 days	Month 6 + 14 days	Month 12, 18 +/-14 days	Month 24 + 14 days
Informed Consent	X						
Inclusion/Exclusion	X						
Demographics	X						
Cardiovascular/ Medical history & Hospitalization/ INTERMACS Patient Profile	X						
Subject training (HeartWare MVAD and BP Management)			X				
Urine Pregnancy Screen	X						
Safety Laboratory Chemistry and Hematology	X	X[1]		X	X	X	X
Hemodynamic Parameter/ Vital signs [2]	X	X		X	X	X	X
IBPM & Diary Assessments[2]			X	X	X	X	X
Echocardiogram [3]	X[3]			X	X	X	X
Implant Data		X[4]					
MVAD Pump Parameters [5]		X		X	X	X	X
Log File Download			X	X	X	X	X
Driveline Care Assessment			X	X	X	X	X
NYHA Classification	X			X	X	X	X
6-Minute Walk	X			X	X	X	X
NIH Stroke Scale / Modified Rankin Scale [6]	X			X	X	X	X
Quality of Life Questionnaire (EuroQol EQ-5D-5L)	X			X	X	X	X
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X			X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

1 Day 3 only **2** Detailed schedules in Section 9.1.5 of CIP **3** Echocardiograms obtained within the 6 months prior to ICF may be used for screening
4 Implant=Day 1 **5** MVAD Pump parameters will also be recorded daily post discharge until the patient s blood pressure is stable as defined in Section 9.1.5.2 and at any subsequent hospitalization **6** In addition obtain MRS and NIHSS at time of stroke and at 12 weeks and 24 weeks post-stroke (+/- 7 days)

17.1.2 Follow- up after Explant of MVAD® Pump

Event / Assessment	Explant	Month 1 post explant +/-7 days	Month 6 post explant +/-30 days	Month 12 post explant +/-30 days
Visit Date / Survival Status		X	X	X
Concomitant Medications	X			
Adverse Events	X			

17.2 New York Heart Association (NYHA) Functional Classification

The subject s functional status will be assessed by a qualified individual at the institution (who is not associated with the trial) by utilizing the NHYA functional classification below:

ACC/AHA vs. NYHA Classification of Heart Failure

ACC/AHA Stage		NYHA Functional Class	
Stage	**Description**	**Class**	**Description**
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	**No comparable functional class**	
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.	**I (Mild)**	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.	**II (Mild)**	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
		III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.	**IV (Severe)**	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA = American College of Cardiology/American Heart Association; HF = heart failure; NYHA = New York Heart Association

17.3 INTERMACS Profiles of Advanced Heart Failure

- **Profile 1: Critical cardiogenic shock:**
  Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypo perfusion, often confirmed by worsening acidosis and/or lactate levels.
  "Crash and burn." Definitive intervention needed within hours.
- **Profile 2: Progressive decline:**
  Patient with declining function despite intravenous inotropic support may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance *"Sliding on inotropes."* Also describes declining status in patients unable to tolerate inotropic therapy.
  Definitive intervention needed within few days.
- **Profile 3: stable but inotrope dependent:**
  Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. *"Dependent stability."*
  Definitive intervention elective over a period of weeks to few months.
- **Profile 4: Resting symptoms**
  Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.
  Definitive intervention elective over period of weeks to few months.
- **Profile 5: Exertion intolerant**
  Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may more at risk than INTERMACS 4, and require definitive intervention.
  Variable urgency, depends upon maintenance of nutrition, organ function and activity.

- **Profile 6: Exertion limited**
  Patient without evidence of fluid overload is comfortable at rest, and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment.
  "Walking wounded." Variable, depends upon maintenance of nutrition, organ function, and activity level.
- **Profile 7: Advanced NYHA III**
  A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.
  Transplantation or circulatory support may not currently be indicated.

17.4 NIH Stroke Scale

NIH Stroke Scale (NIHSS)[7, 8]

The NIH Stroke Scale (Brott et al. 1989) is a widely used simple neurological evaluation that assesses acute cerebral vascular accident symptoms such as ataxia, change in consciousness, dysarthria, extra ocular movement, language, motor strength, neglect, sensory loss and visual-field loss. The NIHSS will be evaluated for all patients in the study.

Modified Rankin Scale (MRS)[9, 10]

Modified Rankin Scale is a valid estimate of global disability based on a patient's ability to independently perform day-to-day activities of daily living. An MRS score will be obtained using a structured interview created by Wilson et al. When used with the structured interview, the MRS is highly reliable. An MRS score greater than 3 (i.e., 4 or 5) will be used to suggest the presence of neurological deficit after a neurological event. If the screening/ pre-implant (pre-existing) score is 4, then a score of 5 will be used to define neurologic deficit after a neurological event.

17.5 Procedure for 6 Minute Walk Test

Location

The 6-minute Walk test (6MWT) should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The distance should be reported in meters walked. The walking course must be 30 meters in length. A 35 meter hallway is required. The length of the corridor should be marked every 3 meters. The turnaround point should be marked with a cone (such as an orange traffic cone). A starting line which marks the beginning and end of each 60-meter lap should be marked on the floor using brightly colored tape.

Patient Preparation

1. Comfortable clothing should be worn
2. Appropriate shoes for walking should be worn
3. Patients should use their usual walking aids during the test (cane, walker, etc.)
4. The patients usual medical regimen should be continued
5. A light meal is acceptable before early morning or early afternoon tests
6. Patients should not have exercised vigorously within 2 hours of beginning the test

Measurements

1. Repeat testing should be performed at about the same time of day to minimize intraday variability.
2. A warm up period before the test should not be performed.
3. The patient should sit at rest in a chair located near the starting position for at least 10 minutes before the test starts. During this time, check for contraindication, measure pulse and blood pressure, and make sure clothing is appropriate.
4. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, worksheet) and move to the starting point.
5. Instruct the patient as follows: The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I m going to show you. Please watch the way I turn without hesitation.

   Demonstrate by walking one lap yourself. Walk and pivot around the cone briskly.

   Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don t run or jog.

   Start now or whenever you are ready.

1. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
2. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once. Let the participant see you do it.

   After the first minute, tell the patient the following (in even tones): You are doing well. You have five minutes to go. Repeat after each minute.

   When the timer is 15 seconds from completion say this: In a moment I m going to tell you to stop. When I do, just stop right where you are and I will come to you.

   When the timer rings, say this: Stop! Walk over to the patient. Consider taking a chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or piece of tape on the floor.

1. Record the number of laps from the counter.
2. Record the additional distance covered using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter and record it on the worksheet.
3. Congratulate the patient on good effort and offer a drink of water.

***Excerpted from the American Thoracic Society, ATS Statement: Guidelines for the Six-Minute Walk Test, March 2002.**

17.6 Quality of life Questionnaire (EuroQol EQ-5D- 5L)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

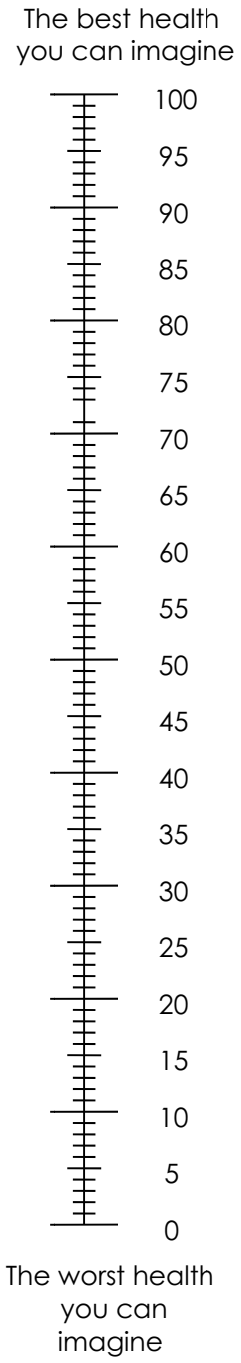
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



17.7 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

---

1. **Heart Failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reason or did not do the activity**
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100m on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed?

My symptoms of **heart failure** have become

Much worse	Slightly worse	Not changed	Slightly better	Much better	I ve had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times a day	At least once a day	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart Failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** Sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks?

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reason or did not do the activity**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

17.8 Subject Training Prior to Discharge

17.8.1 HeartWare MVAD® Training

Purpose

The purpose of discharge training is to assure that patients and caregivers are trained on the routine use, responses to alarms and emergency procedures associated with the MVAD System.

Indications

All of the clinical sites participating in the HeartWare MVAD Trial will have experience discharging patients with VADs to home. For the most part, centers will follow the patient training procedures already in place at their institution. A Technical Training Checklist template and a template describing Aspects of Daily Care are included for the clinical centers convenience. The centers are not required to use these templates. The patient and caregiver/companion should be trained together in MVAD Pump management so that each realizes the competence of the other. This will lead to mutual trust and comfort with the device. Other family members and/or close friends who live with or near the patient and are able to take an active role in the patient's new lifestyle with an MVAD Pump may also be included in training.

Training for Discharge

Training the patient and caregiver/companion is essential for a safe and successful discharge. To be eligible for discharge, both the patient and caregiver/companion must be able to demonstrate proficiency in operating the MVAD Pump and responding to alarms and emergencies. In order to evaluate their understanding and ability, they will be tested using hands-on demonstrations with mock training equipment. Once the patient and caregiver/companion have successfully completed the Hands On training, the PI/VAD/Transplant Team will determine the appropriateness for discharge. At the end of the training, the patient and caregiver/companion should be able to:

- Identify the power cable and successfully connect the cable to the controller and electrical outlet
- Identify slots on the controller for rechargeable battery packs and successfully replace the batteries as indicated
- Successfully recharge battery packs with the battery charger
- Accurately estimate the remaining battery time on each battery pack according to LED light displays
- Hear audible alarms and identify alarm messages on the controller
- Understand the meaning of alarms and demonstrate appropriate responses to alarm conditions
- Successfully switch from one controller to another controller

- Understand the importance of not pulling, twisting or kinking of driveline and power cable and battery packs
- Understand the importance of having back up controller and power sources available at all times

In addition, patients and/or caregiver/companions should be able to:

- Change the MVAD Pump exit site dressing using appropriate technique
- Identify the signs and symptoms of infection
- Take medications as prescribed
- Understand all situations when the HeartWare team, hospital medical staff or emergency medical service should be contacted
- Return to the hospital or physician s office as required

Copies of the following materials will be available to the patient/family/health care providers from HeartWare:

- Patient Manual
- Instructions for Use which contains Infection Control, Driveline Care
- Anticoagulation Guidelines

Equipment Requirements for Hospital Discharge

- 1 Patient Manual
- 1 Back-up controller
- 3 - 4 batteries
- 1 DC adapter
- 1 Battery charger
- 2 AC adapters
- 1 Carrying case
- 1 Night case
- 1 Shower bag
- 1 Back up equipment carrying case

A Check of all Equipment needs to be performed before discharge of the patient.

17.8.2 Sample Patient Education and Skills Checklist

Patient Education Certification	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
Received overview of MVAD System components				
Received MVAD System Patient Manual				
Reviewed life style recommendations, including travel procedures, emergency preparedness, activity limitations, etc.				
Reviewed what constitutes an emergency and emergency directions, including who and when to call.				
Review of anticoagulation medications				

PATIENT EDUCATION AND SKILLS CHECKLIST	Review and Demonstration			Successful Demon-stration
	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
POWER SOURCES				
Identify the requirement to always have one external power source connected				
Successfully identify the amount of power remaining on a battery using battery LED lights				
Successfully identify the amount of time remaining on external battery using the battery indicator on the PAL™ Controller display				
Successfully identify the amount of time remaining on internal battery using the PAL™ Controller display				
Successfully remove and connect external battery				
Successfully remove and connect adapter power				
Successfully remove and connect controller cap				

PATIENT EDUCATION AND SKILLS CHECKLIST	Review and Demonstration			Successful Demon-stration
	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
BATTERY CHARGER				
State the meaning of each status light on the battery charger				
Identify the power indicator light for the battery charger				
Successfully place and remove a battery in and out of the battery charger				
PAL™ CONTROLLER				
State the alarm situation that warrants a controller exchange				
Successfully complete a controller exchange				
Identify the indicators of a non-critical priority alarm (visual, vibratory and audible)				
Identify the indicators of a critical priority alarm (visual, vibratory and audible)				
Identify the silencing of alarms				
Successfully navigate through multiple alarms (information screens of controller and battery health)				
Successfully charge the internal battery on the backup controller				
Explain significance of flashing i on home screen				
Explain what a smiley-face (or all is well icon) under the information screen represents				
ACCESSORY PACKS				
Successfully place controller and battery in patient carry bag				
Successfully place controller and cap in patient night bag				
Successfully place controller and battery in patient shower bag				
Successfully place supplies in backup equipment carrying case				
DRIVELINE EXIT SITE CARE				
State the signs and symptoms of driveline exit site infection				

PATIENT EDUCATION AND SKILLS CHECKLIST	Review and Demonstration			Successful Demon-stration
	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
Successfully demonstrate driveline exit site care				
OTHER				

PATIENT:
My signature below indicates that I have completed the above listed requirements for hands-on training certification of the MVAD System and that all of my questions have been answered to my satisfaction.

_____ _____
(Patient signature) (Date)

CAREGIVER:
My signature below indicates that I have completed the above listed requirements for hands-on training certification of the MVAD System and that all of my questions have been answered to my satisfaction.

_____ _____
(Caregiver signature) (Date)

CERTIFIER:
My signature below indicates that the patient/caregiver has successfully completed the above listed requirements for hands-on training certification of the MVAD System.

_____ _____
(Certifier signature) (Date)

17.8.3 Blood Pressure Management Training

Purpose

The purpose of blood pressure management training is to assure that subjects and caregivers are trained on the BPC or BPC/Doppler cuffs use for measuring the subject blood pressure at home, after discharge from the hospital. Suggested recommendations of the blood pressure values associated with the MVAD System along with the site specific medical recommendations for the subject specific blood pressure care.

Indications

All of the clinical sites participating in this trial will have experience discharging patients with VADs to home. Blood Pressure Patient Education and Skills Checklist templates are included for the clinical centers. The centers are required to use these templates. The patient and caregiver/companion should be trained together in BP management. Other family members and/or close friends who live with or near the patient and are able to take an active role in the patient's new lifestyle with an VAD may also be included in training.

Training Requirements for Discharge

Training the subject and caregiver/companion is essential for a safe and successful discharge. To be eligible for discharge, both the subject and caregiver/companion must be able to demonstrate proficiency in BP management and responding to out of range values. In order to evaluate their understanding and ability, they will be tested using hands-on demonstrations with the blood pressure/ doppler devices provided to them for home monitoring for the study. Once the subject and caregiver/companion have successfully completed the Hands On training, the PI/VAD/Transplant Team will determine the appropriateness for discharge. Other family members and/or close friends who live with or near the subject and are able to take an active role in the subject's new lifestyle with an MVAD may also be included in training.

17.8.4 Sample Blood Pressure Patient Education and Skills Checklist

Patient / Caregiver Blood Pressure Education and Skills Certification	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
Overview of the Blood Pressure devices and components provided				
Patient Blood Pressure Management Instructions provided (frequency or measurements, expected patient specific values, etc)				
Review of the patient diary completion at home and patient responsibilities				
Review what is an emergency and emergency directions, including who and when to call.				

PATIENT & CAREGIVER/COMPANION BLOOD PRESSURE EDUCATION AND SKILLS CHECKLIST	Review and Demonstration			Successful Demonstration
	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
BLOOD PRESSURE CUFF/DOPPLER				
State the requirement to always place it on the same arm				
Successfully complete placement of the cuff				
Successfully identify the pulse by auscultation and Doppler				
Successfully identify the device to be used (for subjects with pulse use BP cuff, for subjects without pulse use Doppler)				
Successfully identify the procedure for BP measurement				
Successfully identify the amount of inflation required for accurate BP measurement				
Successfully complete 2 blood pressure measurements				
Successfully identify the measurements to be recorded (systolic and diastolic blood pressure or mean arterial pressure)				
State how often to measure blood				

PATIENT & CAREGIVER/COMPANION BLOOD PRESSURE EDUCATION AND SKILLS CHECKLIST	Review and Demonstration			Successful Demonstration
	Patient Initials	Caregiver Initials	Educator Initials	Certifier Initials and Date
pressure				
PATIENT DIARY				
State the importance of the BP patient diary recording				
State when are you expected to start completing the diary				
State what is required to be completed in the patient diary				
State how often is required to complete the diary				
State what is the target/range of optimal BP				
State what you have to do if BP is not optimal				
State when do you stop completing the diary				
State who makes the determination when to stop recording in the diary				
State what do you have to do with the diary at your follow-up visit with the study nurse				
Successfully complete 2 entries in the diary after taking the BP				
OTHER				

PATIENT/CAREGIVER
My signature below indicates that I have completed the above listed requirements for hands-on training certification of the blood pressure management and that all of my questions have been answered to my satisfaction.

_____ _____
(Patient/Caregiver signature) (Date)

CERTIFIER
My signature below indicates that the patient/care giver has successfully completed the above listed requirements for hands-on training certification of the blood pressure management.

_____ _____
(Certifier signature) (Date)

17.9 Adverse Event Definitions

Adverse event definitions continue to evolve. The adverse event definitions below may be revised according to the published adverse event definitions as determined by the National Institutes of Health (NIH) funded Mechanical Circulatory Support Database Registry (INTERMACS Manual of Operations Version 4.0; May 15, 2013).

HEMOLYSIS:

Minor Hemolysis: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half time (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.

Major Hemolysis: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level 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 one or more 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%, with predominately indirect component)
- Pump malfunction and/or abnormal pump parameters

RIGHT HEART FAILURE:

Definition: Symptoms or findings of persistent right ventricular failure characterized by **both** of the following:

- Documentation of elevated central venous pressure (CVP) by:
  - Direct measurement (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg.
    or
  - Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography,
    or
  - Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient.
- Manifestations of elevated central venous pressure characterized by:
  - Clinical findings of peripheral edema (≥2+ either new or unresolved),
    or
  - Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging,

or

- Laboratory evidence of worsening hepatic (total bilirubin > 2.0) or renal dysfunction (creatinine > 2.0).

IF the patient meets the definition for right heart failure, the severity of the right heart failure will be graded according to the following scale below.

(NOTE: For right heart failure to meet severe or severe acute severity, direct measurement of central venous pressure or right atrial pressure must be one of the criteria)

Right Heart Failure Severity Grade

Mild Right Heart Failure

VAD Implant Admission

Patient meets both criteria for RHF plus:

- Post-implant inotropes, inhaled nitric oxide or intravenous vasodilators not continued beyond post-op day 7 following VAD implant

AND

- No inotropes continued beyond post-op day 7 following VAD implant

Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant

Patient meets both criteria for RHF plus:

- No readmissions for RHF since last surveillance period

AND

- No inotropes since last surveillance period.

Moderate Right Heart Failure

VAD Implant Admission

Patient meets both criteria for RHF plus:

- Post-implant inotropes, inhaled nitric oxide or intravenous vasodilators continued beyond post-op day 7 and up to post-op day 14 following VAD implant

Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant

Patient meets both criteria for RHF plus:

- Limited to **one (1)** readmission for intravenous diuretics/vasodilators to treat RHF since last surveillance period

AND

- No inotropes since last surveillance period

Severe Right Heart Failure

VAD Implant Admission

Patient meets both criteria for RHF plus:

- Central venous pressure or right atrial pressure greater than 16mm Hg

  AND
- Prolonged post-implant inotropes, inhaled nitric oxide or intravenous vasodilators continued beyond post-op day 14 following VAD implant

Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant

Patient meets both criteria for RHF plus:

- Need for inotropes at any time since last surveillance period

  OR
- Two (2) or more readmissions for intravenous diuretics/vasodilators to treat RHF since last surveillance period

  OR
- Requiring RVAD support at any time after hospital discharge

  OR
- Death at any time following discharge from the VAD implant hospitalization with RHF as the primary cause.

Severe-Acute Right Heart Failure

VAD Implant Admission

Patient meets both criteria for Right Heart Failure plus:

- Central venous pressure or right atrial pressure greater than 16 mmHg

  AND
- Need for right ventricular assist device at any time following VAD implant

  OR
- Death during the VAD implants hospitalization with RHF as the primary cause.

DEVICE MALFUNCTION:

A **Device Malfunction** occurs when any component of the MCSD system ceases to operate to its designed performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Device malfunctions can be further defined as **major** or **minor**:

1. **Major device malfunction**, otherwise known as failure, occurs when of one or more of the components of the MCSD system either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. A device malfunction or failure is considered major when one of the following conditions occurs:
    a. Suspected or confirmed pump thrombus (see below)
    b. Urgent transplantation (immediate 1A listing for transplant)
    c. Pump replacement
    d. Pump explant
    e. Breach of integrity of drive line that required repair
    f. Death
2. **Minor device malfunction** includes inadequately functioning external components which require repair or replacement but do not result in 1a-f. Device malfunction does not apply to routine maintenance which includes repair/replacement of: external controller, pneumatic drive unit, electric power supplies, batteries and interconnecting cables.

Pump Thrombus represents a special case of major device malfunction and can be delineated as **suspected pump thrombus** or **confirmed pump thrombus**. Pump thrombus will be classified as SUSPECTED (see definition below) based upon clinical, biochemical, or hemodynamic findings or CONFIRMED (see definition below) based upon device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirms thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

1. **Suspected pump thrombus** is a pump-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:
    a. Presence of hemolysis
    b. Presence of heart failure not explained by structural heart disease
    c. Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

i. treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
ii. pump replacement
iii. pump explantation
iv. urgent transplantation (UNOS status 1A)
v. stroke
vi. arterial non-CNS thromboembolism
vii. death

2. **Confirmed pump thrombus** is a major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

If a Suspected Pump Thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be adjudicated by the CEC for reclassification to Confirmed Pump Thrombus.

MAJOR BLEEDING:

An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:

a. Death,
b. Re-operation,
c. Hospitalization,
d. Transfusion of red blood cells as follows:

If transfusion is selected, then apply the following rules:

During first 7 days post implant

- ≥ 50 kg: ≥ 4U packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.
- < 50 kg: ≥ 20 cc/kg packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.

After 7 days post implant

- A transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

MAJOR INFECTION:

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD).

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

NEUROLOGICAL DYSFUNCTION:

Any new, temporary or permanent, focal or global neurologic dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as a cerebrovascular event as defined below or as a non-vascular acute neurologic event. A neurologic event may be recognized by a clinically evident sign or symptom, or by clinically-silent electrographic seizure activity, or as a clinically silent lesion detected by surveillance neuroimaging. Each neurologic event should be classified by the clinical provider following complete neurologic assessment as one of the following event types:

a. Transient ischemic attack, defined as an acute transient neurologic deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI*).
b. Ischemic stroke, defined as a new acute neurologic deficit (or acute encephalopathy or seizures in children <6 months**) of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit. Ischemic stroke should be sub classified as due to arterial-distribution ischemia or due to venous thrombosis.
c. Acute symptomatic intracranial hemorrhage, defined as new acute neurologic deficit (or acute encephalopathy or seizures in children < 6 months**) attributable to Intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of the following types: subarachnoid, intraventricular, parenchymal, subdural.
d. Clinically covert ischemic stroke or ICH: infarction or ICH seen by surveillance imaging, without clinical findings of stroke or ICH at the time of event recognition.
e. Hypoxic-Ischemic Encephalopathy: Acute new encephalopathy*** due to hypoxic-ischemic injury (HIE), manifest as clinically- evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
f. Acute new encephalopathy*** due to other causes, manifest as clinically-evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable causes other than stroke, ICH or HIE, as defined above. This category of "other" acute encephalopathy includes neurologic signs or symptoms or subclinical seizures found to be attributable to other conditions such as meningitis, toxic-metabolic or drug-related processes.

*** Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

CARDIAC ARRHYTHMIAS:

Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure). Cardiac arrhythmias are classified as 1 of 2 types:

1) Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure.
2) Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure.

PERCARDIAL FLUID COLLECTION:

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

MYOCARDIAL INFARCTION:

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction

The presence at > 7 days post-implant of two of the following three criteria:

a) Chest pain which is characteristic of myocardial ischemia,

b) ECG with a pattern or changes consistent with a myocardial infarction, and

c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

PSYCHIATRIC EPISODE:

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress and requires intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

RESPIRATORY FAILURE:

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

VENOUS THROMBOEMBOLISM:

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

WOUND DEHISCENCE:

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

ARTERIAL NON-CNS THROMBOEMBOLISM:

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) standard clinical and laboratory testing
2) operative findings
3) autopsy findings

This definition excludes neurological events.

OTHER SAE:

An event that causes clinically relevant changes in the patient s health (e.g. cancer).

HEPATIC DYSFUNCTION:

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/**AST and** alanine aminotranferease/**ALT**) to a level greater

than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

HYPERTENSION:

New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg mean pressure (rotary pump).

PediMACS: **Hypertension is defined as systolic, diastolic, or mean blood pressure greater than the 95th percentile for age which requires the addition of a new IV or oral therapy for management. The event shall be considered resolved upon the discontinuation of the treatment.**

RENAL DYSFUNCTION:

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL **(in children,** creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

17.10 Infection Control Guidelines

Please note that these guidelines will be reviewed throughout the study by the HeartWare Investigators and possibly revised according to patient experience.

The infection control guidelines for the prevention of infection was developed by James Long, MD (LDS Hospital, Salt Lake City, UT), Walter Dembitsky, MD (Sharp Memorial Hospital, San Diego, CA), and Soon Park, MD (Pacific California Medical Center, San Francisco, CA), on behalf of the REMATCH Trial Surgical Working Group. The guidelines (used with permission) will identify the infection control measure to be used for the HeartWare MVAD clinical trial.

Pre-Operative

1) Consider risk factors for developing device infections, such as:
   - Established or suspected infections
   - Co-morbidity such as multi-organ dysfunction or immunosuppression
   - Poorly controlled diabetes
   - Prolonged intubation
2) Remove unnecessary IV lines and replace old IV lines 12-24 hours pre-op.
3) Administer antimicrobial prophylaxis based on the hospital s nosocomial and microbial sensitivity profile with sufficient coverage for staphylococcus aureus, staphylococcus epidermidis and enterococcus.
4) Use pre-operative scrub with antiseptic the night before and again the morning of the operation.

Intra-Operative

1) Operating Room (OR) Precautions:
   - All OR staff must wash hands and arms with antimicrobial soap and wear fresh scrubs, shoe covers and headgear that covers all hair.
   - Restrict traffic through OR and restrict opening of the door.
   - Consider using OR air ultra-filtering system at air inlet or portable HEPA filtration unit to recycle ambient air.
2) Plan for device and percutaneous tube position to minimize trauma to exit site.
3) Prepare skin with antiseptic scrub, alcohol (allow to dry), then betadine gel or equivalent, which is allowed to dry, and drape patient.
4) Avoid opening sterile LVAD components prematurely.
5) Cover LVAD after it has been tested prior to implant.
6) Massage antibiotic solution into the external surface of the percutaneous tube s woven polyester velour.
7) Percutaneous lead management
   - Using the tunneler, tunnel the driveline lead to the point of exit. Adjust distance of exit site from costal margin to fit body habitus and prevent rubbing against the costal margin.
8) Prior to close, irrigate all surfaces with antibiotic solution prior to closing (e.g. Vancomycin 2 g/L NS and Gentamicin 160 mg/L NS).

9) Consider immobilizing percutaneous lead with retaining sutures.

Postoperative

1) Continue systemic antimicrobials prophylaxis for 48 to 72 hours.
2) After discontinuation of prophylactic antibiotics, start broad spectrum antibiotic coverage (e.g. Zinacef 1.5 g IV every 15 hours) until chest tubes are removed or until drainage from stab wound incisions (from drains and chest tube) has stopped.
3) Remove mediastinal and pleural drains as soon as appropriate (e.g., < 150 cc/12 hours).

Driveline Care

For consistency and simplicity and to minimize infection, routine daily exit site/driveline care should be the responsibility of the patient and/or primary caregiver. Routine driveline dressings should be changed once per day. The MVAD Pump driveline exit site dressing change includes:

1) Use good hand-washing technique before and after dressing change
2) Always use aseptic technique
3) Dressing change protocol as per institutional guidelines:
   - Change once daily 24-48 hours after implant (or if saturated)
   - Change twice daily for drainage, trauma or infection
   - Change daily when all drainage has stopped, the site has good tissue ingrowth and there is no evidence of infection or trauma
   - If present, remove sutures used to retain driveline 2-3 weeks post-op, when driveline has good circumvental tissue ingrowth
4) Once the exit site dressing is removed, the driveline should be visually inspected for kinks, tears or any traumatic damage. If blood is seen within the lumen of the driveline the implanting center should be notified immediately.
5) Daily exit site care is performed using an antiseptic cleansing agent such as a diluted chlorhexidine scrub solution. Following aseptic cleansing, the site should be rinsed and dried to avoid tissue injury. Aseptic technique should be followed anytime the dressing is removed and the exit site is exposed, inspected, dressed or handled. Exit site cleaning and dressing changes should be performed as per hospital policy. Prophylactic topical antibiotic ointments such as silver sulfadiazine, betadine or polymixin-neomycin-bacitracin should not be used. These ointments can injure the tissue adjacent to the exit site.
6) Immobilize the percutaneous lead with a commercially available immobilization binder, belt or tube/catheter stabilization device. Keep the extra external length of the driveline under a binder or clothing such as a shirt. Do not kink or twist the driveline when it s being secured.
7) Complicated, non-routine driveline dressing changes that involve exit site infections may require assistance/supervision from a health care professional such as a visiting nurse.
8) For wounds/incisions other than the driveline exit site requiring dressing changes and/or other care, the ability of the patient and caregiver to provide that care will

be evaluated by the implanting center. Treatment plans will be dependent on this evaluation.

17.11 Anticoagulation Guidelines

Anticoagulation Guidelines
Please note that these guidelines will be reviewed throughout the study by the HeartWare Investigators and possibly revised according to patient experience.

Anticoagulation should be individualized for each patient. If heparin is used in the post-operative period, begin **low dose heparin** at 10 units/kg/hr on postoperative day one to a target PTT of 40-50 seconds. Prior to initiation of anticoagulation, chest tube drainage should be less than 40 ml/hr for approximately three hours, the hematocrit should be stable without the need for transfusion of blood products and coagulation factors should be approaching normal. Gradually increase the heparin dosage to maintain the aPTT in a range of 50-60 seconds.

The recommended long term oral anticoagulation regimen for the MVAD Pump is a combination of **warfarin** and **acetylsalicylic acid (ASA)**. In general, ASA should be started at a dose between 75 and 150mg/day within 24 hours after implant if there are no postoperative bleeding complications. Check for ASA resistance with a reliable test (e.g. VerifyNow) and adjust ASA mono-therapy accordingly. Other multi drug options include;

- Aggrenox (25 mg ASA plus 200 mg extended release dipyridamole)
- ASA 81 mg plus clopidogrel 75 mg daily

For patients who are aspirin sensitive or otherwise intolerant, clopidogrel at doses of 75-150 mg/day is a viable alternative. A clopidogrel loading dose of 300 mg followed by 75 mg/day is recommended to reduce the lag time in reaching full therapeutic benefit (typically a 3-4 day lag). Warfarin should be started within 4 days post-op and titrated to maintain an INR of 2.0 to 2.5.

17.12 Download of MVAD® Pump Controller Log Files

The download function allows the clinician to:

- Transfer alarm, trend, and event data from the controller to the monitor.
- Transfer the data from the monitor to a USB flash drive.

To download log files from the controller to the monitor:

1. Use the monitor data cable to connect the data port (blue) on the controller to the monitor. As soon as the cable is connected, the Data Download icon in the lower left hand corner of the monitor screen flashes grey to indicate that the download has begun.
2. Wait until the Data Download icon stops flashing and turns black, and then disconnect the monitor data cable from the controller.

NOTE: DO NOT disconnect the controller from the monitor when the Data Download icon is flashing, as data is being transferred. If the message, [**Log Transfer Not Complete!**] appears, re-connect the controller to the monitor to complete the transfer of data.

To download log files from the monitor to a USB flash drive:

1. Press the Pump  icon to access the System screen and enter the password.
2. Press [**Setup**] tab.
3. Press [**Patient**] tab.
4. Shortly after disconnecting the data cable, the [**Log Files**] button will appear. Press this button and a list of the patient logs will be displayed.
5. Place a HeartWare Monitor compatible USB memory stick into the USB port on the right side of the monitor.
6. Select the logs to be saved. Press the [**Save to USB**] button.
7. A confirmation screen will appear to affirm selection. If correct, press [**Yes**] button.
8. A [**Download complete**] message will appear when data download is complete. Press [**OK**].
9. Remove the USB flash drive and email the three files: data, alarm, and events (three separate files) to mvadlogsintl@heartware.com.

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19.0 SUB- STUDY FLOW ESTIMATION ALGORITM (SELECTED SITES ONLY)

SUB-STUDY

Clinical Assessment of the Flow Estimation Algorithm with the MVAD® System at selected sites

to Clinical Investigational Plan

Multi Center, Prospective, Non-Randomized, Single-Arm Trial Evaluating the Clinical Safety and Performance

Of the HeartWare MVAD® System

For the Treatment of Advanced Heart Failure

Investigational Product:	**MVAD® System**
CIP Number/ Version:	**HW-MVAD-01/ 7.0**
Sub – Study Version:	**1.0**
IDE Number:	**N/A**
Date:	**11 Nov 2014**

1.0 PURPOSE

This testing will be conducted at Austrian and Australian sites to assess the flow estimation algorithm of the MVAD pump blood in the clinical setting.

2.0 INTRODUCTION

Estimated MVAD Pump blood flow is calculated using motor parameters and the patient s hematocrit. Flow estimation operates at speeds of ≥11000 RPM. At set speeds of <11000 RPMs the flow estimation will display as --- .

The valid range of estimated MVAD Pump average blood flow is 0 to 7 L/min. The maximum error is – 2.5 L/min. For the most accurate flow estimation, ensure current hematocrit values are entered for this protocol.

3.0 MEASUREMENTS

The table below shows the parameters of interest:

Parameters
Hematocrit (%)
Pump Speed (RPM)
Pump Power (W)
Pump Estimated Flow (LPM)
Pump Measured Flow (LPM)
Pulsatility of Pump Measured Flow
Mean Arterial Pressure (mmHg)
Mean Arterial Pulse Pressure (mmHg)

4.0 PROTOCOL

4.1 Methodology

1. Implant patient with MVAD Pump per MVAD System IFU.
2. Instrument the patient with following two sensors
    a. 12 mm Transonic Flow Probe is placed on the outflow graft
    b. Pressure transducer is inserted into arterial vasculature for measurement of mean arterial pressure. Choice of pressure sensor is based on site preference.
3. Using the MVAD system monitor, ensure the following settings are in place prior to initiating the speed ramp:
    a. qPulse = OFF
    b. Suction = ALARM ONLY
    c. Pump Pressure Algorithm = ENABLED
4. Start/set MVAD pump speed to 8 kRPM. Wait at least 1 minute to achieve hemodynamic stability and then record parameters as indicated in Table 1 of the Appendix.
5. Increase MVAD pump speed by increments of 1 kRPM to 18 kRPM (or the speed that will remain the patient s normal set speed). Wait a period of at least 1 minute in between each speed increase and record parameters as indicated in Table 1 of the Appendix.
6. Once speed ramp is complete, remove all unnecessary

5.0 SAMPLING PLAN AND JUSTIFICATIONS

This protocol covers the normal patient operating range. Mean arterial pressure as well as other hemodynamic and echocardiographic parameters may be used to monitor the patient state and ensure appropriate setting of pump speed.

6.0 DATA ANALYSIS/ ACCEPTANCE CRITERIA

Pump flow estimation data will be analyzed for accuracy by comparing values to measured pump flow values. Acceptance criteria for this protocol will be if the difference between estimated pump flow and measured pump flow is within the specified tolerance (– 2.5 L/min).

7.0 APPENDIX: DATA COLLECTION TABLE

In addition to noting the patient s hematocrit, the below table will be used for data collection of parameters of interest.

Patient Hematocrit: _____

Table 1. Parameters of Interest

Set Speed (kRPM)	Power (W)	Est. Flow (L/min)	Meas. Flow (L/min)	Meas. Flow Pulsatility (L/min)	MAP (mmHg)	Mean Arterial Pulse Pressure (mmHg)
8		X				
9		X				
10		X				
11						
12						
13						
14						
15						
16						
17						
18						