Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®)

# Protocol

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# 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.

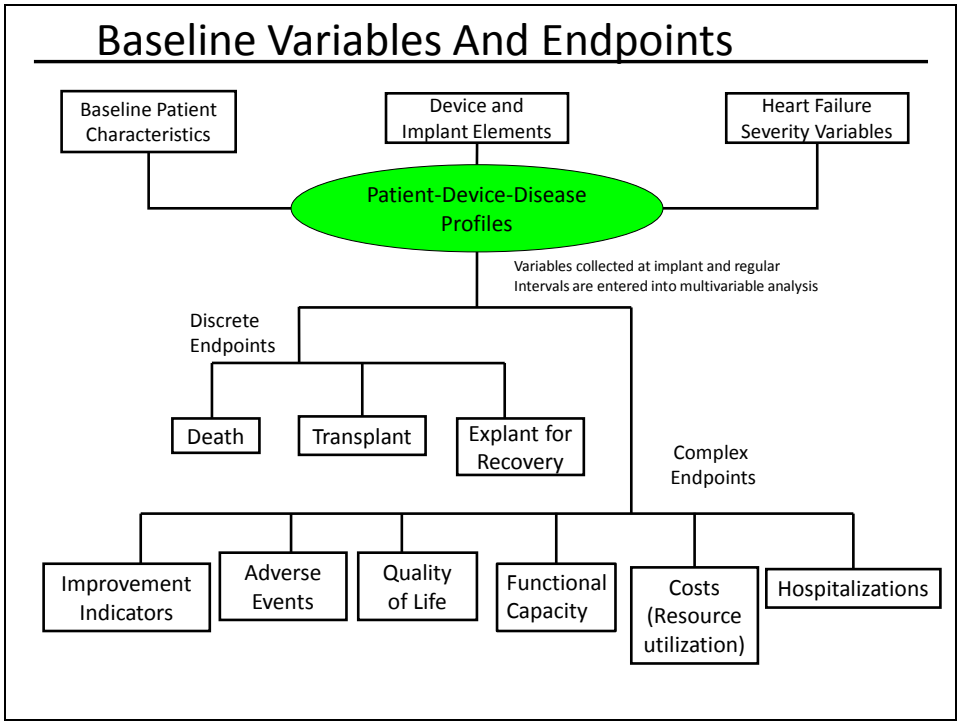
### A.1.2 Design

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

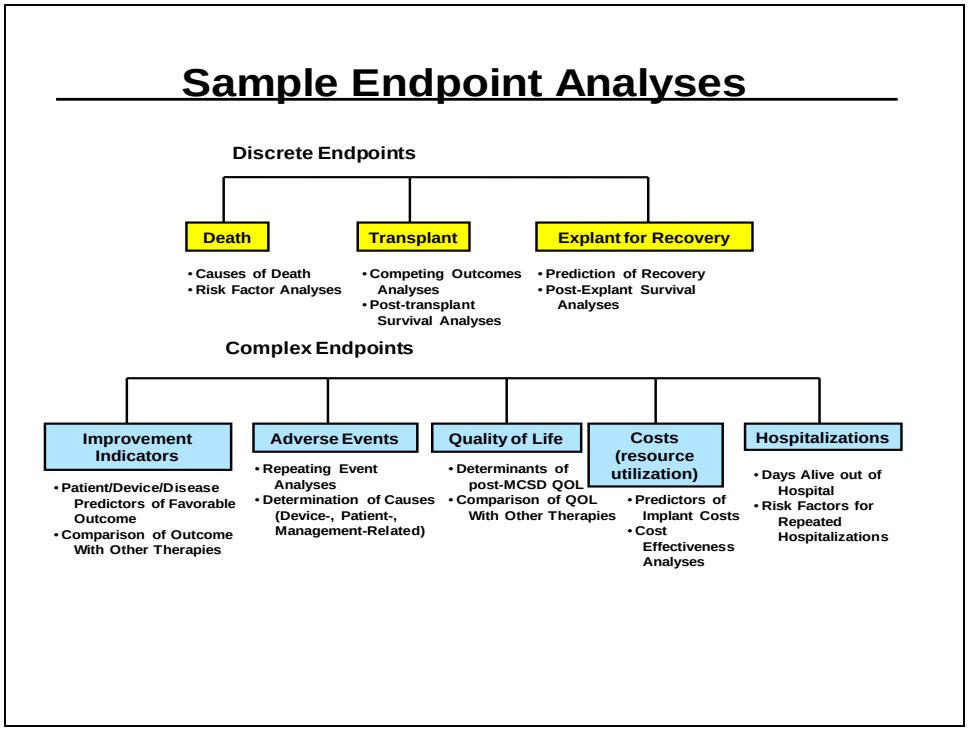
- Evaluate safety and efficacy of MCSD implants
- Determine the time-related costs (resource utilization) of MCSDs and the risk factors associated with increased costs
- Compare the costs (resource utilization) of MCSD therapy to other treatments for advanced heart failure
- Evaluate quality of life 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.

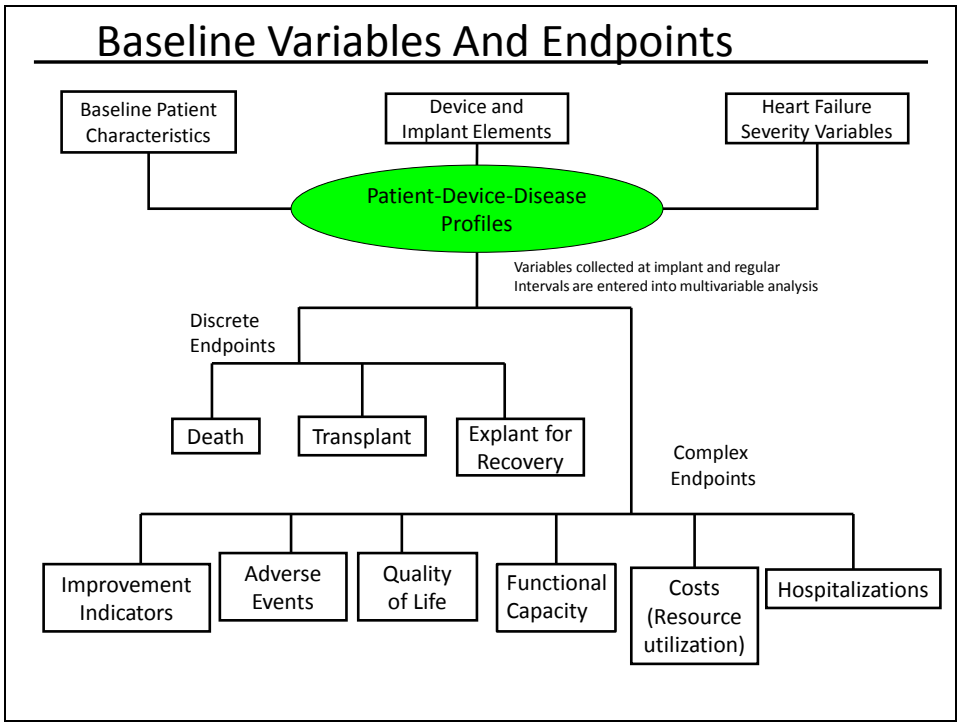
## B.1.2 Design

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 therafter 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

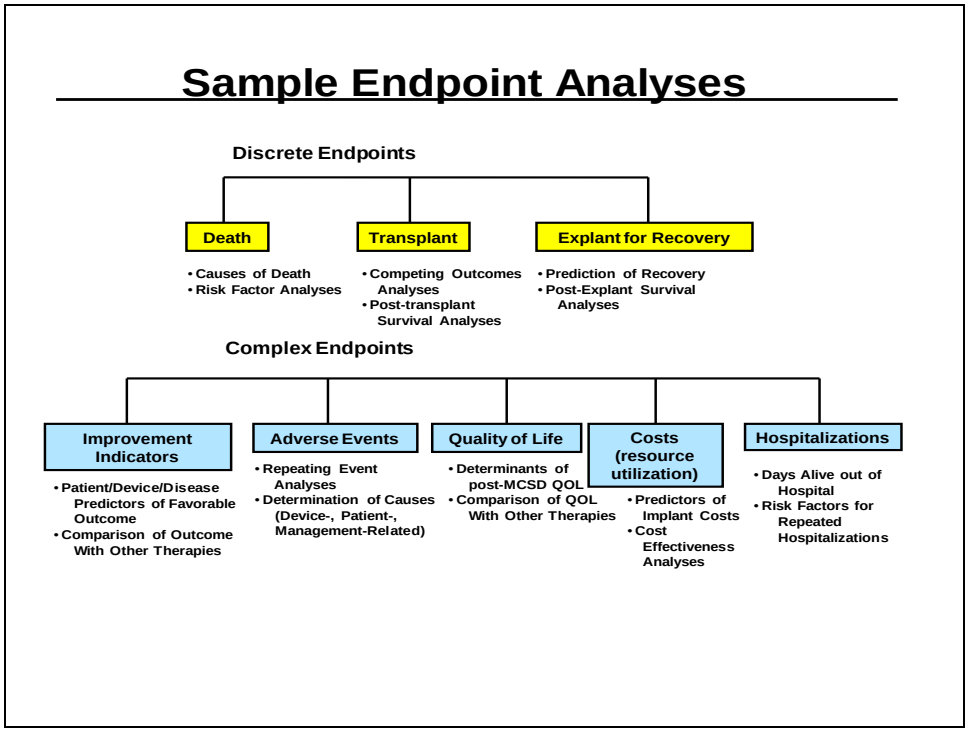
- Summarize the characteristics of the patients *who* are receiving MCSDs, *when* (in relation to progression of disease) they are receiving MCSDs and *why* (bridge to transplant, bridge to recovery, rescue therapy, or bridge to decision), and outcomes of the therapy
- Summarize the characteristics of 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 isanalyzed 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/herfirst event. The patientis 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 includean 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,andall 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]*.