A Prospective, Single Arm, Multi-Center Clinical Study in Collaboration with the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) to Evaluate the Thoracotomy Implant Technique of the HeartWare HVAD® System in Patients with Advanced Heart Failure

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NCT Number: NCT02268942

Document Name and Date: Clinical Study Protocol, 24 October 2018

CLINICAL STUDY PROTOCOL

A Prospective, Single Arm, Multi-Center Clinical Study in Collaboration with the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) to Evaluate the Thoracotomy Implant Technique of the HeartWare HVAD® System in Patients with Advanced Heart Failure

Investigational Product:	**HeartWare® Ventricular Assist Device System (HVAD®)**
Protocol Number:	**HW006**
Version Number:	**7.3**
IDE Number:	**G130279 (through PMA approval; 10 Jul 2018)**
PMA Number:	**100047**
Date:	**24 October 2018**

1. ADMINISTRATIVE INFORMATION

1.1 Contacts

Medical, Clinical and Operational Support

Sponsor Name:	Medtronic / HeartWare Cardiac Rhythm and Heart Failure Mechanical Circulatory Support
Sponsor Contact:	Sonali Dewan, Sr Prin Regulatory Affairs Specialist
Sponsor Telephone Number:	1 305 364 1579
Manufacturer and Sponsor Address:	14400 NW 60th Avenue Miami Lakes, FL 33014 USA

1.2 Administrative Information

Protocol Number:	HW006
Revision Number:	7.3
Protocol Date:	24 Oct 2018
Investigational Product:	HeartWare® Ventricular Assist Device System (HVAD)

1.3 Amendment History

Date	Amendment Number	Amendment Type
18 November 2013	1.0	Original Protocol
04 February 2014	2.0	Revised Submission
07 April 2014	3.0	Revised Submission
07 May 2014	4.0	Revised Submission
11 Aug 2014	5.0	Revised Submission
15 Sep 2014	6.0	Revised Submission
3 Feb 2015	7.0	Revised Submission
06 July 2015	7.1	Revised Submission
10 Feb 2016	7.2	Revised Submission
24 Oct 2018	7.3	Revised Submission

1.4 Sponsor Approval

Representatives of Medtronic HeartWare

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this Protocol and all applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

Sponsor Signatory:	**Signature:**	**Date:**
Name & Title	e-signature	e-signature
	Thomas Vassiliades Jr., M.D., Chief Medical Officer, Mechanical Circulatory Support	
Name & Title	e-signature	e-signature
	Jeff Cerkvenik, Distinguished Statistician	
Name & Title	e-signature	e-signature
	Theresa McGovern, Senior Regulatory Affairs Director	
Name & Title	e-signature	e-signature
	Alejandra Ochoa, Clinical Research Specialist	
Name & Title	e-signature	e-signature
	Arundhati Datye, M.D., Medical Safety Advisor/Strategist	
Name & Title	e-signature	e-signature
	Dana Chesness, Principal Clinical Quality Specialist Compliance	
Name & Title	e-signature	e-signature
	Taryn Randall, Senior Clinical Monitoring Manager	

1.5 Investigator Agreement

I will provide copies of the clinical study protocol 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 products and the conduct of the study.

I also understand that this study will not be initiated without approval of the appropriate IRB/CREB and that all administrative requirements of the governing body of the institution will be complied with fully.

I will use only the informed consent forms approved by the Sponsor, INTERMACS® and the Institutional Review Board (IRB)/Clinical Research Ethics Board (CREB), or its representative.

I will obtain written informed consent from all participating subjects according to the INTERMACS® protocol defined process using the approved INTERMACS® protocol, informed consent and health privacy documents, and will fulfill all responsibilities for submitting pertinent information to the IRB/CREB. In addition, I will obtain a HeartWare specific written informed consent from subjects who will receive a HeartWare® HVAD via a thoracotomy procedure.

I also agree to record all information or data in the INTERMACS® registry in accordance with the INTERMACS® protocol and procedures, in particular, I agree to report without unjustified delay, all Adverse Events (AEs) and Serious Adverse Events (SAEs).

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

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

I further agree not to originate or use the name of HeartWare Inc. and/or HVAD, 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 protocol, 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 protocol described in detail in this document and agree to conduct the study in accordance with the protocol 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. STUDY SUMMARY

Name of Sponsor(s): Medtronic / HeartWare (hereafter referred to as HeartWare)	
Title of protocol: **A Prospective, Single Arm, Multi-Center Clinical Study in Collaboration with the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) to Evaluate the Thoracotomy Implant Technique of the HeartWare HVAD® System in Patients with Advanced Heart Failure**	
Study Number: HW006	
Number of Subjects: 145 subjects implanted via thoracotomy with the HeartWare HVAD® System. It is anticipated that each site will enroll at least 1 subject. No site will implant more than 20 patients into the study without prior written approval from HeartWare.	**Number of Sites:** Up to 30 Sites in the US and 1 site in Canada

Study Design:

This is a multi-center, prospective, single arm study that will evaluate the thoracotomy implant technique in up to 145 subjects implanted via thoracotomy with the HeartWare HVAD® System and enrolled in the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) protocol and database.

All participating centers will be current enrolled INTERMACS® sites in good standing and will follow the INTERMACS® protocol and procedures.

Primary Endpoint:

The primary endpoint is success at 6 months defined as all enrolled and implanted subjects:

- Alive on the originally implanted device at 6 months, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Transplanted by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Explanted for recovery by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event).

All subjects with stroke events from implant to Month 6 will be required to remain in follow-up until the post-stroke mRS measure (≥3 months post stroke event) is obtained, even if this occurs after the 6-month visit. If a stroke subject is alive at 6 months, but dies before the post-stroke mRS is obtained, the subject will be considered a failure with regard to the primary endpoint.

Secondary Endpoint:

The secondary endpoint is an improvement in the mean length of initial hospital stay (initial recovery and step down unit) for all enrolled and implanted subjects. The mean length of initial hospital stay is estimated to be 26.1 days for median sternotomy subjects.

[redacted]

Safety Assessments:

Safety assessments will be collected according to the INTERMACS® protocol and procedure, as summarized in Section 9.

Device: HeartWare® System

The HeartWare® System is an implantable ventricular assist device, with the following major components: Implantable Centrifugal Rotary Blood Pump (HVAD® Pump) with Inflow and Outflow Conduits, Controller and Power Sources, Monitor, Power Sources, Battery Charger, Surgical Tools and Carrying Case.

Intended Use:

The HeartWare® HVAD is intended for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure.

The HeartWare® HVAD is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.

The HeartWare® HVAD is contraindicated in patients who cannot tolerate anticoagulation therapy.

Period of Evaluation:

Subjects will be followed according to the INTERMACS® protocol and standard of care at the enrolling institution. Data recorded in the INTERMACS® database to the primary endpoint at 6 months post implant of the HeartWare® HVAD will be evaluated.

- Subjects who have been transplanted prior to month 6 will be considered complete at the primary endpoint time-point.
- Subjects, who have a device exchange prior to month 6, will be evaluated according to the original implant date.
- Subjects who remain on device support after the primary endpoint time-point, either the original device or exchange device, will be followed according to the INTERMACS® protocol until transplant, or until 2.5 years post implant of the original device. A subject's study participation is considered complete at either the time of induction of anesthesia for transplant, or at the 2.5 year post implant visit.
- Subjects who have been explanted for recovery prior to month 6 will be followed until their next scheduled follow-up visit according to the INTERMACS® protocol, at which time their participation in the study is considered complete.
- The per-protocol analysis population will include those thoracotomy subjects with the outflow in the ascending aorta only. As a result, enrollment may exceed sample size requirements.
- The per-protocol analysis population will include those thoracotomy subjects with the procedure performed on-pump only. As a result, enrollment may exceed sample size requirements.

Subject data will be evaluated for a maximum of 2.5 years.

Estimated start date: October 2014	**Estimated end date:** October 2018

Background:

Heart failure is a progressive disease for which there are numerous therapies to reduce symptoms; however, presently there is no cure and a more definitive therapy is not on the horizon. Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts the use of heart transplantation to fewer than 2,500 patients per year in the United States[1]. In 2012, 2169 heart transplants were performed at approximately 125 heart transplant centers in the United States (United Network for Organ Sharing website accessed February 23, 2013)[1]. Currently there are more than 3400 patients on the UNOS heart transplant list, with 68% of those having a waiting time to transplant of longer than six months[1].

Clinical studies have shown a survival and quality of life benefit for patients supported by a left ventricular assist device (LVAD) when compared to those receiving medical therapy [2, 3]. Approximately 35% of the patients who receive heart transplants are bridged with ventricular assist devices[4].

The US bridge-to-transplant trial (i.e. ADVANCE) was a multi-center, prospective, clinical trial designed to evaluate the safety and efficacy of the HeartWare® System in heart failure patients listed for cardiac transplantation [5]. The trial was conducted between 18 August 2008 and 25 February 2010 with a total enrollment of 160, including 140 implants at 30 sites. The implant procedure chosen for placement of the HVAD® Pump in this trial was via a median sternotomy[5], and the current Instructions for Use (IFU) and patient materials reference this implant method and describe the associated risks.

Since the HVAD® Pump is small and designed to be placed within the pericardial space alternative implant procedures have been developed. Surgeons in Europe, Canada, and the United States and throughout the world have successfully implanted the HVAD® Pump using both thoracotomy and sternotomy approaches [6-8]. It is believed that the addition of the thoracotomy implant procedure will provide clinicians an additional option to optimize results and expand the potential patient population. There is a growing trend toward the use of less invasive non-sternotomy incisions in all fields of cardiac surgery. While a median sternotomy provides the best access to the heart and great vessels, the same exposure could be accomplished with several smaller thoracotomy incisions. The potential benefit to the subject participating in this study is the implantation of a blood pump using a technique that is less obtrusive and that may be more comfortable. Morbidity rates and time of recovery may also be positively affected. The thoracotomy technique for implant may provide benefits not currently available with existing technology such as less tissue trauma and shorter hospital stays.

Main Criteria for Inclusion:

1. Must be ≥19 years of age at time of informed consent to participate in the INTERMACS® registry.
2. Subject receives a HeartWare® HVAD (The device should be the subject's first VAD implant).
3. Subject signed an INTERMACS® informed consent if required by local IRB/CREB policy.
4. Subject signed a HeartWare® informed consent

Main Criteria for Exclusion:

The INTERMACS® protocol has no exclusion for age, gender, race, ethnicity, or any other demographic limit. The following are exclusions currently described by the INTERMACS® protocol:

1. Subject is incarcerated (prisoner).
2. Subject did not sign the informed consent at sites where waiver of consent was not granted.

In addition, for this study, the following exclusion criteria will be applied after enrollment into the INTERMACS® protocol:

3. Body Surface Area (BSA) < 1.2 m^2.
4. Prior cardiac transplant or cardiomyoplasty.
5. Subject is receiving a BiVAD.
6. Subject is receiving the device as an RVAD.
7. Subject data is generated from non- INTERMACS® centers.
8. Pediatric subjects (< 19 years of age).
9. Subjects who receive a temporary LVAD (e.g., ECMO, TandemHeart, Impella, etc.)
10. Subjects whose device strategy is listed as "Destination Therapy" at the time of implant.
11. Severe Right Heart failure, defined as mean central venous or right arterial pressure > 20 mmHg on multiple inotropes, or right ventricular ejection fraction (RVEF) <15% with clinical signs of severe right heart failure

(e.g. ascites, treatment with diuretics and two inotropic drugs).
12. ≥ 2+ Aortic insufficiency or mechanical aortic valve
13. Planned concomitant procedure (e.g. valve repair or replacement, CABG, septal defect repair).
14. Known LV thrombus

Study Procedures:

All participating centers will follow the INTERMACS® protocol and procedures. A summary of the INTERMACS® protocol and procedures can be found in Section 9.

Main Criteria for Evaluation and Analyses:

The primary endpoint is success at 6 months compared to a pre-specified performance goal.

The secondary endpoint is an improvement in the mean length of initial hospital stay.

Additional observational endpoints will also be assessed at 6 months. Statistical tests will not be conducted.

Sample Size Justification and Statistical Considerations:

Primary Endpoint:

Success at 6 months for thoracotomy is estimated to be 86% compared to a performance goal of 77.5%. Using an exact binomial test, with a one-sided alpha of 0.05, and 80% Power, a sample size of 145 implanted subjects is required.

Secondary Endpoint:

The mean length of initial hospital stay is estimated to be 26.1 days with a standard deviation of 22.8 days and a median of 20 days based on data from the BTT CAP population (N=242). Using a one sample t-test, with a one-sided alpha of 0.05, a sample of 145 implanted subjects with an average value of 21.3 days or less will result in Power greater than 80%.

Due to the skewed nature of this data, a non-parametric test (one-sample Sign test with a one-sided alpha of 0.05) to assess a reduction in median days (from the estimated 20 days) will also be conducted for support.

3. 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
AE	Adverse Event
AHA	American Heart Association
AI	Aortic insufficiency
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AR	Aortic regurgitation
ASD	Atrial septal defect
AST	Aspartate Aminotransferase
ASA	Acetylsalicylic Acid
BiVAD	Biventricular Assist Device
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
BSA	Body Surface Area (m2)
BTT	Bridge to Transplantation
BUN	Blood Urea Nitrogen
cc	Cubic Centimeter (equal to a milliliter)
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
CHF	Chronic Heart Failure
CK	Creatine Kinase
CK- MB	Creatine Kinase MB Isoenzyme
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CREB	Clinical Research Ethics Board
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C- Reactive Protein
CRT	Cardiac Resynchronization Therapy
CSS	Clinical Summary Score of KCCQ

Abbreviation	Definition
CT	Computed Tomography
CVA	Cerebral Vascular Accident (stroke)
CVP	Central Venous Pressure
dL	Deciliter
Dy	Day / Days
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EEG	Electro Encephalogram
EuroQol	European Quality of Life (EQ-5D)
EU	European Union
FDA	United States Food and Drug Administration
FEV_1	Forced expiratory volume in one second
GCP	Good Clinical Practice
g	Gram
HCT	Hematocrit
HEPA	High-Efficiency Particulate Arresting
HF	Heart Failure
Hgb	Hemoglobin
hr	Hour
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
INR	International Normalized Ratio
INTERMACS	InterAgency Registry for Mechanical Assisted Circulatory Support
IRB	Institutional Review Board
ISHLT	International Society for Heart and Lung Transplantation
ITT	Intent to Treat
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
KCCQ	Kansas City Cardiomyopathy Questionnaire (tool)
Kg	Kilogram
LCD	Liquid Crystal Display
LDH	Lactate Dehydrogenase
LED	Light Emitting Diode
Li-Ion	Lithium ion

Abbreviation	Definition
L/min	Liters per minute
LLT	Left lateral thoracotomy
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
M	Meter
Mg	Milligram
MI	Myocardial Infarction
mL	Milliliter
Mm	Millimeter
MR	Mitral regurgitation
N or n	Number of Patients
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
OPC	Objective Performance Criteria
OSS	Overall Clinical Summary Score of KCCQ
PA	Physician Assistant
PCWP	Pulmonary Capillary Wedge Pressure
PFO	Patent Foramen Ovale
PI	Principal Investigator
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
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SVO_2	Mixed Venous Oxygen Saturation
TE	Thromboembolic Event
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
TVR	Tricuspid Valve Replace/Repair
TX	Transplant
UADE	Unanticipated Adverse Device Event
USB	Universal Serial Bus
VAD	Ventricular Assist Device
VO2 max	Maximal Rate of Oxygen Consumption
VSD	Ventricular septal defect
WBC	White Blood Cell
Wk	Week
Yr	Year

4. INTRODUCTION

4.1 Background and Rationale

Heart failure is a progressive disease for which there are numerous therapies to reduce symptoms; however, presently there is no cure and a more definitive therapy is not on the horizon. Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts the use of heart transplantation to fewer than 2,500 patients per year in the United States[1]. In 2012, 2169 heart transplants were performed at approximately 125 heart transplant centers in the United States (United Network for Organ Sharing website accessed February 23, 2013)[1]. Currently there are more than 3400 patients on the UNOS heart transplant list, with 68% of those having a waiting time to transplant of longer than six months[1].

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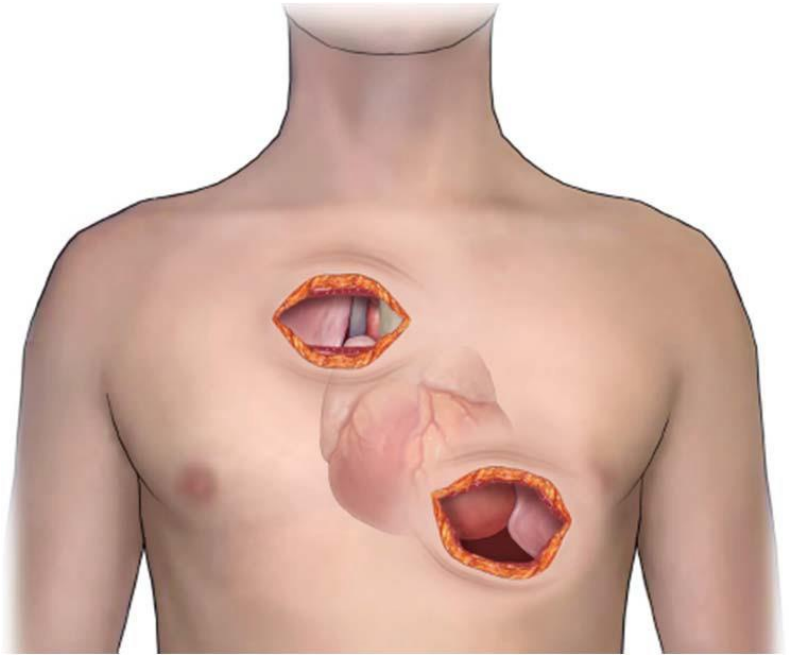
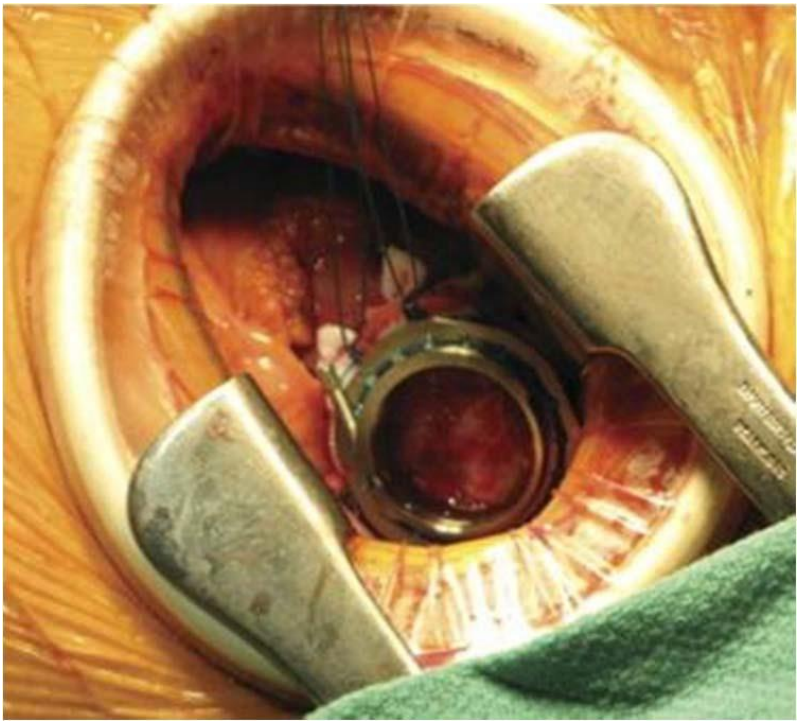
The thoracotomy procedure most often includes a small hemi-sternotomy for placement of the outflow graft in the ascending aorta, although the descending aorta may be selected in some cases. While most cases have been done on CPB, many cases in Europe no longer use CPB. For this study it is recommended that cases be done on cardiopulmonary bypass and that the outflow be

attached to the ascending aorta. An artist's depiction of the thoracotomy procedure is shown in the figure below:



And an actual photograph of the thoracotomy opening is shown in the second figure: The sewing ring can be seen through the surgical opening.



4.2 Previous Patient Experience

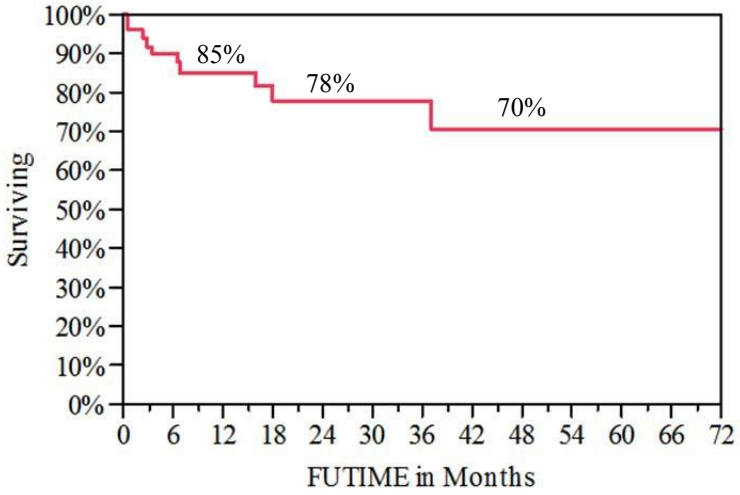
4.2.1 International Bridge to Transplant Study

Between March 2006 and June 2009 the HeartWare® HVAD was evaluated as a bridge to cardiac transplantation at five centers in Europe and Australia. Fifty patients were enrolled in the trial with the last patient reaching the 180 day endpoint on June 2, 2009. This summary covers the period from March 3, 2006 through June 2, 2009. The pump was implanted in the pericardial space in all patients using a midline sternotomy and cardiopulmonary bypass. There were 43 males and 7 females ranging in age from 20 to 75 years (mean 48.6 ± 13.6) of which 40% had ischemic disease. BSA ranged from 1.40 to 2.56 m2 (mean 1.9 ± 0.23). The total duration of support was 47.8 patient years. The mean duration of support was 349 ± 223 days with 20 patients supported > 1 year and 3 patients supported > 2 years. The most common significant adverse events were:

	0-180 days		180-365 days		> 365 days	
	# of Events	Event Rate*	# of Events	Event Rate*	# of Events	Event Rate*
Infection	9 (9pts)	0.4	7 (6pts)	0.5	4 (2pts)	0.34
Bleeding	14 (12pts)	0.63	3 (2pts)	0.22	1 (1pt)	0.08
Ischemic Stroke	2 (2pts)	0.09	0	0	0	0
Hemorrhagic Stroke	0	0	1 (1pt)	0.07	3 (3pts)	0.26
Pump Replacement	6 (6pts)	0.27	0	0	1 (1pt)	0.08
	22.3 pt years (n=50)		**13.8 pt years (n=38)**		**11.7 pt years (n=20)**	

*Events per patient year

Update as of October 25, 2013, 45 patients reached endpoint, 29 patients were transplanted, four were weaned from support after recovery, 11 died on support and 6 remain supported. Twenty eight patients were supported longer than one year and 13 greater than two years. Six patients remain well on support with five patients on support greater than five years. Kaplan Meier actuarial survival for the 50 patients in the trial is shown below.



4.2.2 ReVOLVE

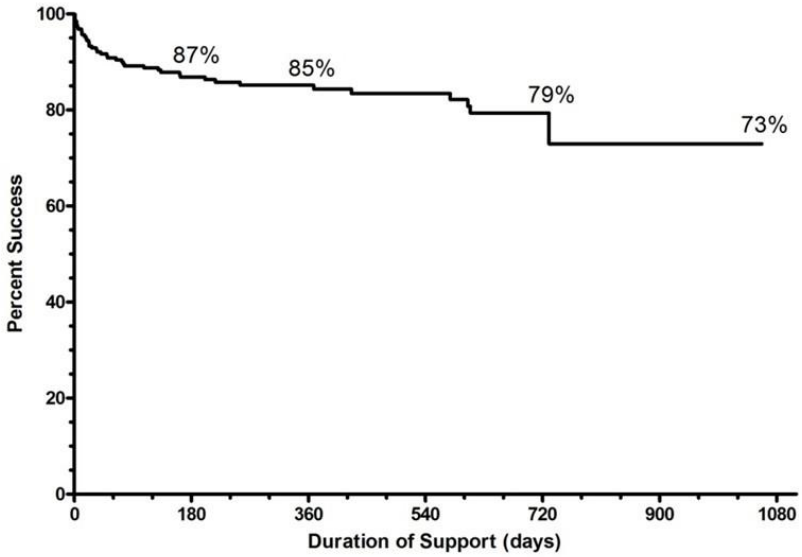
The ReVOLVE registry was an investigator-initiated registry of commercial implants performed between February of 2009 and November 2012. Patients receiving the HeartWare® HVAD System for labeled indications only are included in this report. Data was collected at nine centers in Europe (7) and Australia (2). The ReVOLVE registry was not sponsored by HeartWare, although HeartWare provided support and assisted in the analysis of the data. While the data was not monitored on-site, steps were taken to verify the accuracy through telephone and email communications with the users at each participating center. The total number of on-label subjects

enrolled for which adverse event data was collected was 254. Mean age of patients was 52.5 ± 12.0 years, and females accounted for 23% of the total patient population. Mean BSA was 1.93 ± 0.23 m^2. The diagnosis or type of cardiomyopathy at baseline includes idiopathic cardiomyopathies in 65% of patients, while ischemic cardiomyopathies accounted for only 27%. The mean duration of support was of 363 ± 280 days (median 299.5 days). Fifty-six of the 254 patients were transplanted, three recovered myocardial function and had the device removed, 43 died on support and 152 patients remained on the device. Patients were transplanted after 19-958 (mean 363 ± 250) days of support. For the patients who died over the observation period, death occurred after a mean of 159 ± 228 days on support. The most common adverse events were:

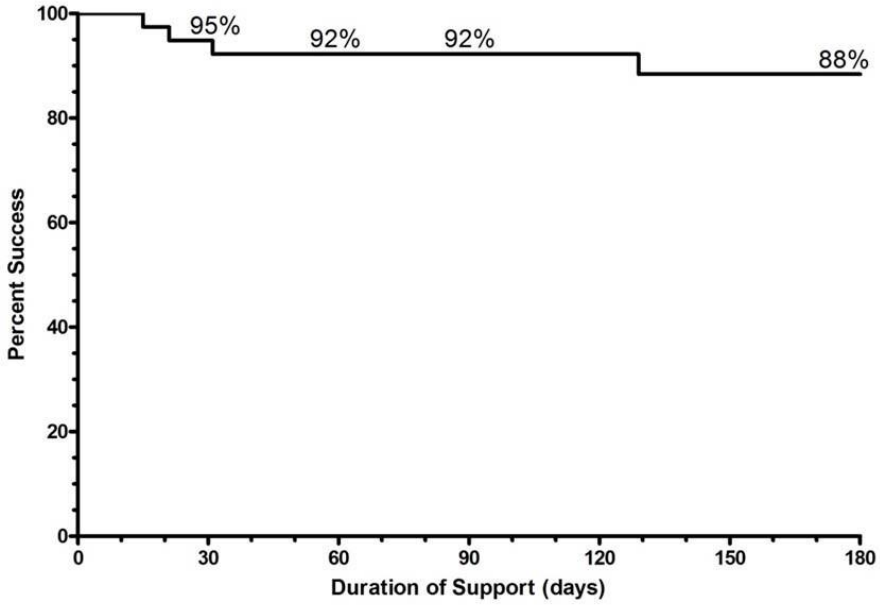
N=254 with 252.6 Patient-Years of Support			
Complication	**Patients with event, n (%)**	**Number of Events**	**Event Rate**
Bleeding	71 (28)	101	0.40
Gastrointestinal Bleeding	12 (5)	16	0.06
Right Heart Failure	24 (9)	24	0.10
Stroke	20 (8)	20	0.08
Driveline Infection	14 (6)	18	0.07
Sepsis	12 (5)	12	0.05
Renal Failure	10 (4)	10	0.04

Note: Bleeding events include all post-op bleeding, tamponade, and those requiring transfusions and reoperation.

One hundred and forty-five (145) patients were supported less than one year, 85 patients between one and two years and 24 patients were supported between two and three years. Survival post-transplant was excellent: of 56 patients transplanted, 2 died post-transplant, one of multiple organ failure and one of intracranial hemorrhage. Post-transplant survival at one month was 96% (54/56). The Kaplan Meier actuarial success estimate is shown. Success was defined as survival to transplant, recovery after explant or on continued HVAD support. The 6, 12, 24 and 36 month success rates were 87%, 85%, 79% and 73% respectively.



In addition, data collected for 40 thoracotomy patients, which is considered 'off-label' was not included in the afore-mentioned report. For the thoracotomy patients, the 6-month success rate was 88%.



4.2.3 US Bridge to Transplant Trial

A bridge-to-transplant trial (i.e. ADVANCE) was conducted in the US. ADVANCE was a multi-center, prospective, clinical trial designed to evaluate the safety and efficacy of the HeartWare® HVAD in heart failure patients listed for cardiac transplantation. Enrollment into the study began on 18 August 2008. The trial ended on 25 February 2010 with a total enrollment of 160, including 140 implants at 30 sites. Subjects were predominately male (72.1%), were 53.3 (± 10.3) years of age and 23% were Black/African American. BMI and BSA were 28.6 (± 6.1) kg/m^2 and 2.1 (± 0.3) m^2, respectively and the average LVEF was 17.8% (± 7.1%). PCWP was elevated at 23 (± 9) mmHg and pulmonary artery pressures were also high: 49 (±15) / 25 (± 9) mmHg. The cardiac index was significantly reduced at 2.0 ± 0.5. The majority of subjects were classified as NYHA class IV (95%). The most common etiologies were ischemic disease in (40.7%) and idiopathic etiology (45.7%). Duration of heart failure was greater than 5 years in 48.6% (68/140) of subjects. It was also observed that 17.9% and 13.6% of subjects had heart failures from 1-3 and 4-5 years, respectively. The most common underlying risk factors for cardiovascular disease were smoking (64.3%) hypertension (62.9%) and hyperlipidemia (54.3%). For prior cardiac surgery, 6.4% (9/140) of subjects reported a prior history of coronary artery bypass grafting (CABG). No subject reported valve replacement, but valve repair was reported in 2.1% (3/140). LV reduction was reported in 7.1% (10/140) and prior sternotomy and prior thoracotomy in 15.7% (22/140) and 3.6% (5/140) of subjects, respectively. Intra-aortic balloon pump therapy at baseline was reported for 25% of subjects and 85% presented with an implantable cardioverter-defibrillator (AICD). At Baseline 80% of subjects in the HVAD treatment group were on intravenous inotropic therapy and 23% were on more than one inotrope, while 82% of subjects received diuretics. Mean hematological and laboratory values at baseline showed an elevated BUN at 26 (+14) mg/dL and a depressed hematocrit of 34.0% (+ 5.8%).

The median time from incision to wire closure of the sternum was 3 hours and 23 minutes and median time on bypass was 70 minutes. Subjects received (median) 1.5 units of packed red blood cells (PRBC). The median parameters for HVAD settings were: 2700 rpm at 3.8 watts, yielding 4.6 L/min of flow. In addition to implant, a number of additional surgical procedures were performed. The most common were patent foramen ovale (PFO)/atrial septal defect (ASD) closures (11/140) and tricuspid valve repair (11/140).

A total of 776 events were reported during the 180 day primary analysis period. Of these 437 (437/776, 56.3%) were INTERMACS defined specific events, and 338/776 (43.6%) events were recorded under the INTERMACS category of “other.” One UADE, chest wall erosion was reported during the 180-day primary endpoint period.

Adverse events defined by INTERMACS criteria during the primary analysis period included the following:

	Date of Event Onset*			
	0-30 Days		31-180 Days	
	Events n	Subjects n (%)	Events n	Subjects n (%)
Bleeding				
Re-operation	23	20 (14.3)	4	4 (2.9)
Transfusion criteria (>=4 within 7 days)	10	10 (7.1)	0	0
Any units after 7 days	31	25 (17.9)	46	20 (14.3)
Infection				
Localized Non-device	20	20 (14.3)	17	17 (12.1)
Driveline Exit Site	5	5 (3.6)	14	11 (7.9)
Sepsis[1]	3	3 (2.1)	8	7 (5)
Neurological Event				
Ischemic CVA	7	7 (5)	3	3 (2.1)
Hemorrhagic CVA	2	2 (1.4)	2	2 (1.4)
TIA	2	2 (1.4)	5	4 (2.9)
Respiratory Dysfunction				
Dysfunction	26	22 (15.7)	8	5 (3.6)
Arrhythmia				
Ventricular	15	14 (10)	14	11 (7.9)
Supraventricular	25	21 (15)	7	6 (4.3)
Right Heart Failure				
Inotropes	17	17 (12.1)	8	7 (5)
RVAD	3	3 (2.1)	1	1 (0.7)
Device Malfunction				
Pump Failure	3	3 (2.1)	4	4 (2.9)
Non-pump Failure	5	4 (2.9)	14	12 (8.6)
Other				
Arterial Thromboembolism	0	0	2	2 (1.4)
Venous Thromboembolism	4	4 (2.9)	3	3 (2.1)
Renal Dysfunction	8	8 (5.7)	6	5 (3.6)
Psychiatric Episode	5	5 (3.6)	4	4 (2.9)
Myocardial Infarction	0	0	1	1 (0.7)
Hypertension	1	1 (0.7)	0	0
Hepatic Dysfunction	3	3 (2.1)	1	1 (0.7)
Hemolysis event[2]	1	1 (0.7)	1	1 (0.7)

[1] A multiple entry (4) of one case was corrected

[2] Two cases were excluded: 1 case hemolysis < 72 hours post-implant; 1 case hemolysis occurring in the presence of tPA/Integrillin for VAD thrombosis

*Events that have an onset date of 0-30 days and which reoccur in the same patient past 30 days are counted in both 0-30 day and 31-180 day periods.

There were eight subject deaths during the 180-day study period. Six deaths occurred in subjects with their originally implanted device and two deaths occurred after device exchange. There were 26 device malfunctions reported for 20 patients during the study period. Seven (5.0%) were due to the LVAD component; of these 6 involved thrombosis events, necessitating exchange.

The pre-specified primary endpoint analysis was a comparison of success rates using a non-inferiority margin of 15%. In the HVAD group the success rate in the Intent-To-Treat (ITT) / Safety Population at 180 days was 90.7% (127/140) and in the Per Protocol population 92.0% (126/137). The success for both Safety and Per Protocol populations in the Control group was 90.1% (448/497). The Primary analysis found that the 95% one-sided upper confidence limit (UCL) on the difference in success rates between HVAD group and controls was 4.5% for the Safety population and 0.9% for the Per Protocol population. Each of these limits was less than the 15% non-inferiority margin ($p < 0.0001$).

Survival was defined as transplanted, or alive on device support, or alive after device explant for recovery. The overall Kaplan-Meier survival at 180 days in the HVAD group was 93.9% in the Safety population and 94.2% in the Per Protocol population. The corresponding survival for the INTERMACS control group was 90.2%. In addition survival status at Day 180 was assessed for all HeartWare® HVAD patients irrespective of meeting a predefined outcome (transplant or explant). There were 130/140 (92.9%) of patients alive at day 180 (88/140 were alive on the original device, 5/140 were alive post device exchange, and 37/140 were alive post-transplant).

The Quality of Life (QoL) determined from KCCQ Overall Summary Score for the subset of 70 patients who had data at both baseline and Month 6 showed a 31 point improvement over the 180 day period. In addition, as measured by the EQ-5D Visual Analog Scale, 72 subjects who had both baseline and 180 day data showed an improvement of 29.5 points over the 180 day period. Functional analyses showed similar improvements. At baseline 133/139 subjects (96%) were classified as NYHA class IV. A Discharge visit was conducted for 128 patients (median duration of hospital stays was 19 days), and data on NYHA was available for 85/128, (66.3%) of these patients, data on 43 was not collected. At discharge, 4/85 (4.7%) were NYHA Class I, 47/85 (55%) of subjects were class II, 26/85 (30.6) Class III and 8/85 (9.4%) Class IV. For the 6-minute walk test, data collected at baseline and month 6 showed similar improvements in functional capacity. A total of 88 patients were still supported on the device at 6 months and of those, 74 (84%), had 6-minute walk data at both baseline and 6 months, and they showed an average improvement in distance walked of 150 meters. Overall, both quality of life and functional capacity showed improvements following HVAD implant.

4.3 Name and Intended Use

As described in the Instructions for Use, the HeartWare® HVAD is intended for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The HeartWare® HVAD is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.

The HeartWare® HVAD is contraindicated in patients who cannot tolerate anticoagulation therapy.

5. DEVICE DESCRIPTION

5.1 HeartWare® Ventricular Assist System

The HeartWare® System consists of a blood pump with an integrated, partially sintered inflow cannula; a 10mm diameter gel impregnated polyester outflow graft, and a percutaneous driveline. A strain relief is used on the outflow graft to prevent kinking and secures the outflow graft to the pump. The driveline cable is wrapped with woven polyester fabric to encourage tissue in-growth at the skin exit site. The small, wearless pump has a displaced volume of 50cc and weighs 160 grams. The pump has one moving part, an impeller, which spins blood to generate up to 10 L/min of flow. There are two motors in the pump housing with one motor providing redundancy. A short integrated inflow cannula is inserted into the left ventricle and the outflow graft connects the HVAD® Pump to the aorta. A sewing ring attaches to the myocardium and allows for pump orientation adjustments intraoperative. The device size and short inflow cannula allow for pericardial placement, which eliminates the need for abdominal surgery and device pockets (Figure 1).

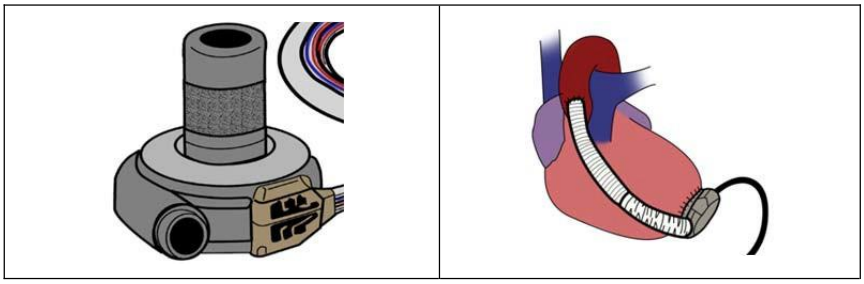


Figure 1: HVAD® Pump and left ventricular (LV) cannulation

5.2 HeartWare® Controller

The controller (Figure 2) is a microprocessor unit that controls and manages HeartWare® System operation. It sends power and operating signals to the blood pump and collects information from the pump. The percutaneous driveline is connected to the controller, which must always be connected to two power sources - an AC adapter or DC adapter and/or rechargeable batteries. The controller's internal, non-replaceable, rechargeable battery is used to power an audible "No Power" alarm when both power sources are disconnected. The controller interfaces with the monitor through a data port.

Figure 2: Controller

1. **Monitor**
2. **Power**
3. **Driveline**
4. **Power**

5.3 HeartWare® Monitor

The monitor (Figure 3) is a touch screen tablet that uses proprietary software to display system performance and to permit adjustment of selected controller parameters. When connected to a controller, the monitor receives continuous data from the controller and displays real-time and historical pump information. The monitor also displays alarm conditions.

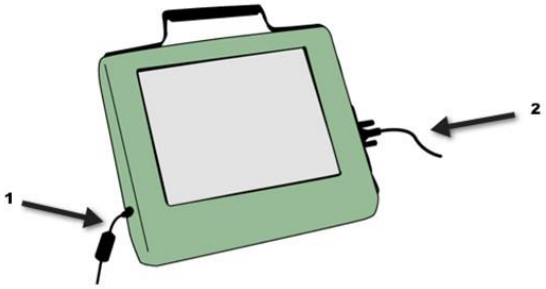


Figure 3: Monitor

1. **Power Cord**
2. **Monitor/Controller Connection**

5.4 HeartWare® Controller Power Sources

The controller requires two power sources for safe operation: either two batteries, or one battery (Figure 4) and an AC adapter (Figure 5) or DC adapter (Figure 6). While active, patients will typically use two batteries. While relaxing or sleeping, patients should use power from an electrical outlet (AC adapter) because it provides power for an unlimited period of time. The batteries should be exchanged when their charge falls below 25% capacity. Spare, fully charged batteries should always be available.

Figure 4: Battery

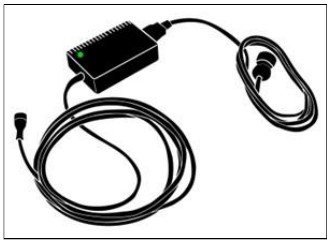


Figure 5: AC adapter

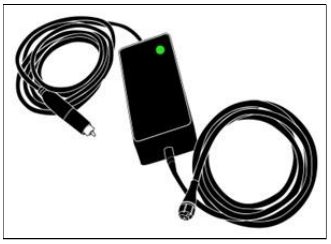


Figure 6: DC adapter

5.5 HeartWare® Battery Charger

The battery charger (Figure 7) is used to simultaneously recharge up to four batteries. It takes approximately 4 to 5 hours to fully charge a depleted battery.

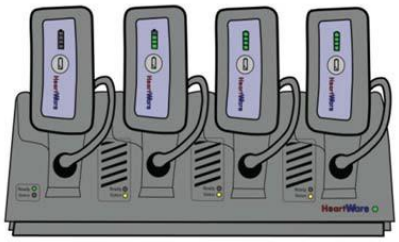


Figure7: Battery charger

5.6 Equipment for Implant

Figure 8 shows the HeartWare® System components used at implant (provided ETO sterilized).

- **HVAD® Pump**
- **Outflow graft** – a 10mm diameter gel impregnated graft
- **Strain relief** – to prevent outflow graft kinking
- **Sewing ring**– to secure the HVAD® Pump to the left ventricle
- **Driveline cap –** to protect the driveline connector when tunneling
- **Inflow cap** – to cover the pump inflow cannula after the wet test and prior to implantation
- **Driveline extension cable -** used during the pre-implant wet test to keep the non-sterile controller isolated from the sterile field

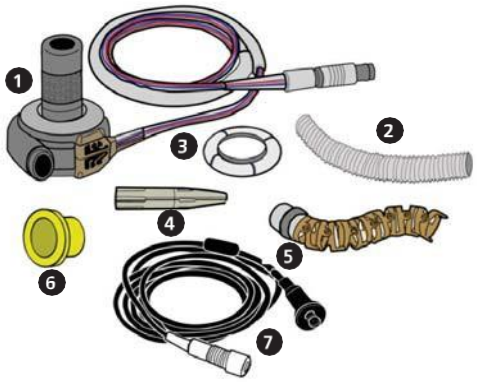


Figure 8: Components used at implant

1. **HVAD® Pump**
2. **Outflow graft**
3. **Sewing ring (made of titanium and polyester)**
4. **Driveline cap**
5. **Strain relief**
6. **Inflow cap**
7. **Driveline extension cable**

A set of surgical tools (provided ETO sterilized) is also required for implantation of the device (Figure 9).

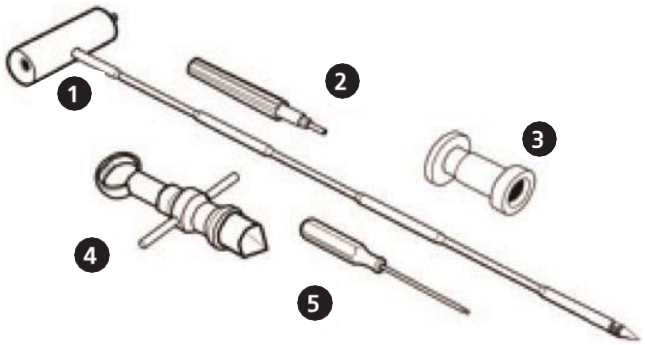


Figure 9: Surgical tools

1. **Tunneler** – to tunnel the pump's percutaneous driveline through the skin to the exit site
2. **Sewing ring wrench** – to tighten the screw on the sewing ring
3. **Driveline cover** – to cover the driveline connection to the controller
4. **Apical coring tool** – to core the LV apex
5. **Hex driver** – to secure the strain relief and outflow graft to the HVAD® Pump

All tools and accessories used during implantation are for single-use only.

5.7 Principles of Operation

Continuous flow pumps contain a rotating impeller that adds energy to the blood by converting the rotational kinetic energy into mechanical energy (Figure 10). 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) or just head, such that the fluid is moved from the inlet to the outlet of the pump. Pump head is the difference between the afterload and the preload. Energy to rotate the impeller is provided through electromagnetic coupling between permanent magnets (rotor magnet) attached or enclosed within the impeller and the motor stators. The motor stators consist of coils of wire that are sequentially charged by electrical current, turning the coils into electromagnets. These electromagnets have the effect of dragging the rotor magnets around an axis of rotation. The HVAD® Pump is efficient at pumping moderate quantities of blood against moderate amounts of resistance.

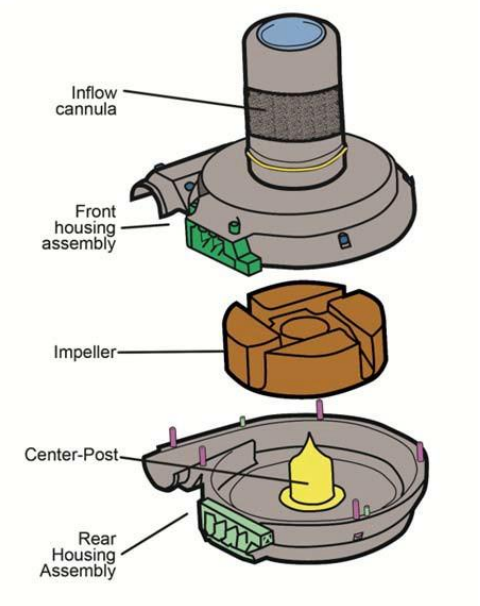


Figure 10: Exploded view of HVAD pump

1. **Inflow Cannula**
2. **Front Housing Assembly**
3. **Impeller**
4. **Center Post**
5. **Rear Housing Assembly**

5.7.1 Blood Flow Characteristics

The amount of flow a rotary 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 that exists across the pump. This allows for in-vitro pump characterization for a specific pump and is the basis for blood flow estimation.

The HeartWare® System estimates blood flow rate using HVAD® Pump characteristics (electrical current, impeller speed) and blood viscosity. Viscosity is calculated from the patient's hematocrit. To obtain the most accurate estimate of blood flow, the patient's hematocrit must be entered into the HeartWare® monitor. Flow estimation should be used as a trending tool only, as it cannot adapt to changing fluid conditions.

The volume of flow generated by the HVAD® Pump is determined by the rotational speed of the impeller and by the pressure differential across the pump. The pressure that the HVAD® Pump must work against is similar to the mean arterial pressure. If the pump speed (RPM) is set too low then the device may not generate enough forward pressure. This can lead to retrograde flow (flow from the aorta back through the device and into the left ventricle). The maximum rotational speed is determined by how much flow is available from the right heart. If the speed is set too high and the pump attempts to pump more blood than is available, ventricular suction may occur.

The controller operates in "Fixed" mode, which maintains a constant motor speed. The motor speed range is between 1800 and 4000 RPM. The appropriate speed should be determined based on the patient condition.

5.7.2 Physiological Control Algorithms

The "Fixed" mode is used for HVAD® Pump operation means the clinician sets the pump speed (RPM). In addition, the HVAD® Pump control algorithms provide clinicians information about device performance and HVAD® Pump blood flow estimation.

5.7.3 Flow Estimation

Estimated HVAD® Pump blood flow is calculated using VAD power, speed parameters, and hematocrit, based on a blood sample from the patient. The default hematocrit setting is 30%, but for accurate flow estimation, the patient's hematocrit should be entered into the monitor. Adjustments to the hematocrit setting on the monitor should be made for hematocrit changes of ± 5% or greater.

5.7.4 Ventricular Suction Detection Alarm

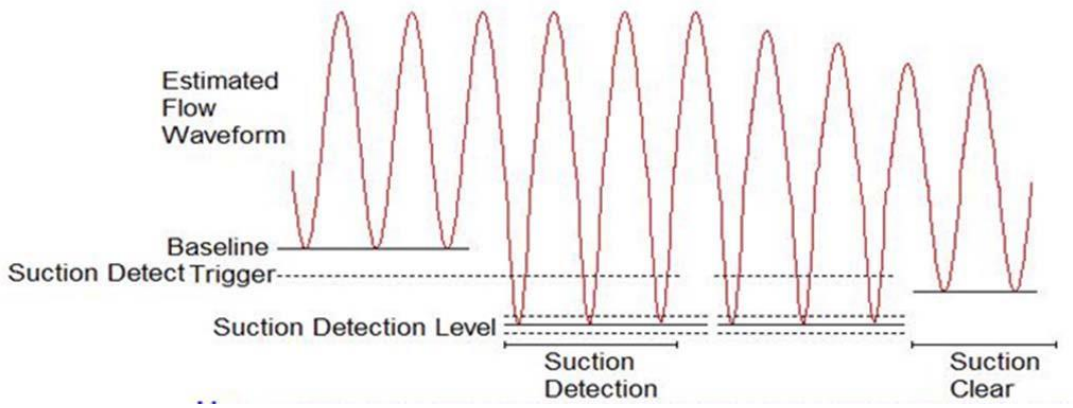
A suction condition may occur due to ventricular collapse or inflow occlusion. Ventricular collapse occurs when a continuous flow VAD attempts to pump more blood from the left ventricle than is available, resulting in considerable reduction in ventricular volume. Left ventricular collapse can be the result of clinical events affecting left ventricular preload, including hypovolemia (bleeding), right heart failure, arrhythmia or pulmonary embolus. An inflow occlusion occurs when the inflow cannula is obstructed by the interventricular septum, also

causing a suction condition. Temporary inflow obstruction can occur as a result of surgical positioning, patient position or during straining (valsalva).

The ventricular suction detection alarm functions by monitoring the estimated flow for sudden decreases in flow rate. A flow baseline is established by continuously tracking the minimum flow values. A trigger value is established at 40% below the estimated flow baseline. An indication of suction is obtained when the minimum flow falls below this trigger level. The alarm will be triggered if this condition is maintained for 10 seconds.

The flow minimum that triggers the suction alarm is also used to define the suction clear limit. The estimated flow baseline is continuously compared to this limit. The suction alarm will be cleared if the flow baseline is maintained above the trigger level for 20 seconds. This is an indication that the suction condition has cleared.

The ventricular suction detection alarm can only be activated from the System Screen of the monitor. Therefore, only the clinician has access to control the state of this alarm. The default setting for Suction Response is off. In this mode, there will be no alarm during a ventricular suction condition. An “Sx Off” message will be displayed on the lower left-hand corner of the monitor screen below the “Fixed” mode display. When Suction Response is enabled (via the “Alarm” button), the “Sx On” message will be displayed on the lower left-hand corner of the monitor screen below the “Fixed” mode display.



The Suction Response “Alarm” 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 “Sx On” message will be displayed on the monitor and the ventricular suction detection 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. This is not possible if the patient is experiencing ventricular suction when the algorithm is initiated. Once the suction condition clears, an accurate baseline will be obtained automatically and the suction detection will proceed. Manual changes to the speed will immediately disable the ventricular suction detection alarm. An “Sx Off” will be displayed on the monitor screen below the “Fixed” Mode display. The clinician will have to reactivate the alarm after adjusting the speed.

The ventricular suction detection function will temporarily deactivate if:

- The estimated flow value becomes invalid. Once the flow estimation is within valid range, then the ventricular suction detection will resume.
- The baseline flow value is less than 1.8 L/min – the algorithm loses sensitivity if the baseline and, therefore, the suction detection level gets too low. Once the baseline value is above 1.8 L/min, then the ventricular suction detection will resume.

The clinician changes the viscosity input – the algorithm recognizes that a change in the fluid viscosity will cause a change in the estimated flow. The ventricular suction detection reactivates once a new baseline is established.

6. STUDY OBJECTIVES AND ENDPOINT MEASURES

6.1 Study Objectives

The objective of this study is to evaluate the safety and effectiveness of implanting the HeartWare® HVAD System via thoracotomy in patients at risk of death from refractory end-stage left ventricular heart failure, who receive the device intended as a bridge to cardiac transplantation.

This is a multi-center, prospective, single arm study that will use data from subjects enrolled in the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) protocol and database.

All participating centers will be current enrolled INTERMACS sites in good standing. Participating centers will follow study subjects as they normally do for patients enrolled into INTERMACS®.

Endpoints will be evaluated for subjects who receive the HeartWare® HVAD System implanted via thoracotomy.

6.2 Estimated Period of Study

6.2.1 Time Schedule

Enrollment of subjects is expected to start in the fourth quarter of 2014 (First Implant) and each subject will be in the study for up to 30 months (including Screening and Follow-up phases).

6.2.2 End of Study

Enrollment of subjects is expected to be completed in the first quarter of 2016 (Last Implant) and the overall end of study 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 2018.

6.3 Primary Endpoint

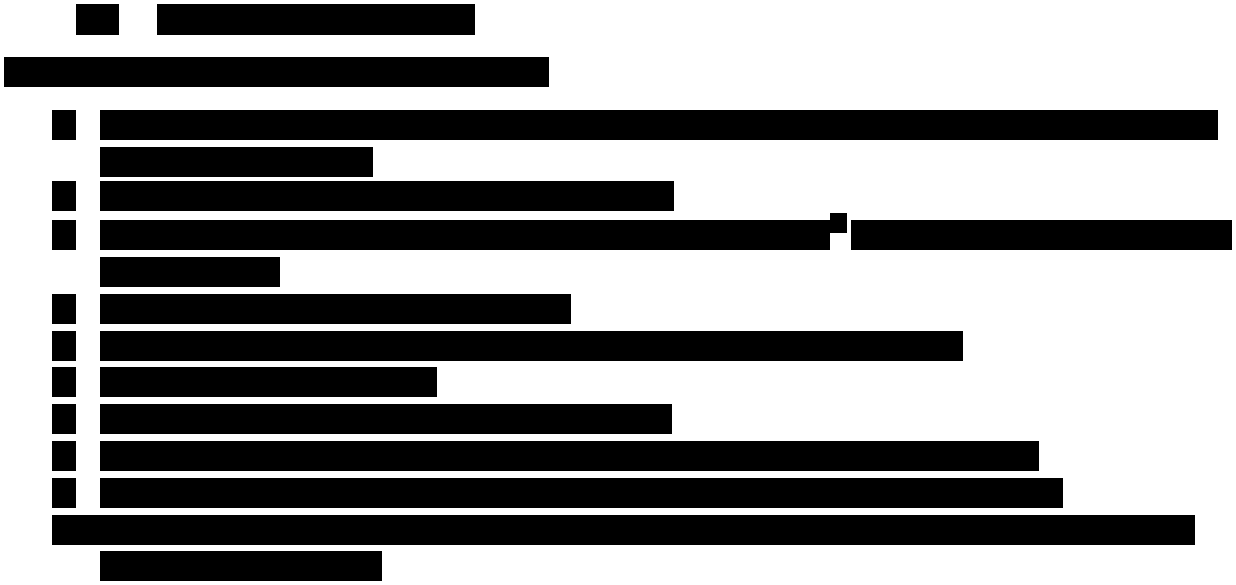
The primary endpoint is success at 6 months defined as all enrolled and implanted subjects:

- Alive on the originally implanted device at 6 months, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Transplanted by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event), or
- Explanted for recovery by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event).

All subjects with stroke events from implant to Month 6 will be required to remain in follow-up until the post-stroke mRS measure (≥3 months post stroke event) is obtained, even if this occurs after the 6-month visit. If a stroke subject is alive at 6 months, but dies before the post-stroke mRS is obtained, the subject will be considered a failure with regard to the primary endpoint.

6.4 Secondary Endpoint

The secondary endpoint is an improvement in the mean length of initial hospital stay (initial recovery and step down unit) for all enrolled and implanted subjects. The mean length of initial hospital stay is estimated to be 26.1 days for median sternotomy subjects.



7. STUDY DESIGN

This a prospective, single arm, multicenter study to evaluate the thoracotomy implant technique in up to 145 subjects implanted via thoracotomy with the HeartWare HVAD® System and enrolled in the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) protocol and database.

7.1 Number of Clinical Sites and Subjects

This study will be conducted at up to 30 sites in the US and 1 site in Canada. All centers will be required to have an approved and active cardiac transplant program, have experience implanting the HeartWare® HVAD System, and must meet the INTERMACS® defined requirements to be eligible for participation:

- All centers will be currently enrolled INTERMACS sites who are participants in good standing and who contribute to the INTERMACS® database. (These organizations and agencies have mechanisms in place to assure basic national standards and survival rates are maintained.)
- All US commercial centers will have a certificate of need to perform cardiac transplants by the state in which they are located.
- US centers will be United Network for Organ Sharing (UNOS) approved with a cardiac transplant program on active status.
- US centers will be Centers for Medicare and Medicaid Services (CMS) and Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) approved for cardiac transplantation.

Centers will be identified by the Principal Investigators of the study in collaboration with HeartWare and will be based upon the center's interest in participating in the study, their academic history, infrastructure, geographic location, and the number and kind of VAD implants per year.

One hundred forty-five (145) subjects will be required to meet the statistical endpoints defined for the study. It is anticipated that each site will enroll at least 1 subject. No site will implant more than 20 patients into the study without prior written approval from HeartWare.

7.2 Subject Participation and Study Duration

All subjects will be followed for the primary endpoint, and at subsequent follow-up visits, according to the approved INTERMACS® protocol and using data from INTERMACS®.

Data collection for analysis and subject status for inclusion in analyses will be assessed as follows:

- Subjects who have been transplanted prior to month 6 post implant will be considered complete at the time of the primary endpoint visit time-point.
- Subjects, who have a device exchange prior to month 6, will be evaluated according to the original implant date.

- Subjects who remain on device support after the primary endpoint time-point, either the original device or exchange device, will be followed according to the INTERMACS® protocol until transplant, or until 2.5 years post implant of the original device. A subject's study participation is considered complete at either the time of at induction of anesthesia for transplant, or at the 2.5 year post implant visit.
- Subjects who have been explanted for recovery prior to month 6 will be followed until their next scheduled follow-up visit according to the INTERMACS® protocol, at which time their participation in the study is considered complete.
- The per-protocol analysis population will include those thoracotomy subjects with the outflow in the ascending aorta only. As a result, enrollment may exceed sample size requirements.
- The per-protocol analysis population will include those thoracotomy subjects with the procedure performed on-pump only. As a result, enrollment may exceed sample size requirements.

Subject data will be evaluated for a maximum of 2.5 years.

8. PATIENT POPULATION, SELECTION AND WITHDRAWAL

8.1 Characterization of Study Population

Subjects will be made up of those patients who are prospectively identified as candidates to receive a HeartWare® HVAD via a thoracotomy implant procedure and who meet the inclusion and exclusion criteria as defined in Sections 8.2 and 8.3 below.

8.2 Inclusion Criteria

1. Must be ≥19 years of age at time of informed consent to participate in the INTERMACS® registry.
2. Subject receives a HeartWare® VAD (The device should be the subject's first VAD implant).
3. Subject signed an INTERMACS® informed consent if required by local IRB/CREB policy.
4. Subject signed a HeartWare ®informed consent

8.3 Exclusion Criteria

The INTERMACS® protocol has no exclusion for age, gender, race, ethnicity, or any other demographic limit. The following are exclusions currently described:

1. Subject is incarcerated (prisoner).
2. Subject did not sign the informed consent at sites where waiver of consent was not granted.

In addition, for this study, the following additional exclusion criteria will be applied after enrollment into the INTERMACS® protocol:

3. Body Surface Area (BSA) < 1.2 m^2.
4. Prior cardiac transplant or cardiomyoplasty.
5. Subject is receiving a BiVAD.
6. Subject is receiving the device as an RVAD.
7. Subject data is generated from non- INTERMACS® centers.
8. Pediatric subjects (< 19 years of age).
9. Subjects who receive a temporary LVAD (e.g., ECMO, TandemHeart, Impella, etc.).
10. Subjects whose device strategy is listed as "Destination Therapy" at the time of implant.
11. Severe Right Heart failure, defined as mean central venous or right arterial pressure > 20 mmHg on multiple inotropes, or right ventricular ejection fraction (RVEF) <15% with clinical signs of severe right heart failure (e.g. ascites, treatment with diuretics and two inotropic drugs).
12. ≥ 2+ aortic insufficiency or mechanical aortic valve.
13. Planned concomitant procedure (e.g. valve repair or replacement, CABG, septal defect repair).
14. Known LV thrombus

9. STUDY COURSE AND PROCEDURES

9.1 Enrollment

The subject data to be included in the study analyses will be recorded in the INTERMACS® database from enrolled subjects implanted via thoracotomy.

9.2 Assessments

All study assessments will be conducted according to the approved INTERMACS® protocol and procedures. There are no other study specific procedures required except the consenting of subjects with a HeartWare Informed Consent Form (ICF).

9.2.1 Baseline / Pre-Implant information

Baseline and pre-implant data recorded in the INTERMACS® database includes:

- Patient demographic data.
- Medical history and co-morbidities.
- Clinical status including INTERMACS® patient profiles and NYHA Class.
- Laboratory values including blood chemistry and hematology.
- Cardiovascular Medications including inotropes, diuretics, anti-arrhythmics, pulmonary hypertensive agents, and anticoagulation therapy.
- Hemodynamic Data.
- Quality of Life as measured by EuroQol and KCCQ.
- Neurocognitive Testing measured by the Trail Making Neurocognitive Test, Part B.
- Exercise Function measured by the six minute walk test.

9.2.2 Implant Information

Implant information recorded in the INTERMACS® database includes: device information and device tracking number, implant technique, concomitant cardiac surgical procedures, and cardiopulmonary bypass / surgery times.

9.2.3 Follow-up Assessments

Follow-up visit time-points specified in the INTERMACS® protocol include: At discharge, 1 week, 1 month, 3 months, 6 months and every 6 months until outcome/ 2.5 years.

At discharge assessments recorded in the INTERMACS® database include: adverse events and discharge date.

Assessments at one week and one month include: hemodynamics, laboratory values, medications, echocardiogram, medical condition as described by NYHA class and adverse events.

Assessments at 3 and 6 months, and then every 6 months until outcome / 2.5 years include: laboratory values, medications, hemodynamics, echocardiogram, medical condition as described by NYHA class and INTERMACS® patient status, neurocognitive testing, quality of life testing, exercise function and adverse events.

Every attempt should be made to perform evaluations at the designated time points. Visits and associated visit windows will be as per the INTERMACS protocol and procedures. While per the INTERMACS protocol, the Month 6 visit has a ±60 day window, it is recommended that the Primary Endpoint visit occur at Month 6 + 60 days, whenever possible.

9.2.4 Re-hospitalizations

Information on re-hospitalizations post initial discharge is recorded in the INTERMACS® database, including date and reason for re-admission, treatment and date of discharge.

9.2.5 Outcomes

Information on the type of outcome (transplant, explant, death) is recorded in the INTERMACS® database, including transplant date, reason for explant, and cause of death.

9.2.6 Adverse Events

Adverse events will be collected throughout the subject's participation in the study according to the INTERMACS® protocol and procedures.

INTERMACS defines 17 specific event that it considers as serious event in patients receiving a VAD as these specific event definitions usually encompass the traditional categorization of serious (i.e. considered life threatening, requires or prolongs hospitalization, results in death, if the event results in disability or permanent damage, or requires an intervention to prevent one of these outcomes).

INTERMACS® also defines a category of "Other" adverse events and collects these as reported by participating centers. These will be summarized and presented in the study reports, but the recording of these 'Other' events does not capture the event seriousness or relationship to device (any events related to the device if applicable are captured under the INTERMACS® categorization of Device Malfunction).

The events listing in the INTERMACS protocol are listed below and definitions included in Appendix C.

Major infection	Major bleeding
Neurological dysfunction	Device malfunction
Cardiac arrhythmia	Renal dysfunction
Hemolysis	Respiratory failure
Hepatic dysfunction	Right heart failure
Hypertension	Arterial non-CNS thromboembolism
Myocardial infarction	Venous thromboembolism
Pericardial fluid collection	Wound dehiscence
Psychiatric episode	Other adverse events

9.2.7 Device Related Adverse Events and Device Malfunctions

All device related adverse events and device malfunctions must be reported as complaints to HeartWare's Quality group.

All device malfunctions as defined by INTERMACS™ will be recorded in the INTERMACS™ database according to their Manual of Operations.

9.2.8 Additional data collection

Post-Transplant

Additional information will be collected to evaluate the effect of the lateral surgical procedure on the pre and post-operative requirements, length and severity of the hospitalization during the procedure and length of hospitalization post-transplant.

The following parameters will be included:

1. Total operative time
2. Cardiopulmonary Bypass time
3. Intraoperative blood/ coagulation products
4. If the surgical procedure was done on a Virgin Chest
5. If the patient had Pneumothorax
6. Severity of pericardial/pleural adhesions
7. Time on ventilator/inotropes
8. Total Days on Intensive Care Unit
9. Total Days in Hospital after transplant

The additional data will be collected on transplanted patients only.

The additional data will not be captured in INTERMACS database.

Follow-Up after stroke if transplanted or explanted

Additional information will be collected for all stroke patients who are transplanted or explanted in order to assess mRS (≥3 months post-stroke) to classify them for the primary endpoint.

The following parameters will be included:

1. Date of assessment
2. mRS

The additional data will be collected only on transplanted or explanted patients who had a stroke with mRS ≥4 less than 3 months prior to the transplant or explant.

The additional data will not be captured in INTERMACS database.

10. SURGICAL IMPLANT PROCEDURE

10.1 Pre-Implant Device Management

Refer to the HeartWare® HVAD Instructions for Use for detailed equipment set-up procedures.

10.2 Implant Procedure

Refer to the Instructions for Use for the thoracotomy implant procedure, which describes HeartWare® HVAD placement in the pericardial space, cannulation techniques and tunneling of the percutaneous lead.

10.3 Postoperative Patient Management including Blood Pressure (BP) Management

Refer to the HeartWare® HVAD Instructions for Use for postoperative patient management guidelines.

HeartWare strongly recommends BP Management for all implanted subjects. Since the HVAD® Pump provides continuous flow, resulting in narrow arterial systolic/diastolic pulse pressures, monitoring of the mean arterial pressure (MAP) is important. The recommended MAP target for subjects supported by the HeartWare® HVAD is < 85 mmHg (as tolerated).

11. STATISTICAL CONSIDERATIONS

11.1 Study Endpoints and Hypotheses

11.1.1 Analysis Populations

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

The Per-Protocol (PP) subject population will include all ITT subjects who were implanted with the HVAD pump® via thoracotomy, on-pump, and with outflow to the ascending aorta. Sample size requirements reflect the minimum number of subjects needed for the PP population.

The primary analysis population is the PP population. All endpoints will be assessed on the ITT and PP populations.

11.1.2 Primary Endpoint

The primary endpoint is success at 6 months defined as all enrolled and implanted subjects:

- Alive on the originally implanted device at 6 months, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Transplanted by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event), or
- Explanted for recovery by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event).

All subjects with stroke events from implant to Month 6 will be required to remain in follow-up until the post-stroke mRS measure (≥3 months post stroke event) is obtained, even if this occurs after the 6-month visit. If a stroke subject is alive at 6 months, but dies before the post-stroke mRS is obtained, the subject will be considered a failure with regard to the primary endpoint.

Hypothesis:

H_0: $\pi_T \leq 77.5\%$

H_a: $\pi_T > 77.5\%$

π_T = the expected proportion of subjects experiencing success for the Thoracotomy group

The success prevalence in the thoracotomy group will be statistically compared to the performance goal (77.5%) using an exact binomial test (i.e., the lower 95% one-sided confidence limit will be greater than 77.5%). Success will be met if the lower bound of the one-sided exact 95% confidence limit is greater than 77.5%.

11.1.3 Secondary Endpoint

The secondary endpoint is an improvement in the mean length of initial hospital stay (initial recovery and step down unit) for all enrolled and implanted subjects, which is calculated by considering the number of days in acute care (ICU/CCU) plus the number of days in intermediate/step-down care, comprising the total number of days post-implant to discharge. The mean length of initial hospital stay is estimated to be 26.1 days for median sternotomy subjects.

Hypothesis:

H_0: $\mu_T \geq 26.1$

H_a: $\mu_T < 26.1$

μ_T = the expected mean length of initial hospital stay for the Thoracotomy group

A responders' analysis will also be assessed to help define the clinical benefit of this endpoint. The length of initial hospital stay will be summarized across outcomes associated with the primary endpoint (success at 6 months).

[redacted]

Strokes are those neurological events specified as an ICVA or an HCVA, as per the current INTERMACS event definition (See Appendix D).

11.2 Sample Size Justification

Primary Endpoint:

Success at 6 months is estimated to be 86% compared to a performance goal of 77.5%. Using an exact binomial test, with a one-sided alpha of 0.05, and 80% Power, a sample size of 145 implanted subjects is required.

The target success estimate of 86% is based on the following:

- The primary endpoint observed in the final BTT IDE Report for the more recent BTT CAP population (N=242), resulted in a success prevalence of 85.8% (205 out of 239 eligible subjects) for sternotomy subjects.
- Post-approval data from the INTERMACS Registry (through Q2 2014), indicates similar results for the sternotomy population of 88.0% (396/450) with a lower prevalence of success for the small subset of thoracotomy (83.3%, 55/66) and thoracotomy on-pump (82.6%, 38/46) subjects.
- The INTERMACS Federal Partners Report (from Q1 2014) indicates an 85% Kaplan-Meier survival estimate at 6 months. This is not the same as "success" in that post-exchange survival is considered.
- The INTERMACS Industry Report for HeartWare (from Q2 2014) indicates an 88% Kaplan-Meier survival estimate at 6 months. This is not the same as "success" in that post-exchange survival is considered.

Success will be met if the lower bound of the one-sided exact 95% confidence limit is greater than 77.5%.

For exploratory purposes, the primary endpoint will also be assessed and observed by:

- Site
- CPB (on pump, off pump)
- Outflow location

Secondary Endpoint:

The mean length of initial hospital stay is estimated to be 26.1 days with a standard deviation of 22.8 days and a median of 20 days based on data from the BTT CAP population (N=242). Using a one sample t-test, with a one-sided alpha of 0.05, a sample of 145 implanted subjects with an average value of 21.3 days or less will result in Power greater than 80%.

Due to the skewed nature of this data, a non-parametric test (one-sample Sign test with a one-sided alpha of 0.05) to assess a reduction in median days (from the estimated 20 days) will also be conducted for support.

For exploratory purposes, the secondary endpoint will also be assessed and observed by:

- Site
- CPB (on pump, off pump)

- Outflow location

The sample size calculations were performed using nQuery Advisor®.

11.3 Site Poolability

The primary and secondary endpoints will be performed on pooled data, however, an Analysis Site poolability assessment will be incorporated into the design of the study. This will involve pooling sites into "Analysis Sites" with a target size of 5 subjects. Sites with at least 5 subjects will serve at their own Analysis Site. Those with less than 5 will be rank ordered by size and sorted secondarily by site identification number to break ties. Starting with the smallest investigative site, subjects are combined site by site until at least 5 subjects are identified, thus establishing an Analysis Site. The next Analysis Site is formed similarly to contain at least 5 subjects. The process continues until all sites and subjects are accounted for. If the last Analysis Site has fewer than 5 subjects, it is combined with the most recently created previous Analysis Site.

A Fisher's exact test will be performed to test the homogeneity of success at 6 months across Analysis Sites. Analysis Site homogeneity is defined if the p-value is 0.15 or greater. If there is an Analysis Site effect (p-value < 0.15), an investigation of prognostic factors (i.e., baseline characteristics, medical history or other covariates of interest) will be reviewed to understand variability between Analysis Sites. As a supplemental analysis, a logistic regression model will be performed to estimate the probability of success controlling for Analysis Site and the selected prognostic factors.

11.4 Handling of Missing Outcomes

Every effort will be made to gather all data associated with the primary, secondary and additional endpoints. A complete case analysis, which includes all subjects with complete follow up will be conducted as the primary analysis of the primary endpoint.

[redacted]

If a subject experiences a stroke and subsequently completes the 6 month follow-up, a post-stroke (greater than 6 months post-event) mRS is still required. If the subject dies prior to the post-stroke mRS but after the 6 month follow-up, the outcome will be considered a failure.

For the secondary endpoint, imputation for missing data regarding duration of hospital stay (in days) will not be performed.

11.5 Early Submission

Early review of the data will be performed when the first 100 subjects complete 6 months of follow-up. Analysis of the results will follow the Haybittle-Peto methodology[7,8], where the interim look will involve an alpha level of 0.001, retaining an alpha level of 0.05 for the final analysis of 145 subjects. This is not intended to serve as a stopping rule, but rather an early submission indicator. A target of 92.5% of the first 100 subjects would need to experience success at 6 months to achieve Power greater than 80% and consideration of early submission.

12. RISK AND BENEFIT ANALYSIS

12.1 Potential Benefits

There is a growing trend toward the use of less invasive non-sternotomy incisions in all fields of cardiac surgery. While a median sternotomy provides the best access to the heart and great vessels, the same exposure could be accomplished with several smaller thoracotomy incisions. For patients who will require more than one cardiac operation (for example, VAD implantation as a bridge to transplantation), avoiding a median sternotomy in the first operation will reduce the surgical risk of a redo sternotomy in the following operations. Less-extensive mediastinal dissection in non-sternotomy incisions could reduce the prevalence and severity of postoperative bleeding. This is particularly important in VAD patients who require early anticoagulation therapy after implant. In addition, with a thoracotomy the pericardium remains mostly intact, which results in the stabilization of right heart function and possibly avoiding right heart dilatation during the procedure, especially when initially starting the HVAD® Pump. Many of these benefits also apply if the second operation is done via thoracotomy. The HVAD® Pump is designed to be implanted in the pericardial space. Its small design allows some versatility in placement and therefore does not limit the implant to a single surgical procedure. This implant versatility provides clinicians multiple options for implant and allows them to best match the patient with the procedure. There are some patients who may fare better with a thoracotomy rather than sternotomy. The potential benefit to the subject participating in this study is the implantation of a blood pump using a technique that is less obtrusive and that may be more comfortable. Morbidity rates and time of recovery may also be positively affected. The thoracotomy technique for implant may provide benefits not currently available with existing technology. The potential benefits as mentioned above include:

Potential Benefit	**Thoracotomy Implant**
Less invasive implant procedure	• Smaller incisions • Shorter hospitalization
Reduced bleeding	• Less tissue trauma • Virgin sternotomy at later procedure • Thoracotomy at second procedure/device exchange
Reduced infection	• Lower infection rates • Less severe infections • Virgin sternotomy at later procedure
Reduction of right heart failure	• Pericardium more intact
Expand patient population	• Include patients who may not tolerate a sternotomy

12.2 Risk Analysis

There are no foreseeable, additional risks associated with the thoracotomy approach for implantation of the HeartWare® System beyond those historically associated with implantable, continuous flow LVAD systems. While no new risks have been identified, there are some events that can be more easily treated via a sternotomy as compared to a thoracotomy. For example, the LV can be examined for thrombus more thoroughly and RVAD support can be more easily initiated using a sternotomy. The complications (LV thrombus, right heart failure) can be mitigated to some degree with patient selection, however, complications are unpredictable. Pneumothorax is a known complication of thoracic surgery which can occur in patients who receive either a sternotomy or thoracotomy, however since the risk of pneumothorax may be higher in thoracotomy patients it was added to the potential complications list. HeartWare believes it has used its best efforts to foresee hardships and potential adverse events of either in-hospital or home use of the HeartWare® System.

Implantation of an LVAD is an invasive operation involving a major thoracic procedure (median sternotomy or left thoracotomy), general anesthesia, mechanical ventilation and frequently cardiopulmonary bypass. These procedures are associated with numerous risks including death. The HeartWare® Ventricular Assist System is implanted in the hostile environment of the human body. This environment places severe challenges to the function of the device. Risks associated with the 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 according to INTERMACS categories:

- 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 / AV malformations
- Cardiac Arrhythmias
  - Supraventricular Arrhythmia
  - Ventricular Arrhythmia
  - ICD shock
- Device Malfunction
  - Battery failure
  - Controller failure
  - Device Exchange
  - Device Thrombosis
  - 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 Stop
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Major Infection
  - Driveline Infection
  - Internal Pump Component, Inflow or Outflow Tract Infection
  - Localized Non-device Infection

Sepsis
- Myocardial Infarction
- Neurological Dysfunction
  Transient Ischemic Attack (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
  Anemia
  Aortic Insufficiency
  Cardiopulmonary Arrest
  Multi-organ failure
  Platelet Dysfunction
  Pleural Effusion
  Sensitivity to Aspirin
  Surgical Complications
    Arterio-venous fistulae
    Organ damage during driveline tunneling
    Pain
    Pneumothorax
    Re-operation
  Syncope
  Tissue Erosion and other tissue damage
  Worsening Heart Failure

No additional risks are known for the HeartWare® System beyond those established for other implantable, continuous flow LVAD systems.

The HeartWare® System should not be used in pregnant women. Any woman receiving a HeartWare System who is of childbearing age and sexually active should use a reliable method of birth control. Use of anticoagulants during pregnancy has been associated with birth defects and bleeding.

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 patient. All investigators and clinical personnel will have previous experience with the HeartWare® System, surgical implant procedures and patient management. Trained and experienced personnel representing HeartWare will be available to support HeartWare® System implants, ongoing education and HeartWare® System technical support/troubleshooting. In addition, patients and companions will undergo an extensive hospital training program and must demonstrate competency prior to discharge from the hospital.

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

13. INVESTIGATOR RESPONSIBILITY

This clinical study will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and Code of Federal Regulations 21CFR Part 820, 21 CFR Part 50, 21CFR Part 54 and 21CFR Part 56, Health Canada Regulations and any country laws, as applicable.

13.1 Institutional Review Board (IRB)/Research Ethics Board (CREB) Approval

All enrolled INTERMACS® sites must have IRB/CREB approval as required by INTERMACS® procedures. In addition, each participating study center will also obtain IRB/CREB approval of the HeartWare IDE protocol and informed consent form.

No subject will be consented for the study until the IRB/CREB has approved the protocol and the Informed Consent Forms. Documentation of approval must be sent to HeartWare or designee. At study termination, a Final Report must be submitted by the Investigator to the IRB/CREB and Sponsor. Copies of all submissions to and correspondence (approvals and disapprovals) from the IRB/CREB must be maintained on file at the study site.

13.2 Informed Consent

All subjects will be consented using the INTERMACS® informed consent and health privacy documents according to the INTERMACS procedures and local IRB/CREB policy and procedures. Additionally, subjects will sign a HeartWare informed consent form and health privacy document prior to implantation of the HeartWare® HVAD via thoracotomy.

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form explains the study procedures, the nature of the study, its objectives, potential risks and benefits, as well as the date enrollment informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. The subject authorization form, describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study.

In the event the subject is not capable of rendering an adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the screening and (2) decide whether or not to participate in the screening and subsequently, if applicable, must be given ample opportunity to: (3) inquire about details of the study and (4) decide whether or not to participate in the study.

If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form must be signed and

dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject screening, or enrolling into the study and any study procedures being performed.

Once signed, the original informed consent form and subject authorization form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form and the signed subject authorization form shall be given to the subject.

13.3 Subject Data Protection

Data on study subjects is collected by INTERMACS® and subject data is protected by their confidentiality procedures.

All information and data sent to HeartWare or their authorized representative, concerning subjects or their participation in this study, will be considered confidential. Subject data provided to HeartWare Inc. will be identified only by a subject identification number. Data for the study will be de-identified data as per INTERMACS standard operating procedures.

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 FDA, Health Canada or other government agencies or review boards, as applicable. This authorization is included as HIPAA Authorization: Authorization to Use and Disclose Health Information. If the institution requires that an IRB or CREB specific Confidentiality Authorization (HIPAA) form be used, then the site must provide a copy of this form to HeartWare for review and approval

13.4 Investigator Agreement

Prior to study initiation, the Investigator must sign an Investigator Agreement (example Investigator Agreement; HeartWare or designee 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 21 CFR Part 820, Part 56, Part 50, and Part 54 or Health Canada Regulations, as applicable..

13.5 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 the 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.

13.6 Protocol Deviations and Medical Emergencies

The Investigator will not deviate from the protocol 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 medical emergencies, prior written approval for protocol deviations will not be required, but HeartWare personnel must be notified via telephone within 24 hours of occurrence.

13.7 Device Accountability

As of version 7.3 of this protocol, the HeartWare® Ventricular Assist Device System is a US marketed device for the destination therapy indication. It is FDA approved for implantation via either thoracotomy or sternotomy approach.

The disposition of all HeartWare® HVAD System components allocated to HW006 study patients prior to protocol version 7.3 were provided to FDA and reviewed in the Annual Report G130279. Under version 7.3 of this protocol, device accountability will be tracked by serial number and/or lot number.

14. MONITORING AND QUALITY CONTROL

14.1 Site Training

The study is being conducted at experienced HeartWare implanting institutions and all participating study centers and relevant staff will have previously completed HeartWare® System training by HeartWare representatives. Training sessions will have included: HeartWare® HVAD implantation and management techniques, how the HeartWare® HVAD works, what to do in an emergency situation, procedures for troubleshooting the HeartWare® HVAD malfunctions, patient discharge training, regulatory requirements and general good clinical practice for the study.

The HeartWare® HVAD Instructions for Use will be provided to assist the healthcare team on the proper care and operation of the HeartWare® HVAD System.

Additional training on the Thoracotomy Implant technique will be provided to participating sites.

Each site will be responsible for ensuring that the hospital staff directly responsible for patient care from the postoperative period to hospital discharge and outpatient follow-up (e.g. ICU nurses, staff nurses and physicians) are adequately trained in the management of these HeartWare® HVAD patients and emergency response procedures.

Training related to the HW006 study protocol will be conducted through an Investigator meeting or through Site Initiation Visits at study start-up. All investigators and relevant staff such as study coordinators will be trained on the protocol.

14.2 Monitoring of the Study

HeartWare will conduct monitoring activities as applicable and appropriate for this trial to ensure that it is conducted in accordance with the protocol. As required during monitoring visits for treatment subjects, informed consent forms and HeartWare® HVAD System accountability will be verified.

HeartWare will conduct site evaluation visits to assure that potential clinical investigators are qualified by training and experience to participate in the trial, and site initiation visits to ensure that investigators and site staff have a full understanding of their obligations, are trained thoroughly, have the appropriate support, and have all the regulatory documentation in place to conduct the study.

14.3 Independent Data Review and Event Adjudication

14.3.1 HeartWare DSMB

To meet the trial's ethical responsibility to its subjects, results will be monitored by a Data Safety Monitoring Board (DSMB). The DSMB will review the study at key points during the conduct. A periodic safety review of study data provided from the INTERMACS database will take place annually aligned with the registries reporting schedule.

14.3.2 INTERMACS® Observational Study Monitoring Board (OSMB

The NHLBI-appointed independent Observational Study Monitoring Board (OSMB), which meets once per year, evaluates the INTERMACS® registry on an ongoing basis as to procedures, findings, and adverse events to assure participant safety, confidentiality of records, and registry integrity. The OSMB advises the NHLBI and the INTERMACS® co-investigators when and if changes should be made.

14.4 Progress Reports to Regulatory Agencies

HeartWare will provide the FDA and Health Canada with progress reports as required. The IRBs/CREBs will be provided with copies of the progress reports.

15. Records and Reports

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, and this system is provided by INTERMACS.

15.2 Data Review

INTERMACS® is responsible for the quality control of the database and confirming the overall integrity of the data according to their standard operating procedures.

15.3 Record Retention

HeartWare and all participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed Informed Consent Forms, IRB/CREB approvals and communications and source documents for at least 4 years after study completion or termination. In accordance with the Investigator Agreement, HeartWare should be contacted if the Principal Investigator plans to leave or otherwise absent themselves from the investigational site.

15.4 Study Insurance

HeartWare's liability is underwritten by an insurance policy secured by HeartWare in accordance with United States laws and regulations. A copy of the insurance certificate is provided upon request.

16. APPENDICES

16.1 Appendix A – INTERMACS® Protocol

This appendix includes the INTERMACS Protocol Version 4.0 date February 27, 2014.

Interagency Registry for Mechanically Assisted Circulatory Support
(INTERMACS®)

Protocol

Principal Investigator: James K. Kirklin, MD

Data Coordinating Center: University of Alabama at Birmingham

NHLBI Contract Number: HHSN268201100025C

Contents

List of Abbreviations

Abbreviation	Definition
CLIA	Clinical Laboratory Improvement Amendment(s)
CMS	Centers for Medicare and Medicaid Services
DAAP	Data Access, Analysis, and Publications Committee
DCC	Data and Clinical Coordinating Center
DCR	Data Collection Repository
DT	Destination Therapy
EB	Ethics Board
EQ-5D-3L	EuroQoL Questionnaire
ET	Eastern Time
FDA	United States Food and Drug Administration
FISMA	Federal Information System Management Act
FWA	Federal Wide Assurance
HHS	Health and Human Services
HICN	Health Insurance Claim Number
IRB	Institutional Review Board
IDE	Investigational Device Exemption
INTERMACS®	Interagency Registry for Mechanically Assisted Circulatory Support
KCCQ	Kansas City Cardiomyopathy Questionnaire
MCSD	Mechanical Circulatory Support Device
MDR	Medical Device Report
MOP	Manual of Operations and Procedures
mRS	modified Rankin Scale
NHLBI	National Heart, Lung, and Blood Institute
NIST	National Institution for Standards and Technology
NYHA	New York Heart Association (heart failure classification)
OPC	Objective Performance Criteria
OPTN	Organ Procurement and Transplant Network
OSMB	Observational Study Monitoring Board
PediMACS	INTERMACS® for pediatric patients
PedsQL	Pediatric Quality of Life Inventory
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QoL	Quality of Life
UAB	University of Alabama at Birmingham
UNOS	United Network for Organ Sharing
VADQoL	Ventricular Assist Device Quality of Life instrument
VLAN	Virtual Local Area Networks

Executive Summary and Background

The initial goal of INTERMACS® (the **Inte**ragency **R**egistry of **M**echanically **A**ssisted **C**irculatory **S**upport) was to establish a registry of adult and pediatric patients receiving a mechanical circulatory support device (MCSD) to treat heart failure. With data collection beginning in 2006, INTERMACS® now serves as the national quality improvement system to assess the characteristics, treatments, and outcomes of patients receiving MCSDs approved by the Food and Drug Administration (FDA). INTERMACS® also includes MCSD-implanting hospitals in Canada. These activities are supported by the INTERMACS® data and clinical coordinating center (DCC) under contract to the National Heart, Lung, and Blood Institute (NHLBI).

The purposes of INTERMACS® include:

1. Collecting pertinent and standardized patient demographic, clinical and device-related data elements from participating hospitals to measure and assess the quality of care and outcomes for patients receiving MCSDs;
2. Providing confidential periodic reports to the participating hospitals, government agencies, and industrial partners to improve the quality of care of patients receiving mechanical circulatory support and to evaluate the effectiveness and optimal utilization and performance of these devices;
3. Fostering collaborative research based upon the data collected by means of INTERMACS®; and
4. Serving as a scalable data infrastructure for pre and post market studies.

Broadly, the registry will enable evaluation of best medical practices for advancement of public health with respect to the use of MCSDs for the treatment of heart failure. Data reports from the registry are shared with the NHLBI, FDA and the Centers for Medicare and Medicaid Services (CMS) through a collaboration agreement. The FDA is interested in patient/device outcomes as a way to monitor safety, and CMS through the Joint Commission utilizes INTERMACS® data for site-based quality improvement assessments. Key performance measures are supplied to every participating hospital each quarter, along with a description of the benchmarking methodology used, to facilitate comparison of one institution's outcomes to aggregated national data. Following review of a request for dissemination, data may be shared with basic and clinical researchers, with consideration for privacy regulations. Analytic strategies and data analyses are conducted resulting in publications, presentations, and potentially follow-up investigations.

INTERMACS® collects information pertaining to patients, care providers, hospitals, and devices. Most of these data are collected through chart review by nurse coordinators and physicians at the clinical sites. Standard of care Quality of life (QoL) and functional capacity data are collected for adults and pediatric patients through administration of instruments and tests. Additionally, standard of care neurocognitive data are collected for adults.

INTERMACS® requires that to be a member in good standing, each participating hospital must enter complete data on consecutively implanted patients into the

INTERMACS® database. To facilitate this requirement, INTERMACS® works closely with the member hospitals.

INTERMACS® collects data on all patients receiving FDA-approved MCSDs at all participating sites. Standardized data collection forms and practices are followed utilizing a web-based system. All Privacy Act provisions are followed in handling and storing patient protected health information (PHI).All participating centers are required to obtain Institutional Review Board (IRB)/Ethics Board (EB) approval before collecting registry data.

An NHLBI-appointed independent Observational Study Monitoring Board (OSMB) evaluates the registry on an ongoing basis as to procedures, findings, and adverse events to assure patient safety, confidentiality of records, and registry integrity. The OSMB advises the NHLBI and the INTERMACS® co-investigators when and if changes should be made.

INTERMACS® is currently supported through a Public-Private Partnership, which includes funding from the NHLBI and fees collected from participating hospitals and device companies manufacturing FDA-approved MCSDs.

Collaborating Institutions receiving funding on this project include:

University of Alabama at Birmingham (UAB)
Brigham and Women's Hospital
University of Pittsburgh
Cleveland Clinic
University of Michigan

Registry Description

The INTERMACS® registry is the national quality improvement system designed to advance the understanding and application of mechanical circulatory support in order to improve the duration and quality of life in patients with advanced heart failure. These activities are supported by the INTERMACS® data and clinical coordinating center (located at UAB and hereafter referred to as the DCC) under contract to the NHLBI. INTERMACS® functions as a partnership between the NHLBI, FDA, CMS, participating hospitals, and industry with the intent of generating outcome standards for current clinical device application, providing a platform for the introduction of new technology, and acting as a vehicle for the evaluation of patient-device interactions.

Registry Organization

A university-based DCC (UAB) is responsible for administrative support, data collection and management, site activation and monitoring, data analysis and reporting, as well as registry coordination. Oversight includes an Executive Committee comprised of NHLBI staff and nationally-recognized investigators in advanced heart failure and MCSDs. A detailed description of the registry organization, its structure, and the various

committees responsible for ensuring the integrity of INTERMACS® can be found in the Manual of Operations and Procedures (MOP).

A. INTERMACS – Adults

A.1.0 Registry Design

A.1.1 Patient Eligibility

Scope

The scope of INTERMACS® for adults encompasses those patients receiving durable MCSDs approved by the FDA for whom discharge from the hospital is feasible. There is no exclusion for gender, race, or ethnicity.

Screening

Each patient who receives an MCSD at an institution will be screened according to the eligibility criteria listed below. For patients who do not meet the inclusion criteria, the following information will be recorded on the screening log: gender, race, age decade, brand of the implanted device (left or right side of the heart), date of implant, patient in an MCSD clinical trial, and death should it occur within 2 days of implant. This basic information is necessary to assess completeness of patient capture and possible bias in the registry. No further information will be collected on patients who do not meet the inclusion criteria.

Inclusion Criteria

All patients ≥19 years of age who receive an FDA-approved durable MCSD* implanted at an INTERMACS®-activated hospital. (NOTE: Patients implanted before the hospital activation date are not eligible for participation in INTERMACS®.)

*Refer to MOP Appendix K for the FDA-approved Adult Device Brands List.

Exclusion Criteria

1) Patients who receive a durable MCSD, which is ***not*** FDA-approved.

2) Patients who are <19 years of age.

3) Patients who are incarcerated persons (prisoners).

Follow-up

All patients will be followed as long as an MCSD is in place. If a patient has an MCSD removed and is not transplanted, then the patient will be followed for 1 year. Vital

status, including transplantation and survival, will be determined during this year. If a patient transfers his/her care to another hospital, the patient is deactivated at the implanting hospital at the time of transfer and is re-activated at a new center provided the new center is an INTERMACS®-participating center. The patient transfer process can be found in the MOP, Section 4.4.

If a patient has an MCSD removed and is transplanted, then the patient is no longer followed in INTERMACS®.At that time, the patient becomes part of the **Organ Procurement and Transplant Network (**OPTN) transplant database and will be followed by that database. A patient undergoing transplantation more than 1 year after MCSD explantation with no re-implant will be followed in INTERMACS® for the first year after explant to determine if they have undergone transplantation or died. If the patient undergoes a transplant, then he/she will be followed through the OPTN database at the time of transplantation.

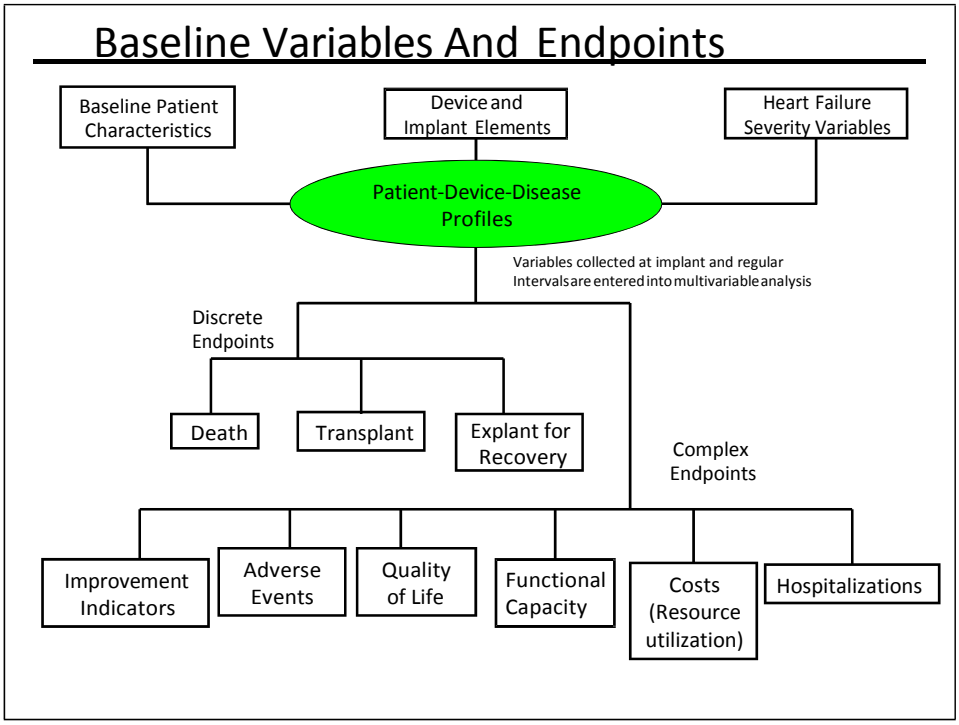
A.1.2 Design

While INTERMACS® was intended to be primarily a prospective registry when it was first established, in actuality the data are collected retrospectively from existing medical records or concurrently in the normal course of treatment on patients who meet the eligibility criteria. Additional standard of care evaluations and contact with the patient outside of the index hospitalization are required for this registry. Specifically, post implant follow up data are collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that for up to 1 year after the device is explanted. Physical examination and functional capacity testing is a routine portion of the care for these patients; the interview consists of survey questions from the EuroQOL (EQ-5D-3L), Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Trail Making Neurocognitive Test, Part B assessment. These interviews are described below in Section A.4.4.

A.1.3 Additional Datasets

With cooperation between industry and INTERMACS®, patients who were part of FDA device approval studies may be moved into INTERMACS®. The process for acquiring these data is developed on a case-by-case basis.

A.1.4 Major End Points



INTERMACS® provides critical and contemporary data on patient outcomes, with additional insight into risk factors and patient-related indices. Death, transplant, and explant for recovery are the major discrete endpoints recorded, to provide the most fundamental outcome statistics.

Information about re-hospitalizations is vital to address the integrated endpoint of days alive out of hospital, which is particularly relevant for the patient population with advanced heart failure receiving ventricular assist devices, as re-hospitalizations are common but not of the same hierarchical importance as death. In addition, the number of in-hospital days is closely tracked as the major resource utilized, after the initial implant. Any subsequent surgery or implants are also noted in addition to the in-hospital days. Specific attention is devoted to capturing this parameter in order to provide a relative estimate of cost.

The complex endpoints that include the patient's functional capacity and QoL are also critical to the evaluation of current MCSD therapy, for which improvements in both survival and function have been compelling. These indices become increasingly important as patient survival improves. When comparing device therapy among various devices, estimates of quality-adjusted survival and cost-effectiveness require quantification of quality and estimates of cost based on resource utilization, as discussed above.

Defining and recording adverse events are important data collected within the Registry. Definitions of adverse events within the registry are fluid and reflect changing clinical practices and device characteristics. The incidence and prevalence of adverse events

are made within the context of device type, management practices, patient co-morbidities, timing of implantation, surgical experience and technique; all are based on uniform adverse event definitions. For each major adverse event (device malfunction, bleeding, infection, neurological, and death), additional variables must be included which potentially allow a determination of whether an adverse event most likely resulted from device design failure or malfunction (**device-related),** patient co-morbid conditions (**patient-related)**, or errors in patient management (e.g., inadequate anti-coagulation) **(management-related)***.*

A.2.0 Site Eligibility and Enrollment

Section A.2.0 contains the steps for determining eligibility and enrollment for each institution. Steps A.2.1 through A.2.7 must be completed to become an active participant in INTERMACS®.

A.2.1 Eligibility

Any medical center in the United States and Canada that has an active MCSD program is eligible to participate in INTERMACS®. In addition, the program must provide **personnel and facilities to record and transmit data.**

A.2.2 Registration

INTERMACS® registration must be completed online at: https://www.intermacs.org/enrollment. The steps necessary for INTERMACS® membership are outlined in detail in the MOP.

1. The medical center is registered by completing the online **Hospital Information** form.
2. The **Personnel Contact Information** form, including staff roles, must also be completed.

In order to complete the registration process, the Center must assign the following roles to qualified personnel:

- **Local Principal Investigator** (PI), responsible for oversight of data submissions and registry compliance
- **Site Administrator**, to act as “point person” for data related inquiries, receipt of reports and audit coordination

A.2.3 IRB/EB Approval

In preparation of materials for IRB/EB review and approval, participating sites will use the INTERMACS® protocol, which is a two-part registry – INTERMACS®- Adults and INTERMACS® - Pediatrics/pediMACS. The hospital must submit the INTERMACS® protocol and supporting documentation (e.g., request for waiver of consent) to the IRB/EB for approval. The guidelines and supporting documents for the medical center's submission of an application to participate in INTERMACS® are located in the MOP. If the IRB/EB approves the application for participation in this registry, documentation of that decision along with the Federal Wide Assurance Number (FWA) and current Clinical Laboratory Improvement Amendments (CLIA) documentation must be submitted to INTERMACS® before a site can be activated. IRB/EB approval documents are submitted to the DCC on a yearly basis. INTERMACS® will send annual reminders to the participating centers at least 30 days prior to expiration of IRB/EB approval. Lapse in local IRB/EB coverage will result in immediate suspension, including data entry capability.

The facility is responsible for obtaining and maintaining all IRB/EB documentation. Documentation of IRB/EB status is subject to INTERMACS® audit.

A.2.4 Agreements and Fees

The Business Associate Agreement and Participation Agreement are provided in the MOP, Appendix D. These agreements are between the local hospital and INTERMACS®. They contain the center's and INTERMACS®'s responsibilities. The signed agreements must be submitted to INTERMACS®.

Each site must pay a required participation fee prior to activation. INTERMACS® is structured to provide value to the hospitals for this fee. For example, INTERMACS®:

- completes and submits Medical Device Reports (MDRs)specific to MCSDs to the FDA in accordance with 21 CFR 803.10 on behalf of each hospital,
- submits 21 CFR 803.10-required reports to device manufacturers for each hospital,
- provides quarterly quality assurance reports to each participating hospital,
- provides datasets for quality improvement purposes to participating hospitals upon request,
- creates patient specific chronological history of the major clinical events after implant, and
- encourages local physicians and coordinators to participate in the administration and activities within the registry.

A.2.5 Financial Disclosure and Conflict of Interest

Site personnel participating in INTERMACS® must complete a financial disclosure and conflict of interest form. The form is provided in the MOP, Appendix E. The form must

be printed, signed, and submitted to INTERMACS® before a site can be activated and must be updated on an annual basis.

A.2.6 Privacy Awareness Training

All staff members are required to complete Privacy Awareness training provided by their local site. If training is not available locally, then the NIH's Privacy Awareness Training (http://irtsectraining.nih.gov/PAC/0501000.aspx) may be substituted.

Copies of the Privacy Awareness Training certification must be submitted to INTERMACS® before a site can be activated, and training will be updated per local IRB/EB policy.

A.2.7 Registry-specific Training

At least one INTERMACS® staff member at the institution must complete the INTERMACS® training process, which requires participation in a live web-based data entry training session. The DCC will schedule the training once the site has completed steps A.2.1 through A.2.6.

A.2.8 Activation

After completing steps A.2.1 through A.2.7, site personnel will be notified of their activation (i.e., access to read or enter data in the INTERMACS® web-based data application). This notification will consist of a secure e-mail that will contain the individual's user name and password.

A.2.9 Annual Re-Certification

To MAINTAIN CERTIFICATION, a site must:

- Maintain and provide INTERMACS® with the annual IRB/EB approval and current FWA Number documentation,
- Provide current CLIA documentation,
- Provide annual participation fee,
- Maintain annual Conflict of Interest disclosure,
- Maintain Privacy Awareness Training, and
- Comply with **data submission requirements** outlined in this protocol and further detailed in the MOP.

A.3.0 Patient Safety

A.3.1 Risks and Benefits

Risks

There is no added procedural risk to patients through involvement in INTERMACS®. No risk or procedures beyond those required for routine care will be imposed. The data collected for this Registry are from medical chart abstraction. The only exception is the concurrent collection of limited functional capacity data, QoL data via patient interviews, and neurocognitive data. The interviews and tests are standard of care for heart failure patients receiving MCSDs and are not considered greater than minimal risk.

There is always the risk of loss of confidentiality. However, safeguards, policies and procedures are in place to keep PHI in each registry record confidential as required under the Information Security clauses of the Federal Acquisition Regulations. All registry information will be sent through a highly secure website to the INTERMACS® database. All INTERMACS® employees have passed background checks for government clearance to handle PHI. PHI is not available to anyone outside of INTERMACS®, unless required by law (e.g., to ensure safety). No published or unpublished report or visual or speaking presentation about the registry will include any material that will identify a patient in this registry.

Benefits

There is no direct benefit to the heart failure patients who participate in this registry. However, future heart failure patients may benefit from the knowledge gained through this registry.

A.3.2 Informed Consent Process

INTERMACS® will not require additional consent other than the routine consent that is required for the MCSD surgical procedure. This is an observational data registry. In general, information will be retrieved from existing medical records. Minimal testing and contact with the patient outside of the index hospitalization is required for follow-up interviews and physical examination. Physical examination, functional capacity testing, and interviews are considered standard of care for these patients. The interview will consist of questions from QoL instruments and neurocognitive assessment. **No data beyond the data gathered in the course of routine care will be collected for this registry.**

Patients will be provided with a summary statement describing the registry when completing the routine MCSD surgical consent form (refer to Attachment 1).

Participating sites will follow their local IRB/EB policies. Refer to the MOP, Section 5.2, for additional guidance and Appendix C for supplementary documents that may be required by local IRBs/EBs.

A.3.3 Registry Interventions

No additional interventions will be performed outside of the standard course of care.

A.3.4 Patient Recruitment, Costs, and Compensation

No recruitment specific to this registry will take place at any participating center. Recruitment is not applicable since the registry obtains information through a review of existing medical records.

There are no costs or compensation to the patient or patient's family for participation in this registry.

A.4.0 Data Collection

A.4.1 Assignment of Registry Identification Number

A registry identification number will be assigned to each patient prior to entry of data into INTERMACS®. This identification number will be used as the primary patient identifier between the site, INTERMACS®, MCSD manufacturers, and government agencies.

A.4.2 Web-based Data Entry and Systems Security

All data will be entered through the INTERMACS® web-based data entry system. Complete documentation is contained at the data entry website (www.intermacs.org), and the INTERMACS® Site User's Guide can be found in the MOP, Appendix M. The forms should be filled out as soon as possible after the implant and at the time of follow-up events (within specific time windows). The data are divided into forms that correspond to the clinical time course of the patient.

Minimal PHI [e.g., patient's name; date of birth; last 5 digits of social security number, or in the event that a social security number is not available, the last 5 digits of the transplant wait list number; health insurance claim number (HICN), if applicable; device serial number; implant date; and optionally the hospital medical records number], are entered into the INTERMACS® database. This information allows the patient to be linked to the United Network for Organ Sharing (UNOS) transplant database should he/she undergo transplantation, to CMS databases, and to FDA medical device safety databases.

INTERMACS® complies with all national patient privacy regulations. All registry data shall be maintained on secure servers with appropriate safeguards in place. All INTERMACS® employees have passed federal Health and Human Services (HHS) background checks for government clearance. Access to the production databases containing PHI is on a need-to-know basis only. INTERMACS® personnel will

periodically review all activities involving PHI to ensure that such safeguards, including standard procedures, are being followed. Any breach of confidentiality and immediate mitigation steps will be reported to the appropriate oversight bodies (e.g., the NHLBI and the IRB/EB according to their institutional policies) and these immediate mitigation steps will be implemented.

The database and web servers reside in an environment that provides multiple layers of physical and systems security. INTERMACS® is compliant with the Security Act of 2002 and the Federal Information System Management Act (FISMA). Regular audits take place to verify compliance.

Systems security is deployed with third party software and hardware, strict adherence to policy, and regular verification and auditing. The servers that host the web applications are built within the Windows 2008R2 framework. They follow Microsoft's best security practices and group policy recommendations from the National Institute for Standards and Technology (NIST).

Each server is monitored 24x7 for both intrusion and vulnerabilities by an integrated third-party software package. Microsoft System Center Configuration Manager 2012R2 is used for deploying any system patches in accordance with security policies. The network is also protected by an automated anti-virus retrieval and deployment system.

Firewall software assists in preventing hacking, virus, and other security risks from the outside. Internally, the servers reside on a segmented part of the Virtual Local Area Networks (VLAN) that is isolated from the rest of the network protecting it from any adverse internal forces. All server access requires use of second level authentication for administrative access. Regular internal and external penetration and vulnerability tests are conducted by third-party contractors to determine any weaknesses in the network.

A.4.3 Clinical Data

Clinical data are collected by medical chart review.

Patient Demographics and Profile Prior to Implant

The standard demographics of age, gender, and patient-described ethnicity will be recorded. Heart failure etiology, duration, and standard prognostic factors will be collected along with hemodynamic and echocardiographic parameters closest to the time of implant. Co-morbidities will be included, as they may affect the likelihood of success of MCSD therapy. A novel aspect of the data elements is the establishment of seven INTERMACS® patient profiles that describe the clinical severity at the time of implant, aid in risk stratification, improve patient selection, and refine the definition of future trial populations (refer to MOP Appendix O for a description of the seven patient profiles). INTERMACS® also seeks to transition away from the artificial distinction of bridge versus destination intent, by recording, before and at intervals after implant, the relative likelihood and limiting factors for transplant eligibility.

Device and Operative Details (implant)

The critical elements which characterize the device and describe the implant procedure will be recorded within 1 week after implant.

Designated Interval Follow-up

A major feature of the database design is the provision of information both by event and by designated time interval. In this way, the crucial events are submitted in real time, but there are also regularly scheduled checkpoints at which any important events during follow-up intervals will be captured. The first routine post-operative follow-up will be at 1 week. The remaining interval follow-up visits occur at 1 month, 3 months, 6 months, and every 6 months for the life of the device. If the device is explanted without transplantation, the patient will be followed for 1 year following explant for the major events of death or transplantation.

The follow-up forms will all include information on vital signs and volume status, medications, basic laboratory values, and device settings. New York Heart Association (NYHA) functional status will be noted. At each time interval beginning with the 3-month follow-up, re-assessment will be documented regarding current intent as bridge to recovery, transplant, likelihood of eligibility for transplant, or permanent support, with a checklist of considerations relevant to that decision. Echocardiographic information will be included regarding function of both ventricles and atrioventricular valves. Hemodynamic measurement regarding filling pressures, pulmonary pressures, and cardiac output will be included when available.

Adverse Events

Data on specific adverse events will be collected by two mechanisms:
(1) The occurrence of **hemolysis**, **hypertension** and **right heart failure** are considered 'triggered events'. These events are 'triggered' based on the relevant medical data collected at follow-up and re-hospitalization.
(2) Other adverse events (see MOP Appendix A for a complete list) will be identified and collected through routine data acquisition at the specified follow-up intervals or at time of event.

A.4.4 Quality of Life Data

QoL will be measured by the EQ-5D-3L instrument (refer to MOP Appendix F), as well as the KCCQ (refer to MOP Appendix H). It is anticipated that completing these instruments will take the patient approximately 20 minutes. Administering the instrument and entering the data into the registry will require approximately 30 minutes of coordinator time. The QoL instruments are completed pre-implant and post-implant (3 months, 6 months, and every 6 months thereafter for the life of the device).

After implantation, the EQ-5D-3L and KCCQ will be completed as scheduled, whether the patient is hospitalized or at a clinic visit. Missing answers will be queried by the coordinator at the time of form completion. Reasons for not collecting the QoL instruments will be recorded.

A.4.5 Neurocognitive Data

Neurocognitive function will be measured by the Trail Making Neurocognitive Test, Part B (refer to MOP Appendix G). This test of general cognitive function also specifically assesses working memory, visual processing, visuospatial skills, selective and divided attention, and psychomotor coordination. It is anticipated that completing this assessment will take less than 5 minutes of the patient's time. In addition, for patients who experience a neurological event, the modified Rankin Scale (mRS) score is recorded. The mRS will be administered at follow-up visits after a post-implant neurological event.

A.4.6. Functional Capacity Data

Functional capacity measures are collected pre-implantation and within follow-up intervals post implant at 3 months, 6 months, and every 6 months thereafter. Included in these functional capacity measures are: 6 minute walk test, gait speed, and cardiopulmonary exercise indices. Refer to the MOP, Appendix M for all functional capacity measures collected.

A.5.0 Analyses of Registry Data

A.5.1 Introduction

The value of any clinical registry lies in the statistical analyses of the data and the clinical relevance of these analyses. The registry will collect a wide array of patient, device, and follow-up information. This section outlines the general analyses and the statistical methods.

A.5.2 Purposes

- Summarize the characteristics of the patients *who* are receiving MCSDs, *when* (in relation to progression of disease) they are receiving MCSDs, and *why*(bridge to transplant, bridge to decision, bridge to recovery, destination therapy, and rescue therapy), as well as outcomes of the therapy
- Summarize the characteristics of MCSDs that are being implanted
- Describe post-implant adverse events and estimate their time-related distribution
- Determine risk factors (both patient-related and MCSD-related) for post implant events
- Contribute to evidence based management of patients with implanted MCSDs
- Provide device specific analyses to aid in MCSD development

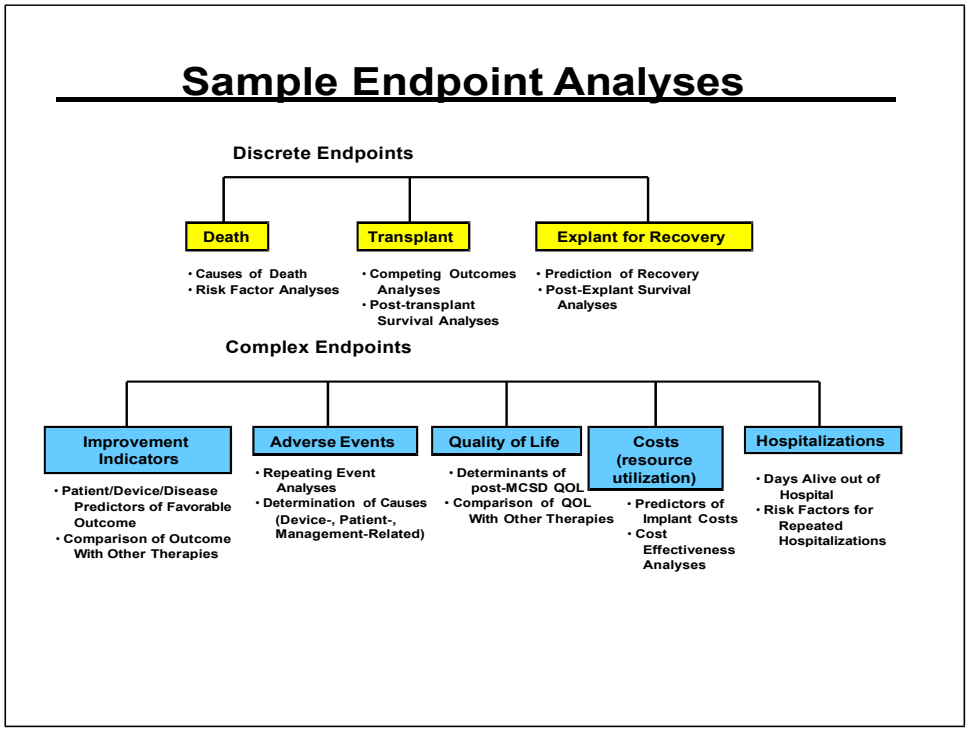
- Evaluate safety and efficacy of MCSD implants
- Determine the time-related costs (resource utilization) of MCSDs and the risk factors associated with increased costs
- Compare the costs (resource utilization) of MCSD therapy to other treatments for advanced heart failure
- Evaluate quality of life pre- and post-MCSD implant
- Compare alternative therapies (MCSD, transplant, medical) for patients with end stage heart failure
- Produce patient-specific predictions of time-related outcomes to aid in clinical decision making and allocation of therapies for advanced heart failure

A.5.3 Patient Profiling

Patients who receive MCSDs will be characterized regarding their demographic data, medical history, and clinical status including descriptors of heart failure, pre-implant laboratory values and pre-implant hemodynamic data.

A.5.4 Primary Endpoints

The discrete endpoints are death, transplant, and explant for recovery. Other endpoints include patient adverse events, re-hospitalization, device related adverse events, change in QoL, costs (resource utilization), functional status and changes in hemodynamic parameters and laboratory values. Each of the endpoints will be analyzed as time related events.



A.5.5 Analytic Methods

Statistical analysis of the MCSD will require a variety of methods including analysis of variance, multiple linear regression, t-tests, chi-square tests of association, correlations, and descriptive statistics. The group of methods generally labeled survival analysis techniques will be the methods most used. In general, survival analysis refers to all methods applicable to time-related events or outcomes. Most of the outcomes that will be documented in the MCSD registry will have time components. For example, time-until-death, time-until-transplant, time-until-infection, time-until-device-malfunction are all events that will have an associated interval post-implant. However, additional analytic methods will be necessary for issues such as costs and QoL.

The Hazard Function

The time-related survival methods will combine more traditional non-parametric or semi-parametric methods with parametric hazard function analysis. Kaplan-Meier non-parametric estimation provides estimates of time-related freedom from an event. While the depiction of these estimates is useful, parametric estimation using hazard models can offer more insight into the timing of an event. The hazard function is the instantaneous (or daily) rate of an event. This function can depict time periods of high risk for an event and can estimate whether the risk is increasing, decreasing or peaking.

Parametric hazard estimation will employ simple to complex hazard models depending on the distribution of the event. Both the parametric survival function and the corresponding hazard function will be displayed to provide a complete description of the event.

Competing Outcomes

Depictions of a single time-related event do not take into account other events. For example, a depiction of death would assume that transplantation does not exist. Patients are censored at time of transplant. If informative censoring does not exist (i.e., if patients are not transplanted due to impending death but instead selected at random for transplant), then the depiction can be thought of as the natural history of mortality after device implant. In reality, this rarely occurs, since patients are usually selected at a given time because of medical necessity. This informative censoring complicates the interpretation of this single event depiction.

Alternatively, one may wish to estimate the simultaneous time-related probability of mutually exclusive events. Competing outcomes estimation allows the time-related probability of actually experiencing each of these events. At any point in time, a patient has either experienced one of the three events or he/she is alive and waiting for one of the events to occur. A probability can be assigned to each of these four possible states and the sum of the four probabilities will be equal to one at each point in time. The non-parametric estimation of these probabilities is an adaptation of the Kaplan-Meier method. In the standard use of the Kaplan-Meier methods, event probabilities are accumulated across time. In competing outcomes analysis, the combined event is

analyzed and then probabilities are accumulated separately according to which event occurred.

Multivariable Risk Factor Analysis

The most common multivariable method for identifying risk factors is Cox proportional hazard regression. This method assumes proportional hazards for different levels of a potential risk factor. The p-value results from testing the null hypothesis that the proportionality parameter is equal to one. The method is often called a semi-parametric technique because it does not require or estimate the form of the underlying parametric hazard. It only requires (assumes) that hazards for different levels of risk factor are proportional across time. This assumption is often incorrect. The magnitude of the effects of the final risk factor model from Cox regression is not easily displayed due to the lack of a specified hazard model. This also prevents a simple, continuous depiction for a specific patient with his unique values of the risk factors.

Consequently, we have pursued a parametric version of survival regression that builds on a framework of hazard functions. The concept is still proportional hazard regression, but the hazard function is estimated and decomposed into additive phases. Each phase is then constructed to be a function of the risk factors. The model of risk is then totally specified as a mathematical equation that can be “drawn” for any time period and any specified set of risk factors. This system also allows the identification of risk factors that impact different phases of risk.

Predictions

This ability to produce time-related expected survival for a specific patient (with his/her specific risk profile) is one of the strengths of parametric hazard analysis. The predictions are a function of the estimated hazard functions and the identified risk factors. The hazard function and risk factors are derived from the actual data.

Repeated Events (Adverse Events)

Most adverse events can occur more than once. For example, once a patient experiences an infection episode, he/she remains at risk for another episode. These repeating events require methods that are an expansion of the previously described methods.

First Events Analysis

The first occurrence of an event can be analyzed exactly as a terminating event such as death (see previous discussion). While this analysis does not appear very useful clinically for events that recur frequently, it does provide a time-related estimate of the proportion of patients who have remained free of the event.

The FDA Approach

Most of the medical device guidance documents from the FDA for analyzing events that can happen multiple times specify a specific analytic approach. First, a calculation of the percent of patients who experience at least one event during the first 30 days post implant is presented. Next, a linearized rate is calculated for events that occur after the first 30 days. Summing all of the post 30-day events and dividing by the total patient follow-up intervals after 30 days calculates this. The rate is usually multiplied by 100. The calculation is then the number of events that are estimated to occur in 100 months of follow-up. This is a useful calculation *but* it assumes a constant hazard rate across time. For many events, for example device malfunction, this may be an incorrect assumption.

Parametric Hazard Approach

The parametric hazard methods can be applied to multiple events. This allows the estimation of the shape of the underlying hazard and specific statistical testing for an increasing hazard or decreasing hazard or peaking hazard. This approach will allow detection of device related events whose occurrence rate is rising to unacceptable levels at some point in time.

Cumulative Event Estimation

Another useful display of repeated events depicts the accumulation of events that will occur, on the average, for a single patient. This method of depiction illustrates the rate of accumulating events as a function of time.

Modulated Renewal

Another method of analyzing repeated events is the modulated renewal method. In this approach, the unit of observation is each episode of an event. A patient is tracked from time of device implant until he/she experiences his/her first event. The patient is then re-entered into the analysis, with a new starting time and is tracked until his/her next episode. This process is continued for event re-occurrences. The analysis of this data structure is then performed in the parametric hazard domain and is particularly amenable to risk factor analysis that incorporates the event history of a patient when predicting his/her next occurrence.

Each of these methods for repeated adverse events contributes to the understanding of the time course of the event and the related risk factors. The methods will be particularly helpful in calculating the time related risk of device related adverse events.

A.5.6 Planned Analyses

Patient Characteristics

Patients who receive MCSDs will be summarized regarding their demographic data, medical history, and clinical status including descriptors of heart failure, pre-implant laboratory values and pre-implant hemodynamic data. Novel aspects of the registry include the seven INTERMACS® patient profiles that describe the clinical severity of disease at the time of implantation. The categorization of patients into INTERMACS® profiles will facilitate risk stratification for outcomes and advance the selection of patients who have sufficient severity of disease to warrant MCSDs. An additional component is the ongoing evaluation of patients with regard to evolving eligibility for transplantation and explantation in order to better understand the factors leading to transplantation or explantation. Subsequent tracking of patients will allow the decision process to be continually refined for better outcomes.

Data will be summarized by frequencies, measures of central tendencies, measures of dispersion, cumulative distribution functions, graphical displays, cross tabulations and correlations.

MCSD Characteristics

MCSDs that are implanted will be summarized according to their physical and physiologic characteristics (e.g., size, weight, pulsatile or continuous flow, range of flow rates, etc.) and their initial flow settings. The Industry Committee, which consists of representatives from each participating device manufacturer, will assist in selecting variables for analysis that are relevant to emerging technologies.

Survival

The analysis of post-implant survival will utilize all of the methods outlined in the previous section. The emphasis will be on the time-related pattern of overall death and each of the causes of death. The investigation of risk factors, especially those risk factors which can be modified for a patient, will be a priority.

Transplantation

Time to transplant will be analyzed similarly to survival. In addition to the examination of patient risk factors and device factors which predict survival to transplant, the prolonged implant duration in many “bridge” patients awaiting a suitable heart donor will facilitate analyses that give insight into longer-term “destination” therapy.

Adverse Events: Patient- and Device-Related

A key feature of the entire registry analysis will be the examination of the time course and risk factors for all of the possible patient-related and device-related adverse events. The methods listed under Analytic Methods will be used to evaluate these interactions.

Competing Outcomes

The major events that "compete" for a patient are death, transplantation and explant for recovery. The simultaneous time-related estimation of the probability of these events will be depicted. Separate risk factor analyses will be performed for each individual outcome event.

Quality of Life (QoL)

Repeated measures methodology will test for changes in pre-implant and follow-up interval measures. Multiple linear regression will be used to identify patient groups who have the least and the greatest improvement in QoL. Analyses will focus on the impact of MCSD therapy on QoL indicators, comparisons with QoL after transplant and other therapies for advanced heart failure (through published studies or parallel patient cohorts).

Costs

Multivariate statistical techniques, most often regression analysis, are used to investigate relationships among the variables of interest. Analytical emphasis will be on resource utilization.

Analysis of MCSD Efficacy

In all of the analyses for death, transplant, recovery, adverse events, QoL, and costs, the effects of device characteristics (pulsatile flow, size, etc.) on outcome will be investigated. A major focus of INTERMACS® will be the identification of the strengths and weaknesses of the different devices for specific patient subsets and facilitation of the evolution of MCSD technology.

Evaluation of Hospital Outcomes

Each hospital that contributes data to INTERMACS® will be periodically evaluated for their outcomes. The basis of the evaluation will be risk-adjusted comparisons using the results of the multivariable analyses. The observed survival, depicted by a Kaplan-Meier, is also represented. The observed and expected deaths will then be statistically compared where the patient-specific risk factors and length of follow-up are explicitly incorporated into the comparison.

A.6.0 Reports

INTERMACS® will provide summaries to the following entities:

A.6.1 National Heart, Lung and Blood Institute (NHLBI)

Quarterly Statistical, Semi-annual and the Final Report will include an overall summary of INTERMACS® patient characteristics, implant characteristics, hospital enrollment/activation, adverse events and significant outcomes. Manuscripts will be provided for review within 30 days of publication.

A.6.2 Centers for Medicare and Medicaid Services (CMS)

CMS will receive copies of the NHLBI Quarterly Statistical Reports and a CMS-specific Quarterly Statistical Report.

A.6.3 Food and Drug Administration (FDA)

In accordance with 21 CFR 803.19, sites participating in INTERMACS® (referred to as "user facilities" by the FDA) are exempt from the normal requirements in 21 CFR 803.30 for adverse events reported to INTERMACS®. Instead, INTERMACS® will make the appropriate reports to both the manufacturer and FDA on behalf of the site.

Also in accordance with 21 CFR 803.19, device manufacturers participating in INTERMACS® are exempt from the 30 calendar day reporting requirement in 21 CFR 803.50. Instead, any adverse event reported to or received from INTERMACS®, which meets the threshold for reporting in accordance with the MDR Regulation(21 CFR 803.50) is due to FDA no later than *90 calendar days* after the device manufacturer becomes aware of the event. FDA is granting this additional time so that the device manufacturer can do a thorough and complete analysis of the event and include their findings in the MDR report. All other FDA requirements concerning adverse event or complaint handling, investigation, retention, etc. remain unchanged.

INTERMACS® (on behalf of participating sites/user facilities) and manufacturer reporting requirements are based on the exemptions granted by FDA under 21 CFR 803.19 as shown in the table below. Refer to Section 7.3 of the MOP for additional information.

Summary of MDR Reporting Requirement Under 21 CFR 803.19 Exemptions

REPORTER	WHAT TO REPORT	WHERE	WHEN
Manufacturer*	Deaths, Serious Injuries, Malfunction	FDA	Within *90 calendar days* of becoming aware
	Events that require remedial action to prevent an unreasonable risk of substantial harm	FDA	Within 5 working days of becoming aware
INTERMACS® (on behalf of User Facility)*	Deaths	FDA and Manufacturer	Within 10 working days
	Serious Injury	Manufacturer	Within 10 working days
Voluntary	Any type of event	FDA	Any time

*Per 21 CFR 803.19 Single Reporter and Time Variance Exemptions granted by FDA.

INTERMACS® also provides reports to FDA, as requested, that inform:

1) Objective performance criteria (OPC): Randomized trials of Investigational Device Exemption (IDE) MCSDs may not be practical. The FDA will often allow single arm studies where the results from an investigational medical device are compared with OPC. These OPC are derived from the literature or existing databases. INTERMACS® can be used to generate OPC for the major safety endpoints after MCSD implant.
2) Unexpected risks: INTERMACS® can be analyzed to identify MCSDs with unexpected risks for major safety events.

A.6.4 Industry

In addition to the reports discussed in Section A.6.3, quarterly reports will be provided to each MCSD manufacturer summarizing data entered into INTERMACS®. A specific manufacturer will not receive identifiable information about any MCSDs from other manufacturers. The reports will provide statistical summaries of patient demographics

and clinical characteristics at the time of implant. Adverse event rates, including death and explant, will be calculated.

A.6.5 Individual Sites

Quarterly reports will be provided to each participating site. A specific site will not receive identified information about any other site. These reports have two components. The first component is a quality assurance report that summarizes and compares the results at the individual hospital with the entire INTERMACS® registry. These benchmark comparisons allow the hospital to evaluate the patients and outcomes as compared to the aggregate data of the other participating hospitals. The second component focuses on patient-specific data and the quality of the site data. A dashboard is available for sites to view a patient's chronological history of major implant-related events. The MDRs that have been submitted to the FDA, as well as reports provided to the device manufacturer, on behalf of the site are also included in this report.

A.6.6 Observational Study Monitoring Board (OSMB)

The OSMB will receive copies of the NHLBI reports along with any specific reports that they may require.

A.7.0 Quality Assurance

A.7.1 Data Quality

INTERMACS® will examine data quality and provide periodic data reports. The focus will be on completeness of periodic follow-up and also on identifying impossible or improbable combinations of variables. Questionable data points will be verified.

A.7.2 Data Monitoring and Checks for Inconsistencies

The database will be subject to analytical quality assurance (QA) audits following the completion of data entry. Depending on the types of discrepancies identified, INTERMACS® will contact participating centers to resolve these issues. Resolution may be accomplished via telephone contact, e-mail and/or hard copy mailings. The discrepancies and their resolutions will be tracked for future reference and further review. Based on a review of the results of the analytical QA processes, additional items may be incorporated into the QA process at the Executive Committee's request. Participating centers will be able to review and modify previously submitted data at any time. Additionally, summary screens and reports of patients and devices reported, current patient status, most recent reported event and other data will be available to the member institutions to assist the institution in assessing the completeness of reporting. INTERMACS® will employ established procedures to maintain the quality of INTERMACS® data. These procedures will be used in completion of all data entry

activities associated with the MCSD and can be found in the MOP. Written internal DCC procedures will be maintained and will provide step-by-step directions for auditing processes involved in data entry, maintenance, and review to ensure data quality and completeness.

A.7.3 Medical Event Review

Medical event review is a function of both the DCC and the Medical Event Review Committee. The Committee will:

- provide guidance on summarizing and evaluating the quality of the adverse event data;
- provide strategies for electronically identifying duplicate events and questionable events;
- focus on the review and categorization of device malfunction; and
- provide guidance to the nurse monitors for auditing the correct capture of adverse events. All data identified as questionable are resolved via direct interactions between the nurse monitors and the local hospital.

A.8.0 Centers: Requirements, Training, Assistance and Audits

A.8.1 Requirements for Centers

Each participating hospital shall: (1) provide dated proof of initial and annual IRB/EB approval, proof of FWA Number, proof of Privacy Awareness Training for the principal site staff (to include the Principal Investigator, Co-Investigators and Site Coordinator), and proof of CLIA documentation;(2) have at least one person complete training;(3) enter complete baseline, implant and follow-up data on all patients; (4) submit to regular and “for cause” data audits; and (5) correct identified errors in a timely fashion.

A.8.2 Training for Centers

Web-based interactive software will be used to conduct training on an ongoing basis. This is a secure, subscription-based service that allows for meetings and their related documents to be conducted in a virtual electronic environment. Participants are allowed to view the trainer’s desktop. Attendees follow along as the trainer shows step-by-step instructions.

A.8.3 Assistance to Centers

A comprehensive **INTERMACS® Site User’s Guide** will provide step-by-step instructions for using the system and will include definitions for all fields collected in the system. The Site User’s Guide will also identify main processes in the application and explain standard procedures for data collection. Refer to MOP Appendix M.

The DCC is available to provide assistance with data collection and entry, regulatory questions, data requests and analyses, and technical support. Refer to the MOP Appendix L for a complete list of contacts.

A.8.4 Audit Process for Centers

The audit process for all participating INTERMACS® sites involves interactions in the form of an on-site visit or a review of the documents submitted to the DCC and discussion with site staff via telephone and/or WebEx (remote review). Sites are notified up to 60 days prior to a routine on-site audit. Audited data include key data fields, as determined by INTERMACS®.

The INTERMACS® monitor contacts the site by phone for a pre-audit review approximately 2 weeks before the scheduled audit. During the call, the monitor reviews site specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explants inconsistencies and any other noted discrepancies. The sites are requested to make corrections and to provide redacted source documentation (as needed for remote review), prior to the actual audit.

During the audit, monitors will review data accuracy of web-based data submissions and information contained in source documents as well as participant performance and progress. “For Cause” audit visits will be made as indicated by the Hospital Standards Committee, which reviews hospital performance and recommends actions to reestablish compliance. All audit results will be reported to the Executive Committee.

The audit process will identify member institutions that perform poorly in data submission compliance. The INTERMACS® monitors, in collaboration with the Hospital Standards Committee, will identify and work with these underperformers to identify reasons for low rates of data collection and/or tardy data submission. These institutions will be retrained on proper data collection methods with the goal of identifying and overcoming obstacles to submission.

B. INTERMACS–Pediatrics (pediMACS)

The INTERMACS® registry for pediatric patients is also referred to as "pediMACS", which is used throughout the remainder of this protocol, to differentiate it from INTERMACS®– Adults.

B.1.0 Registry Design

B.1.1 Patient Eligibility

Scope

The scope of pediMACS encompasses pediatric patients receiving durable or temporary MCSDs approved by the FDA. There is no exclusion for gender, race, or ethnicity.

Screening

Each patient who receives an MCSD at a pediMACS institution will be screened according to the eligibility criteria listed below. For patients who do not meet the inclusion criteria, the following information will be recorded on the screening log: gender, race, age decade, brand of the implanted device (left or right side of the heart), date of implant, patient in an MCSD clinical trial, and death should it occur within 2 days of implant. This basic information is necessary to assess completeness of patient capture and possible bias in the registry. No further information will be collected on patients who do not meet the eligibility criteria.

Inclusion Criteria

All patients <19 years of age who receive an FDA-approved durable or temporary MCSD* implanted at an INTERMACS®-activated hospital. (NOTE: Patients implanted before the hospital activation date are not eligible for participation in pediMACS.)

* Refer to MOP Appendix K for the FDA-approved Pediatric Device Brands List.

Exclusion Criteria

1) Patients who receive an MCSD, which is ***not*** FDA-approved.

2) Patients who are ≥19 years of age.

3) Patients who are incarcerated persons (prisoners).

Once a patient is entered as a pediatric patient, the patient will remain in pediatric status until the implanted device is explanted.

Follow-up

All patients will be followed as long as an MCSD is in place. If a patient has an MCSD removed and is not transplanted, then the patient will be followed for 1 year. Vital status, including transplantation and survival, will be determined during this year. If a patient transfers his/her care to another hospital then the patient is deactivated at the implanting hospital at the time of transfer and is re-activated at the new center provided the new center is a pediMACS-participating center. The patient transfer process can be found in the MOP, Section 4.4.

If a patient has an MCSD removed and is transplanted, then the patient is no longer followed in pediMACS**.** At that time, the patient becomes part of the OPTN transplant database and will be followed by that database. A patient undergoing transplantation more than 1 year after explantation due to recovery will be followed in pediMACS for the first year after explant to determine if they have undergone transplantation or died. If the patient undergoes a transplant, then he/she will be followed through the OPTN database at the time of transplantation.

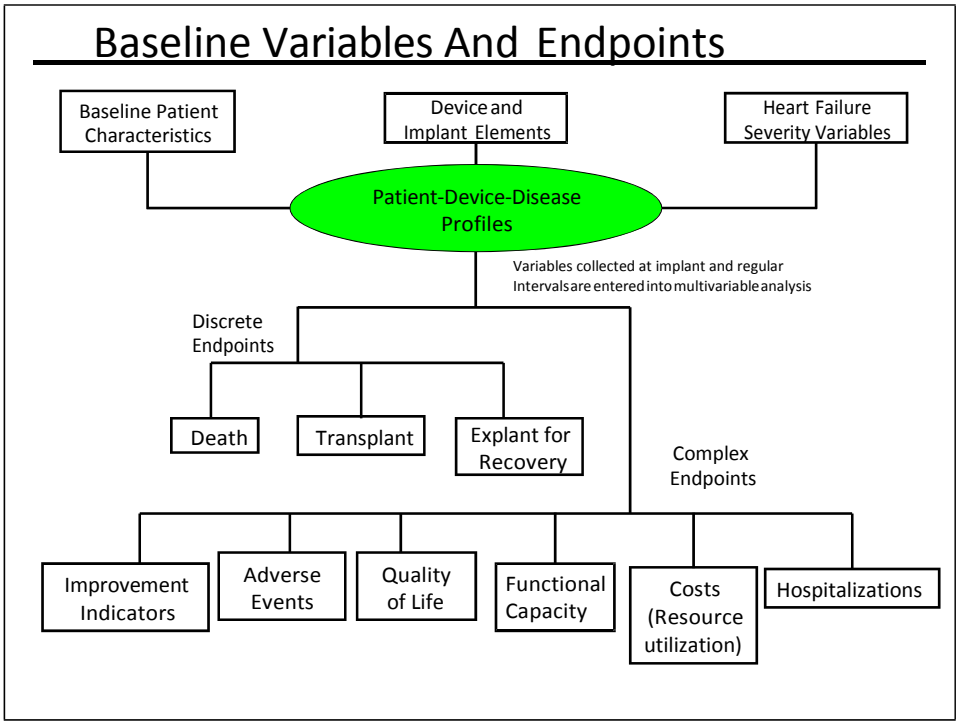
B.1.2 Design

PediMACS data are collected retrospectively from existing medical records or concurrently in the normal course of treatment on patients who meet the eligibility criteria. Additional standard of care evaluations and contact with the patient outside of the index hospitalization is required for this registry. Specifically, post implant follow-up data is collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that for up to 1 year after the device is explanted. Physical examination is a routine portion of the care for these patients. The interview will consist of survey questions from the Pediatric Quality of Life Inventory (PedsQL) and Ventricular Assist Device Quality of Life (VADQoL) instruments described in Section B.4.4.

B.1.3 Additional Datasets

With cooperation between industry and pediMACS, patients who were part of FDA device approval studies may be moved into pediMACS. The process for acquiring these data is developed on a case-by-case basis.

B.1.4 Major End Points



PediMACS provides critical and contemporary data on patient outcomes, with additional insight into risk factors and patient-related indices. Death, transplant, and explant for recovery are the major discrete endpoints recorded, to provide the most fundamental outcome statistics.

Information about re-hospitalizations is vital to address the integrated endpoint of days alive out of hospital, as re-hospitalizations are common but not of the same hierarchical importance as death. In addition, the number of in-hospital days will be closely tracked as the major resource utilized, after the initial implant. Any subsequent surgery or implants are also noted in addition to the in-hospital days. Specific attention will be devoted to capturing this parameter in order to provide a relative estimate of cost.

The complex endpoints that include the patient's functional capacity and QoL are also critical to the evaluation of current MCSD therapy, for which improvements in both survival and function have been compelling. These indices become increasingly important as patient survival improves. When comparing device therapy among various devices, estimates of quality-adjusted survival and cost-effectiveness require quantification of quality and estimates of cost based on resource utilization, as discussed above.

Defining and recording adverse events are important data collected within this registry. Definitions of adverse events within the registry are fluid and reflect changing clinical practices and device characteristics. The incidence and prevalence of adverse events are made within the context of device type, management practices, patient co-

morbidities, timing of implantation, surgical experience and technique; all based on uniform adverse event definitions. For each major adverse event (device malfunction, bleeding, infection, neurological, death), additional variables must be included which potentially allow a determination of whether an adverse event most likely resulted from device design failure or malfunction (**device-related),** patient co-morbid conditions (**patient-related)**, or errors in patient management (e.g., inadequate anti-coagulation) **(management-related)**.

B.2.0 Site Eligibility and Enrollment

Section B.2.0 contains the steps for determining eligibility and enrollment for each institution. Steps B.2.1 through B.2.7 must be completed to become an active participant in pediMACS.

B.2.1 Eligibility

Any medical center in the United States and Canada that has an active pediatric MCSD program is eligible to participate in pediMACS. In addition, the program must provide **personnel and facilities to record and transmit data**

B.2.2 Registration

Registration must be completed online at: https://www.intermacs.org/enrollment. The steps necessary for pediMACS membership are outlined below and in described detail in the MOP.

1. The medical center is registered by completing the online **Hospital Information** form.
2. The **Personnel Contact Information** form, including staff roles, must also be completed.

In order to complete the registration process, the Center must assign the following roles to qualified personnel:

- **Local PI**, responsible for oversight of data submissions and registry compliance
- **Site Administrator**, to act as “point person” for data related inquiries, receipt of reports and audit coordination

B.2.3 IRB/EB Approval

In preparation of materials for IRB/EB review and approval, participating sites will use the INTERMACS® protocol, which is a two-part registry – INTERMACS® - Adults and INTERMACS® - Pediatrics/pediMACS. The hospital must submit the protocol and

supporting documentation (e.g., request for waiver of consent) to their IRB/EB for approval. The guidelines for the medical center's submission of an application to participate in pediMACS are located in the MOP. If the IRB/EB approves the application for participation in this registry, documentation of that decision along with the FWA Number and current CLIA documentation must be submitted to pediMACS before a site can be activated. IRB/EB approval documents are to be submitted to the DCC on a yearly basis. PediMACS will send annual reminders to the participating centers at least 30 days prior to expiration of IRB/EB approval. Lapse in local IRB/EB coverage will result in immediate suspension, including data entry capability.

The facility is responsible for obtaining and maintaining all IRB/EB documentation. Documentation of IRB/EB status is subject to pediMACS audit.

B.2.4 Agreements and Fees

The Business Associate Agreement and Participation Agreement are provided in MOP Appendix D. These agreements are between the local hospital and pediMACS. They contain the center's and pediMACS's responsibilities. The signed agreements must be submitted to pediMACS.

The annual fee for participation in pediMACS is waived for the first year. After the first year, each site must pay a required participation fee. PediMACS is structured to provide value to the hospitals for this fee. For example, pediMACS:

- provides quarterly quality assurance reports to each participating hospital,
- provides site-specific datasets to aid in quality improvement at that hospital on an as requested basis,
- creates patient specific chronologic history of the major clinical events after implant, and
- encourages local physicians and coordinators to participate in the administration and activities within the registry.

B.2.5 Financial Disclosure and Conflict of Interest

Site personnel participating in pediMACS must complete a financial disclosure and conflict of interest form. The form is provided in MOP Appendix E**.** The form must be printed, signed, and submitted to pediMACS before a site can be activated and must be updated on an annual basis.

B.2.6 Privacy Awareness Training

All staff members are required to complete Privacy Awareness Training provided by their local site. If training is not available locally, then the NIH's Privacy Awareness Training (http://irtsectraining.nih.gov/PAC/0501000.aspx) may be substituted.

Copies of the Privacy Awareness Training certification must be submitted to pediMACS before a site can be activated, and training will be updated per local IRB/EB policy.

B.2.7 Registry-specific Training

At least one pediMACS staff member at the institution must complete the pediMACS training process, which requires participation in a live web-based data entry training session. The DCC will schedule the training once the site has completed steps B.2.1 through B.2.6.

B.2.8 Activation

After completing steps B.2.1 through B.2.7, site personnel will be notified of their activation (i.e., able to read or enter data in the pediMACS web-based data application). This notification will consist of a secure e-mail that will contain the individual's username and password.

B.2.9 Annual Re-Certification

To MAINTAIN CERTIFICATION, a site must:

- Maintain and provide pediMACS with the annual IRB/EB approval and current FWA Number documentation,
- Provide current CLIA documentation,
- Provide annual participation fee,
- Maintain annual Conflict of Interest,
- Maintain Privacy Awareness Training, and
- Comply with **data submission requirements** outlined in this protocol and further detailed in the MOP.

B.3.0 Patient Safety

B.3.1 Risks and Benefits

Risks

There is no added procedural risk to patients through involvement in pediMACS. No risk or procedures beyond those required for routine care will be imposed. The data collected for this Registry are from medical chart abstraction. The only exception is the concurrent collection of limited functional capacity data and QoL data via patient/parent interviews. The interviews and tests are standard of care for pediatric heart failure patients receiving MCSDs and are not considered greater than minimal risk.

There is always the risk of loss of confidentiality. However, safeguards, policies and procedures are in place to keep the PHI in each registry record confidential as required under the Information Security clauses of the Federal Acquisition Regulations. All registry information will be sent through a highly secure website to the pediMACS

database. All employees involved in the pediMACS registry have passed background checks for government clearance to handle PHI. PHI is not available to anyone outside of pediMACS, unless required by law (e.g., to ensure safety). No published or unpublished report or visual or speaking presentation about the registry will include any material that will identify a patient in this registry.

Benefits

There is no direct benefit to the pediatric heart failure patients who participate in this registry. However, future patients with heart failure may benefit from the knowledge gained through this registry.

B.3.2 Informed Consent Process

PediMACS will not require additional consent other than the routine consent that is required for the MCSD surgical procedure. This is an observational data registry. In general, information will be retrieved from existing medical records. Minimal testing and contact with the patient/parents outside of the index hospitalization is required for follow-up interviews and physical examination. Physical examination, functional capacity testing, and interviews are considered standard of care for these patients. The interview will consist of questions from QoL instruments for patients and their legally authorized representatives. **No data beyond the data gathered in the course of routine care will be collected for this registry**.

Patients/parents will be provided with a summary statement describing the registry when completing the routine MCSD surgical consent form (refer to Attachment 2).

Participating sites will follow their local IRB/EB policies. Refer to the MOP, Section 5.2, for additional guidance and MOP Appendix C for supplementary documents that may be required by local IRBs/EBs.

B.3.3 Registry Interventions

No additional interventions will be performed outside of the standard course of care.

B.3.4 Patient Recruitment, Costs, and Compensation

No recruitment specific to this registry will take place at any participating center. Recruitment is not applicable since the registry obtains information through a review of existing medical records.

There are no costs or compensation to the patient or patient's family for participation in this registry.

B.4.0 Data Collection

B.4.1 Assignment of Registry Identification Number

A registry identification number will be assigned to each patient prior to entry of their data into pediMACS. This identification number will be used as the primary patient identifier between the site, pediMACS, MCSD manufacturers, and government agencies.

B.4.2 Web-based Data Entry and Systems Security

All data will be entered through the pediMACS web-based data entry system. Complete documentation is contained at the data entry website (www.intermacs.org), and the pediMACS Site User's Guide can be found in the MOP, Appendix N. The forms should be filled out as soon as possible after the implant and at the time of follow-up events (within specific time windows). The data are divided into forms that correspond to the clinical time course of the patient.

Minimal PHI (e.g., patient's name; date of birth; last 5 digits of social security number, or in the event that a social security number has not yet been issued, the last 5 digits of the transplant wait list number; device serial number; implant date; and optionally, the hospital medical records number), are entered into the pediMACS database. This information allows the patient to be linked to the UNOS transplant database should he/she undergo transplantation and to FDA medical device safety databases.

PediMACS complies with all national patient privacy regulations. All registry data shall be maintained on secure servers with appropriate safeguards in place. All pediMACS employees have passed federal HHS background checks for government clearance. Access to the production databases containing PHI is on a need-to-know basis only. PediMACS personnel will periodically review all activities involving PHI to ensure that such safeguards, including standard procedures, are being followed. Any breach of confidentiality and immediate mitigation steps will be reported to the appropriate oversight bodies (e.g., the NHLBI and IRB/EB according to their institutional policies), and these immediate mitigation steps will be implemented.

The database and web servers reside in an environment that provides multiple layers of physical and systems security. PediMACS is compliant with the Security Act of 2002 and FISMA. Regular audits take place to verify compliance.

Systems security is deployed with third party software and hardware, strict adherence to policy, and regular verification and auditing. The servers that host the web applications are built within the Windows 2008R2 framework. They follow Microsoft's best security practices and group policy recommendations from the NIST.

Each server is monitored 24x7 for both intrusion and vulnerabilities by an integrated third-party software package. Microsoft System Center Configuration Manager 2012R2

is used for deploying any system patches in accordance with security policies. The network is also protected by an automated anti-virus retrieval and deployment system.

Firewall software prevents hacking, virus, and other security risks from the outside. Internally, the servers reside on a segmented part of the VLAN that is isolated from the rest of the network protecting it from any adverse internal forces. All server access requires use of second level authentication for administrative access. Regular internal and external penetration and vulnerability tests are conducted by third-party contractors to determine any weaknesses in the network.

B.4.3 Clinical Data

Clinical data are collected by medical chart review.

Patient Demographics and Profile Prior to Implant

The standard demographics of age, gender, and patient-described ethnicity will be recorded. Heart failure etiology, duration, and standard prognostic factors will be collected along with hemodynamic and echocardiographic parameters closest to the time of implant. Co-morbidities will be included, as they may affect the likelihood of success of MCSD therapy. Data elements include seven patient profiles that describe the clinical severity at the time of implant, aid in risk stratification, improve patient selection, and refine the definition of future trial populations (refer to MOP Appendix O for a description of the seven patient profiles). PediMACS also records, pre and post implant (at defined intervals), the relative likelihood and limiting factors for transplant eligibility.

Device and Operative Details (implant)

The critical elements which characterize the device and describe the implant procedure will be recorded within 1 week after implant.

Designated Interval Follow-up

A major feature of the database design is the provision of information both by event and by designated time interval. In this way, the crucial events are submitted in real time, but there are also regularly scheduled checkpoints at which any important events during follow-up intervals will be captured. The first routine post-operative follow-up will be at 1 week. If the patient is in the hospital at 1 month post implant then the 1 month follow-up form will be completed. The remaining interval follow-up visits occur at 3 months, 6 months, and every 6 months for the life of the device. If the device is explanted without transplantation, the patient will be followed for 1 year following explant for the major events of death or transplantation.

The follow-up forms will all include information on vital signs and volume status, medications, basic laboratory values, and device settings. NYHA functional status and

Ross Class (for children<2 years of age) will be noted. At each time interval beginning with the 3-month follow-up, re-assessment will be documented regarding current intent as bridge to recovery, transplant, likelihood of eligibility for transplant, or permanent support, with a checklist of considerations relevant to that decision. Echocardiographic information will be included regarding function of both ventricles and atrioventricular valves. Hemodynamic measurement regarding filling pressures, pulmonary pressures, and cardiac output will be included when available.

Adverse Events

Data on specific adverse events will be collected by two mechanisms:

(1) The occurrence of **hemolysis**, **hypertension**, and **right heart failure*** are considered 'triggered events'. These events are 'triggered' based on the relevant medical data collected at follow-up and re-hospitalization.
(2) Other adverse events (see MOP Appendix A for a complete list) will be identified and collected through routine data acquisition at the specified follow-up intervals or at time of event.

*Refer to the pediMACS User's Guide, Appendix N, for reporting of right heart failure.

B.4.4 Quality of Life Data

QoL will be measured by the PedsQL and VADQoL instruments (refer to MOP Appendix F). It is anticipated that completing these instruments will take the patient/parent 20 minutes per instrument. Administering the instrument and entering the data into the registry will require approximately 30 minutes of coordinator time. The QoL instruments will be completed pre-implant and post-implant (3 months, 6 months, and every 6 months thereafter for the life of the device).

After implantation, the PedsQL and VADQoL instruments will be completed as scheduled, whether the patient is hospitalized or at a clinic visit. Missing answers will be queried by the coordinator at the time of form completion. Reasons for not collecting the QoL instruments will be recorded.

B.4.5 Functional Capacity Data

Functional capacity measures for pediatric patients ages 10-18 years are collected pre-implantation and within follow-up intervals post implant at 3 months, 6 months, and every 6 months thereafter. Included in these functional capacity measures are: 6 minute walk test, gait speed, and cardiopulmonary exercise indices.

For pediatric patients <10 years of age, general functional capacity data is collected pre-implant, implant discharge, and at follow-up intervals (i.e., 3 and 6 months and every 6 months thereafter for as long as the MCSD is in place). These data include the child's functional capacity (e.g., sedated, paralyzed, intubated, ambulating), primary nutrition,

and if the patient has had non-medically required excursions off the unit (collected at 1 week and 1 month post implant and at implant discharge).

B.5.0 Analyses of Registry Data

B.5.1 Introduction

The value of any clinical registry lies in the statistical analyses of the data and the clinical relevance of these analyses. The registry will collect a wide array of patient, device, and follow-up information. This section outlines the general analyses and the statistical methods.

B.5.2 Purposes

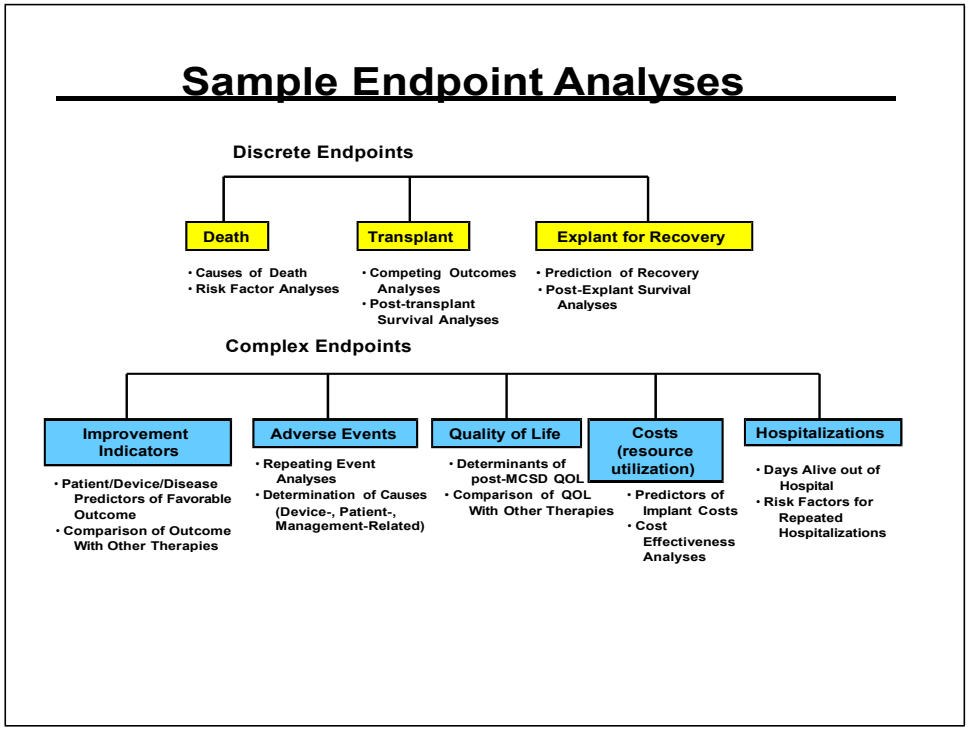
- Summarize the characteristics of the patients *who* are receiving MCSDs, *when* (in relation to progression of disease) they are receiving MCSDs and *why* (bridge to transplant, bridge to recovery, rescue therapy, or bridge to decision), and outcomes of the therapy
- Summarize the characteristics of MCSDs that are being implanted
- Describe post-implant adverse events and estimate their time-related distribution
- Determine risk factors (both patient related and MCSD related) for post-implant events
- Contribute to evidence based management of patients with implanted MCSDs
- Provide device specific analyses to aid in MCSD development
- Evaluate safety and efficacy of MCSD implants
- Determine the time-related costs (resource utilization) of MCSDs and the risk factors associated with increased costs
- Compare the costs (resource utilization), of MCSD therapy to other treatments for pediatric patients with advanced heart failure
- Evaluate QoL pre- and post-MCSD implant
- Compare alternative therapies (MCSD, transplant, medical) for pediatric patients with advanced heart failure
- Produce patient-specific predictions of time-related outcomes to aid in clinical decision making and allocation of therapies for pediatric patients with advanced heart failure

B.5.3 Patient Profiling

Patients who receive MCSDs will be characterized regarding their demographic data, medical history, and clinical status including descriptors of heart failure, pre-implant laboratory values and pre-implant hemodynamic data.

B.5.4 Primary Endpoints

The discrete endpoints are death, transplant, and explant for recovery. Other endpoints include patient adverse events, re-hospitalization, device related adverse events, change in QoL, costs (resource utilization), functional status, and changes in hemodynamic parameters and laboratory values. Each of the endpoints will be analyzed as time related events.



B.5.5 Analytic Methods

Statistical analysis of the MCSD will require a variety of methods including analysis of variance, multiple linear regression, t-tests, chi-square tests of association, correlations, and descriptive statistics. The group of methods generally labeled survival analysis techniques will be the methods most used. In general, survival analysis refers to all methods applicable to time-related events or outcomes. Most of the outcomes that will be documented in the MCSD registry will have time components. For example, time-until-death, time-until-transplant, time-until-infection, time-until-device-malfunction are all events that will have an associated interval post implant. However, additional analytic methods will be necessary for issues such as costs and QoL.

The Hazard Function

The time-related survival methods will combine more traditional non-parametric or semi-parametric methods with parametric hazard function analysis. Kaplan-Meier non-parametric estimation provides estimates of time-related freedom from an event. While the depiction of these estimates is useful, parametric estimation using hazard models

can offer more insight into the timing of an event. The hazard function is the instantaneous (or daily) rate of an event. This function can depict time periods of high risk for an event and can estimate whether the risk is increasing, decreasing or peaking.

Parametric hazard estimation will employ simple to complex hazard models depending on the distribution of the event. Both the parametric survival function and the corresponding hazard function will be displayed to provide a complete description of the event.

Competing Outcomes

Depictions of a single time-related event do not take into account other events. For example, a depiction of death would assume that transplantation does not exist. Patients are censored at time of transplant. If informative censoring does not exist (i.e., if patients are not transplanted due to impending death but instead selected at random for transplant), then the depiction can be thought of as the natural history of mortality after device implant. In reality, this rarely occurs, since patients are usually selected at a given time because of medical necessity. This informative censoring complicates the interpretation of this single event depiction.

Alternatively, one may wish to estimate the simultaneous time-related probability of mutually exclusive events. Competing outcomes estimation allows the time related probability of actually experiencing each of these events. At any point in time, a patient has either experienced one of the three events or he/she is alive and waiting for one of the events to occur. A probability can be assigned to each of these four possible states and the sum of the four probabilities will be equal to one at each point in time. The non-parametric estimation of these probabilities is an adaptation of the Kaplan-Meier method. In the standard use of the Kaplan-Meier methods, event probabilities are accumulated across time. In competing outcomes analysis, the combined event is analyzed and then probabilities are accumulated separately according to which event occurred.

Multivariable Risk Factor Analysis

The most common multivariable method for identifying risk factors is Cox proportional hazard regression. This method assumes proportional hazards for different levels of a potential risk factor. The p-value results from testing the null hypothesis that the proportionality parameter is equal to one. The method is often called a semi-parametric technique because it does not require or estimate the form of the underlying parametric hazard. It only requires (assumes) that hazards for different levels of risk factor are proportional across time. This assumption is often incorrect. The magnitude of the effects of the final risk factor model from Cox regression is not easily displayed due to the lack of a specified hazard model. This also prevents a simple, continuous depiction for a specific patient with his unique values of the risk factors.

Consequently, we have pursued a parametric version of survival regression that builds on a framework of hazard functions. The concept is still proportional hazard regression,

but the hazard function is estimated and decomposed into additive phases. Each phase is then constructed to be a function of the risk factors. The model of risk is then totally specified as a mathematical equation that can be "drawn" for any time period and any specified set of risk factors. This system also allows the identification of risk factors that impact different phases of risk.

Predictions

This ability to produce time-related expected survival for a specific patient (with his/her specific risk profile) is one of the strengths of parametric hazard analysis. The predictions are a function of the estimated hazard functions and the identified risk factors. The hazard function and risk factors are derived from the actual data.

Repeated Events (Adverse Events)

Most adverse events can occur more than once. For example, once a patient experiences an infection episode, he/she remains at risk for another episode. These repeating events require methods that are an expansion of the previously described methods.

First Events Analysis

The first occurrence of an event can be analyzed exactly as a terminating event such as death (see previous discussion). While this analysis does not appear very useful clinically for events that recur frequently, it does provide a time-related estimate of the proportion of patients who have remained free of the event.

The FDA Approach

Most of the medical device guidance documents from the FDA for analyzing events that can happen multiple times specify a specific analytic approach. First, a calculation of the percent of patients who experience at least one event during the first 30 days post implant is presented. Next, a linearized rate is calculated for events that occur after the first 30 days. Summing all of the post 30-day events and dividing by the total patient follow-up intervals after 30 days calculates this. The rate is usually multiplied by 100. The calculation is then the number of events that are estimated to occur in 100 months of follow-up. This is a useful calculation *but* it assumes a constant hazard rate across time. For many events, for example device malfunction, this may be an incorrect assumption.

Parametric Hazard Approach

The parametric hazard methods can be applied to multiple events. This allows the estimation of the shape of the underlying hazard and specific statistical testing for an increasing hazard or decreasing hazard or peaking hazard. This approach will allow detection of device related events whose occurrence rate is rising to unacceptable levels at some point in time.

Cumulative Event Estimation

Another useful display of repeated events depicts the accumulation of events that will occur, on the average, for a single patient. This method of depiction illustrates the rate of accumulating events as a function of time.

Modulated Renewal

Another method of analyzing repeated events is the modulated renewal method. In this approach, the unit of observation is each episode of an event. A patient is tracked from time of device implant until he/she experiences his/her first event. The patient's then re- entered into the analysis, with a new starting time and is tracked until his/her next episode. This process is continued for event re-occurrences. The analysis of this data structure is then performed in the parametric hazard domain and is particularly amenable to risk factor analysis that incorporates the event history of a patient when predicting his/her next occurrence.

Each of these methods for repeated adverse events contributes to the understanding of the time course of the event and the related risk factors. The methods will be particularly helpful in calculating the time related risk of device related adverse events.

B.5.6 Planned Analyses

Patient Characteristics

Pediatric patients who receive either durable or temporary MCSDs will be summarized regarding their demographic data, medical history, and clinical status including descriptors of heart failure, pre-implant laboratory values and pre-implant hemodynamic data. Novel aspects of the registry include the seven patient profiles that describe the clinical severity of disease at the time of implantation. The categorization of pediatric patients into these profiles will facilitate risk stratification for outcomes and advance the selection of pediatric patients who have sufficient severity of disease to warrant MCSDs. An additional component is the ongoing evaluation of pediatric patients with regard to evolving eligibility for transplantation and explantation in order to better understand the factors leading to transplantation or explantation. Subsequent tracking of patients will allow the decision process to be continually refined for better outcomes.

Data will be summarized by frequencies, measures of central tendencies, measures of dispersion, cumulative distribution functions, graphical displays, cross tabulations and correlations.

MCSD Characteristics

MCSDs that are implanted will be summarized according to their physical and physiologic characteristics (e.g., size, weight, pulsatile or continuous flow, range of flow rates, etc.) and their initial flow settings. The Industry Committee, which consists of

representatives from each participating device manufacturer, will assist in selecting variables for analysis that are relevant to emerging technologies.

Survival

The analysis of post implant survival will utilize all of the methods outlined in the previous section. The emphasis will be on the time related pattern of overall death and each of the causes of death. The investigation of risk factors, especially those risk factors which can be modified for a patient, will be a priority.

Transplantation

Time to transplant will be analyzed similarly to survival. In addition to the examination of patient risk factors and device factors which predict survival to transplant, the prolonged implant duration in many "bridge" patients awaiting a suitable heart donor will facilitate analyses that give insight into longer-term "destination" therapy.

Adverse Events: Patient- and Device-Related

A key feature of the entire registry analysis will be the examination of the time course and risk factors for all of the possible patient related and device related adverse events. The methods listed under Analytic Methods will be used to evaluate these interactions.

Competing Outcomes

The major events that "compete" for a patient are death, transplantation and explant for recovery. The simultaneous time-related estimation of the probability of these events will be depicted. Separate risk factor analyses will be performed for each individual outcome event.

Quality of Life (QoL)

Repeated measures methodology will test for changes in pre-implant and follow-up interval measures. Multiple linear regression will be used to identify patient groups who have the least and the greatest improvement in QoL. Analyses will focus on the impact of MCSD therapy on QoL indicators, comparisons with QoL after transplant and other therapies for advanced heart failure (through published studies or parallel patient cohorts).

Costs

Multivariate statistical techniques, most often regression analysis, are used to investigate relationships among the variables of interest. Analytical emphasis will be on resource utilization.

Analysis of MCSD Efficacy

In all of the analyses for death, transplant, recovery, adverse events, QoL, and costs, the effects of device characteristics (pulsatile flow, size, etc.) on outcome will be investigated. A major focus of pediMACS will be the identification of the strengths and weaknesses of the different devices for specific patient subsets and facilitation of the evolution of MCSD technology.

Evaluation of Hospital Outcomes

Each hospital that contributes data to pediMACS will be periodically evaluated for their outcomes. The basis of the evaluation will be risk-adjusted comparisons using the results of the multivariable analyses. The observed survival, depicted by a Kaplan-Meier, is also represented. The observed and expected deaths will then be statistically compared where the patient-specific risk factors and length of follow-up are explicitly incorporated into the comparison.

B.6.0 Reports

INTERMACS will provide summaries to the following entities:

B.6.1 National Heart, Lung and Blood Institute (NHLBI)

Quarterly Statistical, Semi-annual and the Final Report will include an overall summary of INTERMACS® patient characteristics, implant characteristics, hospital enrollment/activation, adverse events and significant outcomes. Manuscripts will be provided for review within 30 days of publication.

B.6.2 Centers for Medicare and Medicaid Services (CMS)

CMS may receive pediMACS-specific reports if requested.

B.6.3 Food and Drug Administration (FDA)

FDA requires “user facilities”, which they define as “a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility”, to report all serious injuries or deaths associated with a medical device to the FDA within 10 working days of their occurrence through an MDR. All sites participating in pediMACS are required to report serious injuries and deaths where the device may have caused or contributed to the event according to 21 CFR 803.10and summarized in the following table. Refer to Section 7.3 of the MOP for additional information.

Summary of MDR Reporting Requirement 21 CFR 803.10

REPORTER	WHAT TO REPORT	WHERE	WHEN
Manufacturer	Deaths, Serious Injuries, Malfunction	FDA	Within 30 calendar days of becoming aware
	Events that require remedial action to prevent an unreasonable risk of substantial harm	FDA	Within 5 working days of becoming aware
User Facility	Deaths	FDA and Manufacturer	Within **10 working days**
	Serious Injury	Manufacturer	Within **10 working days**
Importer	Deaths and Serious Injuries	FDA and Manufacturer	Within 30 calendar days
	Malfunctions	Manufacturer	Within 30 calendar days
Voluntary	Any type of event	FDA	Any time

PediMACS also provides reports to FDA, as requested, that inform:

1) OPC: Randomized trials of IDE MCSDs may not be practical. The FDA will often allow single arm studies where the results from an investigational medical device are compared with OPC. These OPC are derived from the literature or existing databases. PediMACS can be used to generate OPC for the major safety endpoints after MCSD implant.
2) Unexpected risks: PediMACS can be analyzed to identify MCSDs with unexpected risks for major safety events.

B.6.4 Industry

In addition to the reports discussed in Section B.6.3, quarterly reports will be provided to each MCSD manufacturer summarizing data entered into pediMACS. A specific manufacturer will not receive identifiable information about any MCSDs from other manufacturers. The reports will provide statistical summaries of patient demographics and clinical characteristics at the time of implant. Adverse event rates, including death and explant, will be calculated.

B.6.5 Individual Sites

Quarterly reports will be provided to each participating site. A specific site will not receive identified information about any other site. These reports have two components. The first component is a quality assurance report that summarizes and compares the results at the individual hospital with the entire pediMACS registry. These benchmark comparisons allow the hospital to evaluate the patients and outcomes as compared to the aggregate data of the other participating hospitals. The second component focuses on patient-specific data and the quality of the site data. A dashboard is available for sites to view a patient's chronological history of major implant-related events. To assist participating pediatric implanting centers in meeting their post-market reporting requirements, PediMACS will provide them with:

- Deaths: completed MDRs to submit to the FDA and the device manufacturer(s)
- Serious Injuries: reports to submit to the device manufacturer(s)

B.6.6 Observational Study Monitoring Board (OSMB)

The OSMB will receive copies of the NHLBI reports along with any specific reports that they may require.

B.7.0 Quality Assurance

B.7.1 Data Quality

PediMACS will examine data quality and provide periodic data reports. The focus will be on completeness of periodic follow-up and also on identifying impossible or improbable combinations of variables. Questionable data points will be verified.

B.7.2 Data Monitoring and Checks for Inconsistencies

The database will be subject to analytical QA audits following the completion of data entry. Depending on the types of discrepancies identified, pediMACS will contact participating centers to resolve these issues. Resolution may be accomplished via telephone contact, e-mail and/or hard copy mailings. The discrepancies and their resolutions will be tracked for future reference and further review. Based on a review of

the results of the analytical QA processes, additional items may be incorporated into the QA process at the Executive Committee's request. Participating centers will be able to review and modify previously submitted data at any time. Additionally, summary screens and reports of patients and devices reported, current patient status, most recent reported event and other data will be available to the member institutions to assist the institution in assessing the completeness of reporting. PediMACS will employ established procedures to maintain the quality of pediMACS data. These procedures will be used in completion of all data entry activities associated with the MCSD and can be found in the MOP. Written internal DCC procedures will be maintained and will provide step-by-step directions for auditing processes involved in data entry, maintenance, and review to ensure data quality and completeness.

B.7.3 Medical Event Review

Medical event review is a function of both the DCC and the Medical Events Review Committee. The Committee will:

- provide guidance on summarizing and evaluating the quality of the adverse event data.
- provide strategies for electronically identifying duplicate events and questionable events.
- focus on the review and categorization of device malfunction.
- provide guidance to the nurse monitors for auditing the correct capture of adverse events. All data identified as questionable are resolved via direct interactions between the nurse monitors and the local hospital.

B.8.0 Centers: Requirements, Training, Assistance and Audits

B.8.1 Requirements for Centers

Each participating hospital shall: (1) provide dated proof of initial and annual IRB/EB approval, proof of FWA Number, proof of Privacy Awareness Training for the principal site staff (to include the Principal Investigator, Co-Investigators and Site Coordinator), and proof of CLIA documentation;(2) have at least one person complete training;(3) enter complete baseline, implant and follow-up data on all patients; (4) submit to regular and "for cause" data audits; and (5) correct identified errors in a timely fashion.

B.8.2 Training for Centers

Web-based interactive software will be used to conduct training on an ongoing basis. This is a secure, subscription-based service that allows for meetings and their related documents to be conducted in a virtual electronic environment. Participants are allowed to view the trainer's desktop. Attendees follow along as the trainer shows step-by-step instructions.

B.8.3 Assistance to Centers

A comprehensive **pediMACS Site User's Guide** will provide step-by-step instructions for using the system and will include definitions for all fields collected in the system. The Site User's Guide will also identify main processes in the application and explain standard procedures for data collection. Refer to MOP Appendix N.

The DCC is available to provide assistance with data collection and entry, regulatory questions, data requests and analyses, and technical support. Refer to the MOP, Appendix L, for a complete list of contacts.

B.8.4 Audit Process for Centers

The audit process for all participating pediMACS sites involves interactions in the form of an on-site visit or a review of the documents submitted to the DCC and discussion with site staff via telephone and/or WebEx (remote review). Sites are notified up to 60 days prior to a routine on-site audit. Audited data include key data fields, as determined by pediMACS.

The pediMACS monitor contacts the site by phone for a pre-audit review approximately 2 weeks before the scheduled audit. During the call, the monitor reviews site specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explants inconsistencies and any other noted discrepancies. The sites are requested to make corrections and to provide redacted source documentation (as needed for remote review) prior to the actual audit.

During the audit, nurse monitors will monitor data accuracy of web-based data submissions and information contained in source documents as well as participant performance and progress. "For Cause" audit visits will be made as indicated by the Hospital Standards Committee, which reviews hospital performance and recommends actions to reestablish compliance. All audit results will be reported to the Executive Committee.

The audit process will identify member institutions that perform poorly in data submission compliance. The pediMACS monitors, in collaboration with the Hospital Standards Committee, will identify and work with these underperformers to identify reasons for low rates of data collection and/or tardy data submission. These institutions will be retrained on proper data collection methods with the goal of identifying and overcoming obstacles to submission.

Attachment 1: Patient Information for Adults

Adult Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®): Patient Information

As a patient receiving a durable, Food and Drug Administration (FDA)-approved mechanical circulatory support device (MCSD) at *[insert institution name or acronym]*, we plan to collect information about your initial device implant as well as your follow-up visits. Information that includes your medical history, quality of life questionnaires, and information about the health care costs will be entered into the **Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®)** database. INTERMACS® is the national quality improvement system used to collect and evaluate the characteristics, treatments, and outcomes of MCSD patients. This means that we will use the information entered into INTERMACS® to learn more about MCSDs and heart failure, which may lead to improvements in the devices and how we treat heart failure patients in the future. We may also use this information in the future to gain a better understanding of quality of life, medical practices, and other factors associated with MCSD implants. While you will not directly benefit from this registry, future heart failure patients may benefit from the knowledge gained through this registry.

INTERMACS® data are used by the FDA to assist them in overseeing the safety and effectiveness of MCSDs and other agencies to measure the quality of health care at MCSD-implanting hospitals. In addition, INTERMACS® works closely with the National Heart, Lung, and Blood Institute of the National Institutes of Health, MCSD-implanting hospitals, device manufacturers, medical teams and scientists to evaluate the best medical practices to improve the treatment of advanced heart failure.

Limited protected health information (e.g., your name; date of birth; last 5 digits of your social security number, or in the event that a social security number is not available, the last 5 digits of the transplant wait list number; health insurance claim number, if applicable; device serial number; implant date; and hospital medical record number) is collected by INTERMACS®. This information will allow your data to be linked to the United Network for Organ Sharing database if you receive a heart transplant, to the Centers for Medicare and Medicaid Services databases for coverage purposes, to cost databases, to FDA databases and to the manufacturer of your MCSD for medical device reporting. Because INTERMACS® complies with all national patient privacy regulations, all registry data are transmitted from *[insert institution name or acronym]* to the INTERMACS® database through a secure website and maintained on secure servers with safeguards in place. All Privacy Act provisions are followed in handling and storing patient data, and all INTERMACS® employees have passed background checks for Federal Government clearance to handle protected health information. Protected health information is **not** available to any employee outside of INTERMACS®, unless required by law (e.g., to ensure your safety), and an INTERMACS®-assigned identification number is used to help maintain your confidentiality. No published or unpublished report or visual or speaking presentation about the registry will include any material that will identify you in this registry.

If other MCSD studies begin that use INTERMACS® data, the hospital may contact you to see if you are interested in participating. If at that time, you are interested in participating in the study, you will be given information about the study and asked to sign an informed consent.

To learn more about INTERMACS®, visit the INTERMACS® website at http://www.uab.edu/intermacs/ or www.clinicaltrials.gov.

If you have any questions about INTERMACS®, please contact your surgeon or surgical nurse at *[insert pager and/or telephone numbers]*.

Attachment 2: Patient Information for Children

Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (pediMACS): Patient Information

Because you/your child is receiving a Food and Drug Administration (FDA)-approved durable or temporary mechanical circulatory support device (MCSD) at *[insert institution name or acronym]*, we plan to collect information about your/your child's initial device implant as well as your/your child's follow-up visits. Information that includes your/your child's medical history, quality of life questionnaires, and information about the health care costs will be entered into the **Pediatric Interagency Registry for Mechanically Assisted Circulatory Support for Pediatric Patients (pediMACS)** database. PediMACS is the national quality improvement system used to collect and evaluate the characteristics, treatments, and outcomes of pediatric MCSD patients. This means that we will use the information entered into pediMACS to learn more about MCSDs and heart failure, which may lead to improvements in the devices and how we treat heart failure patients in the future. We may also use this information in the future to gain a better understanding of quality of life, medical practices, and other factors associated with MCSD implants. While you/your child will not directly benefit from this registry, future pediatric heart failure patients may benefit from the knowledge gained through this registry.

PediMACS data are used by the FDA to assist them in overseeing the safety and effectiveness of MCSDs and other agencies to measure the quality of health care at MCSD-implanting hospitals. In addition, pediMACS works closely with the National Heart, Lung, and Blood Institute of the National Institutes of Health, MCSD-implanting hospitals, device manufacturers, medical teams and scientists to evaluate the best medical practices to improve treatment of advanced heart failure.

Limited protected health information (e.g., your/your child's name; date of birth; last 5 digits of your/your child's social security number, or in the event that a social security number has not yet been issued for your child, the last 5 digits of the transplant wait list number; device serial number; implant date; and hospital medical record number) is collected by pediMACS. This information will allow your/your child's data to be linked to the United Network for Organ Sharing database if you/your child receive a heart transplant and to FDA databases, to cost databases, and to the manufacturer of your/your child's MCSD for medical device reporting. Because pediMACS complies with all national patient privacy regulations, all registry data are transmitted from *[insert institution name or acronym]* to the pediMACS database through a secure website and maintained on secure servers with safeguards in place. All Privacy Act provisions are followed in handling and storing patient data, and all pediMACS employees have passed background checks for Federal Government clearance to handle protected health information. Protected health information is **not** available to any employee outside of pediMACS, unless required by law (e.g., to ensure your/your child's safety), and a pediMACS-assigned identification number is used to help maintain your confidentiality. No

published or unpublished report or visual or speaking presentation about the registry will include any material that will identify you/your child in this registry.

If other MCSD studies begin that use PediMACS data, the hospital may contact you to see if you/your child are interested in participating. If at that time, you/your child are interested in participating in the study, you/your child will be given information about the study and asked to sign an Informed consent/assent.

To learn more about pediMACS, visit the pediMACS website at http://www.uab.edu/intermacs/pedimacs or www.clinicaltrials.gov.

If you/your child have any questions about pediMACS, please contact your surgeon or surgical nurse at *[insert pager and/or telephone numbers]*.

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16.4 Appendix D – INTERMACS® 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;2014).

The most current version of Adverse Event definitions will be used in the study.

INTERMACS Adverse Event Definitions: Adult and Pediatric patients

Approved by the INTERMACS Executive Committee: May 15, 2013

This document contains the following adverse event definitions:

- Hemolysis
- Right Heart Failure
- Device Malfunction
- Major Bleeding
- Major Infection
- Neurological Dysfunction
- Cardiac Arrhythmias
- Pericardial Fluid Collection
- Myocardial Infarction
- Psychiatric Episode
- Respiratory Failure
- Venous Thromboembolism
- Wound Dehiscence
- Arterial Non-CNS Thromboembolism
- Other SAE
- Hepatic Dysfunction
- Hypertension
  - *Adult definition*
  - *Pediatric definition*
- Renal Dysfunction

Additional Notes:

Medical Device Reports:

INTERMACS reports MDRs (FDA mandated Medical Device Reports) on behalf of hospitals that participate in INTERMACS. Each device malfunction adverse event that is reported to the registry generates a reportable MDR. This is the only mechanism for an MDR. Other events (hemolysis, death, etc.) may lead to an MDR only if the event is associated with a device malfunction and the device malfunction is reported to the registry.

Triggered Adverse Events:

The adverse events, hypertension, hemolysis and right heart failure are not directly entered into the registry. Each of these events is a result of direct clinical measurements. The clinical information collected at the specific follow-up information is used to identify these adverse events. For example, blood pressure is collected at each follow-up visit. If the recorded mean blood pressure is above 110, then the event “hypertension” is internally identified. This strategy allows future adjustment of the “cut points” for an adverse event depending on the evolving clinical understanding of the event.

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.

Pericardial 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.

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