Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs®)

Protocol

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List of Abbreviations

Abbreviation	Definition
CLIA	Clinical Laboratory Improvement Amendment(s)
CMS	Centers for Medicare and Medicaid Services
DCC	Data and Clinical Coordinating Center
DT	Destination Therapy
EB	Ethics Board or Body (for MCSD-implanting centers outside the US)
EQ-5D	EuroQoL Questionnaire
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
IDE	Investigational Device Exemption
IDS	Intrusion Detection Software
Intermacs®	Interagency Registry for Mechanically Assisted Circulatory Support
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
MCSD	Mechanical Circulatory Support Device
MOP	Manual of Operations and Procedures
MRS	Modified Rankin Scale
NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NIST	National Institution for Standards and Technology
NPI	National Provider Identifier
NYHA	New York Heart Association (heart failure classification)
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
PHTS	Pediatric Heart Transplant Study
PI	Principal Investigator
QA	Quality Assurance
QoL	Quality of Life
SRTR	Scientific Registry of Transplant Recipients
UAB	University of Alabama at Birmingham
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 for **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 advanced 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 legally utilized MCSDs. Intermacs® also includes MCSD-implanting centers outside the United States (US), including Canada. These activities are supported by the Intermacs® Data and Clinical Coordinating Center (hereafter referred to as the 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 centers to measure and assess the quality of care and outcomes for patients receiving MCSDs;
2. Providing confidential periodic reports to the participating centers, 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, Food and Drug Administration (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 center-based quality improvement assessments. Key performance measures are supplied to every participating center each quarter, along with a description of the benchmarking methodology used, to facilitate comparison of one center'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, centers, and devices. Most of these data are collected through chart review by clinicians at the clinical centers. 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 center must enter complete data on consecutively implanted patients into the Intermacs® database. To facilitate this requirement, Intermacs® works closely with the member centers.

Intermacs® collects data on all patients receiving legally utilized MCSDs at all participating centers. 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). Prior to enrollment, all newly participating centers are required to meet minimum enrollment requirements as outlined in Sections A.2.2 and B.2.2, which includes but is not limited to obtaining Institutional Review Board (IRB)/ Ethics Board (EB) review and documentation of their decision regarding waiver of consent and authorization 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 centers and device companies manufacturing legally utilized MCSDs.

Institutions within the Intermacs® organization include:

University of Alabama at Birmingham (UAB)
Boston Children's Hospital
Brigham and Women's Hospital
University of Pittsburgh
Cleveland Clinic
University of Michigan
National Heart, Lung, and Blood Institute (NHLBI), its designated partners and assigns

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® DCC under contract to the NHLBI. Intermacs® functions as a partnership between the NHLBI, FDA, CMS, participating centers, 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

The DCC is responsible for administrative support, agreement development and execution, data collection and management, center activation and auditing, 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 legally utilized MCSDs. There is no exclusion for gender, race, or ethnicity.

Screening

Each patient who receives an MCSD at an Intermacs® center 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 a legally utilized MCSD***** implanted at an Intermacs®-activated center. (NOTE: Patients implanted before the center activation date are not eligible for participation in Intermacs®.)

*****Refer to MOP Appendix K for the list of legally utilized adult MCSDs currently accepted by Intermacs®.

Exclusion Criteria

1) Patients who receive a MCSD, which is ***not*** legally utilized.

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 center, the patient is deactivated at the implanting center 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.

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 a transplant database (e.g., the Organ Procurement and Transplant Network, OPTN**,** for US patients) 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 appropriate transplant database at the time of transplantation.

A.1.2 Design

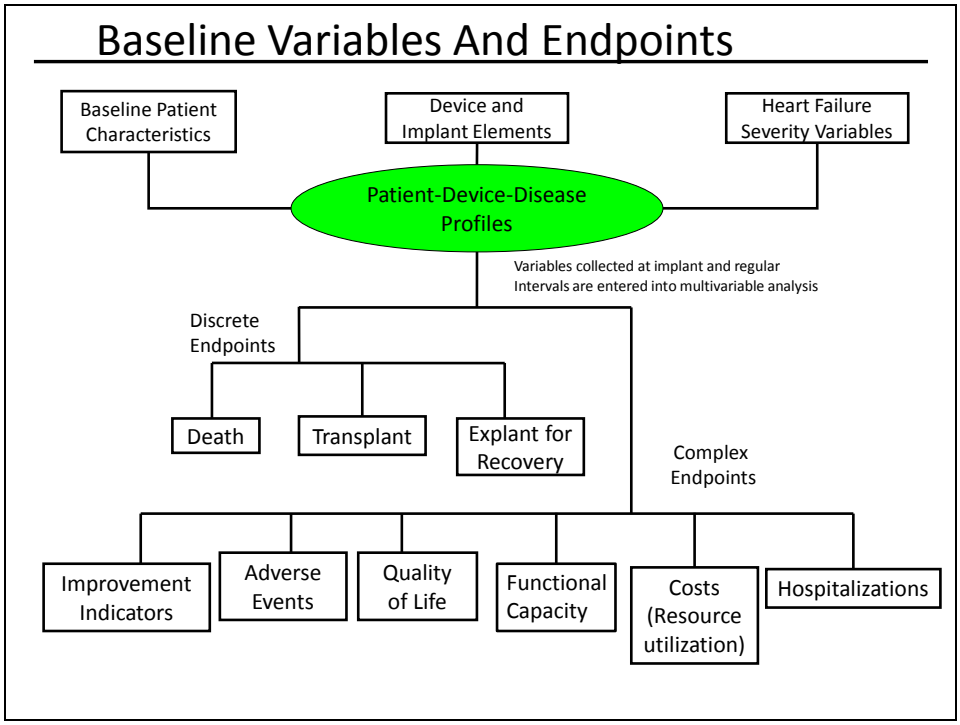
The data are collected retrospectively from existing medical records or concurrently in the normal course of treatment on patients who meet the eligibility criteria. Additional standard of care evaluations and contact with the patient outside of the index hospitalization are recorded in this registry. 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 standard of 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.

NOTE: No data beyond the data gathered in the course of routine care will be collected for this registry.

A.1.3 Additional Datasets

With cooperation between industry and Intermacs®, data from patients who are part of device approval studies may be merged with Intermacs® data. The process for acquiring these data is developed on a case-by-case basis. Additionally, data collected by Intermacs® may be used for FDA or other health agency-mandated device approval studies, in accordance with applicable privacy regulations.

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 dysfunction, and/or 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 Center Eligibility and Enrollment

Section A.2.0 contains the steps for determining eligibility and enrollment for each center. 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 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, which requires center and personnel contact information, must be completed online at: www.intermacs.org (refer to the "Join Intermacs" button). The steps necessary for Intermacs® membership are outlined in detail in the MOP.

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 and distribution of reports and other materials, as well as audit coordination

A.2.3 IRB/EB Review

In preparation of materials for IRB/EB review, new centers will use the Intermacs® protocol, which is a two-part registry – Intermacs®- Adults and Intermacs®- Pediatrics/Pedimacs. The center must submit the Intermacs® protocol and supporting documentation (e.g., request for waiver of consent and authorization) to the IRB/EB for review. The guidelines and supporting documents for the medical center's submission of an application to participate in Intermacs® are located in the MOP. After the IRB/EB reviews the application for participation in this registry, documentation of their decision and, as applicable, the Federal Wide Assurance Number (FWA) and current Clinical

Laboratory Improvement Amendments (CLIA) certification must be submitted to Intermacs® before a center can be activated.

The center is responsible for obtaining and maintaining all relevant 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 center and The Board of Trustees of the University of Alabama, on behalf of Intermacs®. They contain the centers' and Intermacs'® responsibilities. The signed agreements must be submitted to Intermacs®.

Each center must pay a required participation fee prior to activation. Intermacs® is structured to provide value to the centers for this fee. For example, Intermacs®:

- provides access to completed web-based data forms in real time for quality improvement activities,
- provides quarterly quality assurance reports to each participating center,
- provides datasets for quality improvement purposes to participating centers upon request,
- creates patient-specific chronological history of the major clinical events after implant, and
- encourages local clinicians 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 center can be activated and must be updated on an annual basis.

A.2.6 Privacy Awareness Training

All staff members are required to complete the NIH's Privacy Awareness Training (currently located at http://irtsectraining.nih.gov/publicUser.aspx). Copies of the Privacy Awareness Training certification must be submitted to Intermacs® before a center can be activated, and training will be updated per local institutional policy or every 2 years, whichever comes first.

A.2.7 Registry-specific Training

At least one Intermacs® staff member at the center 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 center has completed steps A.2.1 through A.2.6.

A.2.8 Activation

After completing steps A.2.1 through A.2.7, center 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 phone call or e-mail that will contain the individual's user name and password.

A.2.9 Annual Re-Certification

The local IRB/EB will determine whether annual review of Intermacs® is required. If they determine annual review of Intermacs®:

- is required, then approval documents are submitted to the DCC on a yearly basis. Intermacs® will send annual reminders to those participating centers under IRB/EB purview at least 30 days prior to expiration of approval. Lapse in local coverage will result in immediate suspension, including data entry capability.
- is *not* required because the project is exempt, then documentation of this exemption will be retained by both the center and the DCC.

To MAINTAIN CERTIFICATION, a center must:

- Maintain and provide Intermacs® with:
  - documentation of the IRB/EB decision that the project is exempt, OR
  - documentation of annual IRB/EB approval and, as applicable, informed consent(s), current FWA Number and CLIA certification,
- Provide annual participation fee,
- Update personnel roster,
- Provide completed annual Financial Disclosure and Conflict of Interest forms,
- 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, and neurocognitive

data via patient interviews. 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 US 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 US 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 informed consent. This is a quality improvement 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.**

As a courtesy, patients may be provided a summary sheet describing the registry. However, this sheet is not a registry requirement.

Participating centers will follow their local institutional policies. Refer to the MOP, for additional guidance and MOP Appendix C for the patient information sheet template and supplementary documents that may be required.

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 center, Intermacs®, MCSD manufacturers, and government agencies.

A.4.2 Web-based Data Entry and Systems Security

All data will be entered through the Intermacs® data entry system. Complete documentation is contained at the data entry website (www.intermacs.org), and the Intermacs® Site Users' Guide is located in the MOP, Appendix M. The implant forms should be filled out within 7 days of 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. Refer to the MOP for all data entry timeline requirements.

Minimal PHI [e.g., patient's name; date of birth; last 5 digits of social security number, social insurance number, or another identifying number, such as the last 5 digits of the transplant wait list number for transplant-eligible patients; health insurance claim number (HICN), if applicable; operator first, middle and last name; operator national provider identifier (NPI) for US centers; 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 other databases, including but not limited to the OPTN, Pediatric Heart Transplant Study (PHTS), and Scientific Registry of Transplant Recipients (SRTR) databases for US transplant recipients, to CMS databases, and to FDA or other health agency medical device safety databases.

Intermacs® complies with all US patient privacy regulations. All registry data shall be maintained on secure servers with appropriate safeguards in place. All Intermacs® employees have passed US 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 local security information official or IRB/EB, if applicable, 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 US Security Act of

2002 and the US 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 2012R2 framework. They follow Microsoft's best security practices and group policy recommendations from the US 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.

Physical and virtual firewalls, including Intrusion Detection Software (IDS), assist in preventing virus and other security risks internally and externally. 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 7 days of 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 switched off or explanted without transplantation, the patient will be followed for 1 year following cessation/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 the clinician's 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 clinician 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 and/or National Institutes of Health Stroke Scale (NIHSS) score is recorded. The MRS and/or NIHSS 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 that can be performed with registry data.

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 (patient-related, facility-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

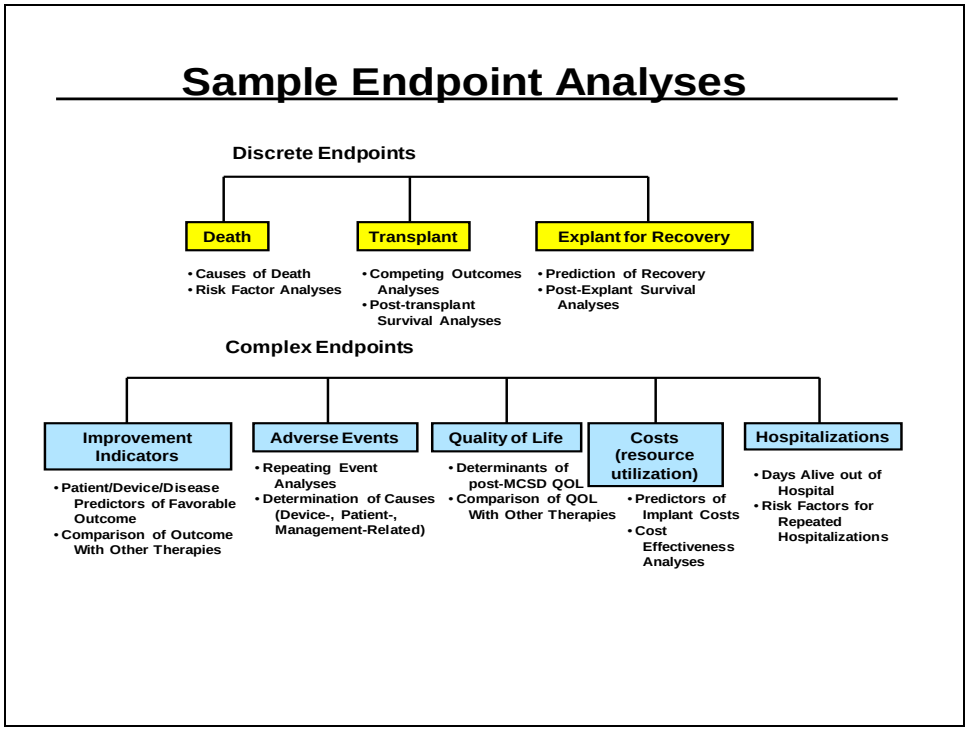
- Evaluate quality of life pre- and post-MCSD implant
- Compare alternative therapies (MCSD, transplant, medical) for patients with end stage heart failure
- Produce patient-specific predictions of time-related outcomes to aid in clinical decision making and allocation of therapies for advanced heart 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 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 representatives from participating device manufacturers will assist the Executive Committee 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 under Analytic Methods in the MOP. 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 in the MOP 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 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 center 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.5.6 Other Analyses

The Intermacs® process for investigator requests to utilize de-identified datasets to further study this patient population in summary is detailed in the MOP and can also be

found on the Intermacs® website at www.intermacs.org under the “Research” tab at the top of the webpage.

The registry utilizes a separate process for requests to further study this patient population in summary within the Intermacs® organization, which permits the use of datasets with the minimal necessary PHI for evaluation purposes. Evaluations may include linking an Intermacs® dataset with datasets from other sources (e.g., the OPTN, PHTS, and SRTR databases for transplant recipients; CMS databases; FDA or other health agency medical device safety databases; and other registries). These evaluations may be used to:

- Inform the practice of care, but not directly impact patient care by virtue of registry participation;
- Revise the data elements collected on the patient populations;
- Develop resources to support the practice of care, but which are independent of participation in the registry;
- Detect emerging MCSD adverse event patterns.

All Executive Committee members and their respective institutional officials are required to sign a contractual instrument, which holds them to the same standards regarding the protection of PHI as UAB and the NHLBI (refer to Section A.4.2).

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 Reports will include an overall summary of Intermacs® patient characteristics, implant characteristics, center 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 ad hoc reports, if requested.

A.6.3 Food and Drug Administration (FDA)

FDA will receive copies of the NHLBI Quarterly Statistical Reports and ad hoc reports, if requested.

A.6.4 Industry

Quarterly reports will be provided to each participating MCSD manufacturer summarizing their device data entered into Intermacs®. 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 Centers

Quarterly reports will be provided to each participating center. A specific center will not receive identified information about any other center. These reports have two components. The first component is a quality assurance report that summarizes and compares the results at the individual center with the entire Intermacs® registry. These benchmark comparisons allow the center to evaluate the patients and outcomes as compared to the aggregate data of the other participating centers. The second component focuses on patient-specific data and the quality of the center data. A dashboard is available for centers to view a patient's chronological history of major implant-related events, as well as real-time access to the center's completed data forms for quality improvement purposes.

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 produce periodic data reports. The focus will be on completeness of MCSD capture as well as periodic follow-up, and also on identifying impossible or improbable combinations of variables. Questionable data points will be verified.

A.7.2 Data Checks for Inconsistencies

The database will be subject to analytical quality assurance (QA) audits following the completion of data entry. This activity will include obtaining copies of Intermacs®-participating centers' MCSD implant logs (redacted). Depending on the types of discrepancies identified, the DCC 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 the

majority of previously submitted data at any time. Additionally, summary screens and reports of patients and devices, current patient status, most recent reported event and other data will be available to the member centers to assist the center 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. Refer to Section A.8.4 for additional information on the audit process.

A.7.3 Major Adverse Events

Major adverse events entered into the Intermacs® database are **not** adjudicated; however, the events may be reviewed periodically by the Executive Committee to inform changes to major adverse event definitions, as well as to provide guidance to the DCC for:

- evaluating the *quality* of the major adverse event data being entered;
- developing strategies for electronically identifying duplicate events and questionable events;
- categorizing device malfunction; and
- auditing the correct capture of major adverse events.

All data identified as questionable are resolved via direct interactions between the nurse monitors and the local center. Refer to Section A.8.4 for further detail on the auditing process.

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

A.8.1 Requirements for Centers

Each participating center shall:

(1) provide dated proof of initial IRB/EB review and,
   a) where the IRB/EB has exempted Intermacs®, documentation of the exemption,
   b) where the IRB/EB has ***not*** exempted Intermacs®, initial and annual IRB/EB approval, and as applicable, proof of FWA Number and CLIA certification;

(2) provide current personnel roster, Financial Disclosure and Conflict of Interest form, and proof of Privacy Awareness Training for all center staff;

(3) have at least one person complete training;

(4) enter complete baseline, implant, and follow-up data on all patients at specified time points;

(5) provide redacted MCSD implant logs upon request (refer to Section A.8.4);

(6) submit to regular and “for cause” data audits; and

(7) 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 Users' Guide** will provide step-by-step instructions for using the system and will include definitions for all fields collected in the system. The Site Users' 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® centers involves multiple interactions between the DCC and center staff. In general, an on-site visit will be conducted when "For Cause" audits are required. Routine audits will be conducted remotely and require source documentation (with patient identifying information redacted) to be sent to the DCC via secure fax or email 30 days in advance of the routine audit. Redacted source documents comprise any items listed by the nurse monitors (including but not limited to MCSD implant logs) so that they can verify legally utilized MSCDs have been entered into the database. Routine audits will involve a review of the data entered into the database for completeness, duplicate entries, and questionable entries, as well as discussion with center staff via telephone and/or WebEx.

Centers are notified up to 60 days prior to a routine audit via email or telephone. Audited data include key data fields, as determined by Intermacs®.
The Intermacs® monitor contacts the center by phone for a pre-audit review approximately 2 weeks before the scheduled audit. During the call, the monitor reviews center-specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explant inconsistencies and any other noted discrepancies. The centers are requested to make corrections and to provide additional 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 center performance and recommends actions to reestablish compliance. All "For Cause" audit results will be reported to the Executive Committee.

The audit process will identify member centers 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 centers will be retrained on proper data collection methods with the goal of identifying and overcoming obstacles to submission. Continued non-compliance will result in the center's being deactivated until the center has implemented corrective actions to re-establish compliance.

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 legally utilized MCSDs. There is no exclusion for gender, race, or ethnicity.

Screening

Each patient who receives an MCSD at a Pedimacs center 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 a legally utilized MCSD***** implanted at a Pedimacs®-activated center. (NOTE: Patients implanted before the center activation date are not eligible for participation in Pedimacs.)

*****Refer to MOP Appendix K for the list of legally utilized pediatric MCSDs currently accepted by Pedimacs.

Exclusion Criteria

1) Patients who receive an MCSD, which is ***not*** legally utilized.

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 turned off or removed.

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 center then the patient is deactivated at the implanting center 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.

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 a transplant database (e.g., the OPTN transplant database for US patients). 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 appropriate transplant database at the time of transplantation.

B.1.2 Design

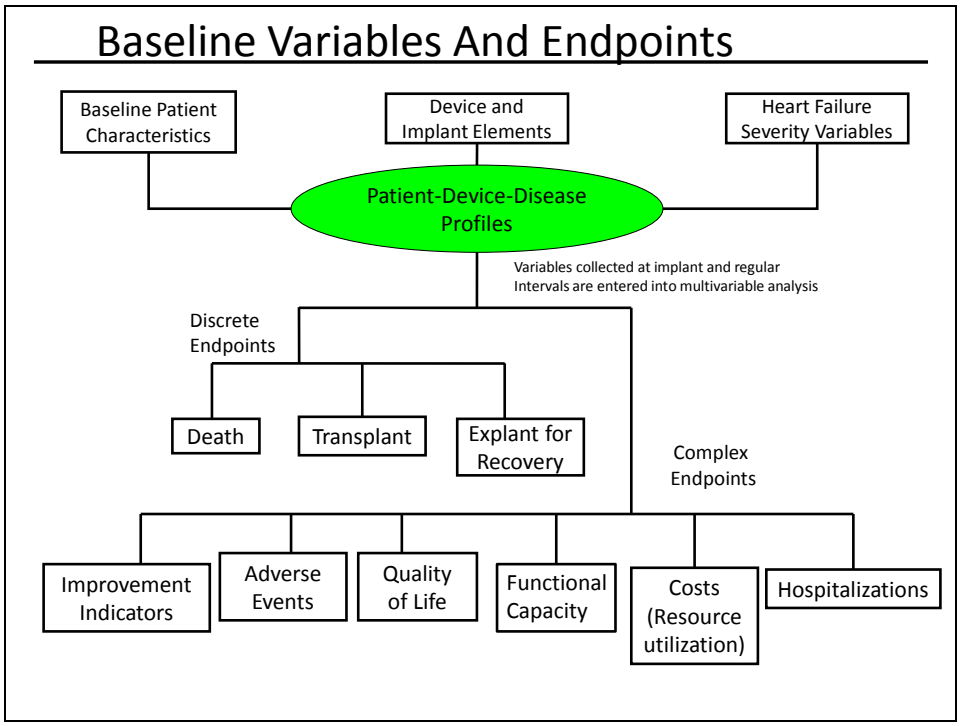
Pedimacs data are collected retrospectively from existing medical records or concurrently in the normal course of treatment on patients who meet the eligibility criteria. Additional standard of care evaluations and contact with the patient outside of the index hospitalization are recorded in this registry. 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 turned off or explanted. Physical examination and age-appropriate functional capacity testing is standard of 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.

NOTE: No data beyond the data gathered in the course of routine care will be collected for this registry.

B.1.3 Additional Datasets

With cooperation between industry and Pedimacs, data from patients who are part of device approval studies may be merged with Pedimacs data. The process for acquiring these data is developed on a case-by-case basis. Additionally, data collected by Pedimacs may be used for FDA or other health agency-mandated device approval studies, in accordance with applicable privacy regulations.

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 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 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 dysfunction, and/or 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 Center Eligibility and Enrollment

Section B.2.0 contains the steps for determining eligibility and enrollment for each center. 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 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, which requires center and personnel contact information, must be completed online at: www.intermacs.org (refer to the "Join Intermacs" button). The steps necessary for Pedimacs membership are outlined in detail in the MOP.

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 and distribution of reports and other materials, as well as audit coordination

B.2.3 IRB/EB Review

In preparation of materials for IRB/EB review, new centers will use the Intermacs® protocol, which is a two-part registry – Intermacs® - Adults and Intermacs® - Pediatrics/Pedimacs. The center must submit the protocol and supporting documentation (e.g., request for waiver of consent and authorization) to their IRB/EB for review. The guidelines and supporting documents for the medical center's submission of an application to participate in Pedimacs are located in the MOP. After the IRB/EB reviews the application for participation in this registry, documentation of their decision and, as applicable, the FWA Number and current CLIA certification must be submitted to Pedimacs before a center can be activated.

The center is responsible for obtaining and maintaining all relevant 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 center and The Board of Trustees of the University of Alabama, on behalf of Intermacs®. They contain the centers' and Pedimacs responsibilities. The signed agreements must be submitted to Pedimacs.

Each center must pay a required participation fee prior to activation. Pedimacs is structured to provide value to the centers for this fee. For example, Pedimacs:

- provides access to completed web-based data forms in real time for quality improvement activities,
- provides quarterly quality assurance reports to each participating center,
- provides center-specific datasets to aid in quality improvement at that center on an as requested basis,
- creates patient specific chronologic history of the major clinical events after implant, and
- encourages local clinicians to participate in the administration and activities within the registry.

B.2.5 Financial Disclosure and Conflict of Interest

Center 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 center can be activated and must be updated on an annual basis.

B.2.6 Privacy Awareness Training

All staff members are required to complete the NIH's Privacy Awareness Training (currently located at http://irtsectraining.nih.gov/publicUser.aspx). Copies of the Privacy Awareness Training certification must be submitted to Pedimacs before a center can be activated, and training will be updated per local institutional policy or every 2 years, whichever comes first.

B.2.7 Registry-specific Training

At least one Pedimacs staff member at the center 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 center has completed steps B.2.1 through B.2.6.

B.2.8 Activation

After completing steps B.2.1 through B.2.7, center 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 phone call or e-mail that will contain the individual's username and password.

B.2.9 Annual Re-Certification

The local IRB/EB will determine whether annual review of Pedimacs is required. If they determine annual review of Pedimacs:

- is required, then approval documents are submitted to the DCC on a yearly basis. Pedimacs will send annual reminders to those participating centers under IRB/EB purview at least 30 days prior to expiration of approval. Lapse in local coverage will result in immediate suspension, including data entry capability.
- is *not* required because the project is exempt, then documentation of this exemption will be retained by both the center and the DCC.

To MAINTAIN CERTIFICATION, a center must:

- Maintain and provide Pedimacs with:
  - documentation of the IRB/EB decision that the project is exempt, OR
  - documentation of annual IRB/EB approval and, as applicable, informed consent(s), current FWA Number and CLIA certification,
- Provide annual participation fee,
- Update personnel roster,
- Provide completed annual Financial Disclosure and Conflict of Interest forms,
- 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 US 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 US 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 informed consent. This is a quality improvement 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**.

As a courtesy, patients/parents may be provided a summary sheet describing the registry. However, this summary is not a registry requirement.

Participating centers will follow their local institutional policies. Refer to the MOP, for additional guidance and MOP Appendix C for the patient information sheet template and supplementary documents that may be required.

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 center, 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 Users' Guide is located in the MOP, Appendix N. The implant forms should be filled out within 7 days of 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. Refer to the MOP for all data entry timeline requirements.

Minimal PHI (e.g., patient's name; date of birth; last 5 digits of social security number, social insurance number, or another identifying number, such as the last 5 digits of the transplant wait list number for transplant-eligible patients; operator first, middle and last name; operator NPI for US centers; 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 other databases, including but not limited to the OPTN, PHTS, and/or SRTR databases for transplant recipients, and to FDA or other health agency medical device safety databases.

Pedimacs complies with all US patient privacy regulations. All registry data shall be maintained on secure servers with appropriate safeguards in place. All Pedimacs employees have passed US 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 local security information official or IRB/EB, if applicable, 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 US Security Act of 2002 and US 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 2012R2 framework. They follow Microsoft's best security practices and group policy recommendations from the US 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.

Physical and virtual firewalls, including IDS, assist in preventing virus and other security risks internally and externally. 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 7 days of 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 3 months, 6 months, and every 6 months for the life of the device. If the device is turned off or explanted without

transplantation, the patient will be followed for 1 year following cessation/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 Users' 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 the clinician's 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 clinician at the time of form completion. Reasons for not collecting the QoL instruments will be recorded.

B.4.5 Functional Capacity Data

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

For pediatric patients <10 years of age, general functional capacity data is collected pre-implant, implant discharge, and at follow-up intervals (i.e., 3 and 6 months and every 6 months thereafter for as long as the MCSD is in place). These data include the child's functional capacity (e.g., sedated, paralyzed, intubated, ambulating), primary nutrition, and if the patient has had non-medically required excursions off the unit (collected at 1 week and 1 month post implant and at implant discharge).

B.5.0 Analyses of Registry Data

B.5.1 Introduction

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

B.5.2 Purposes

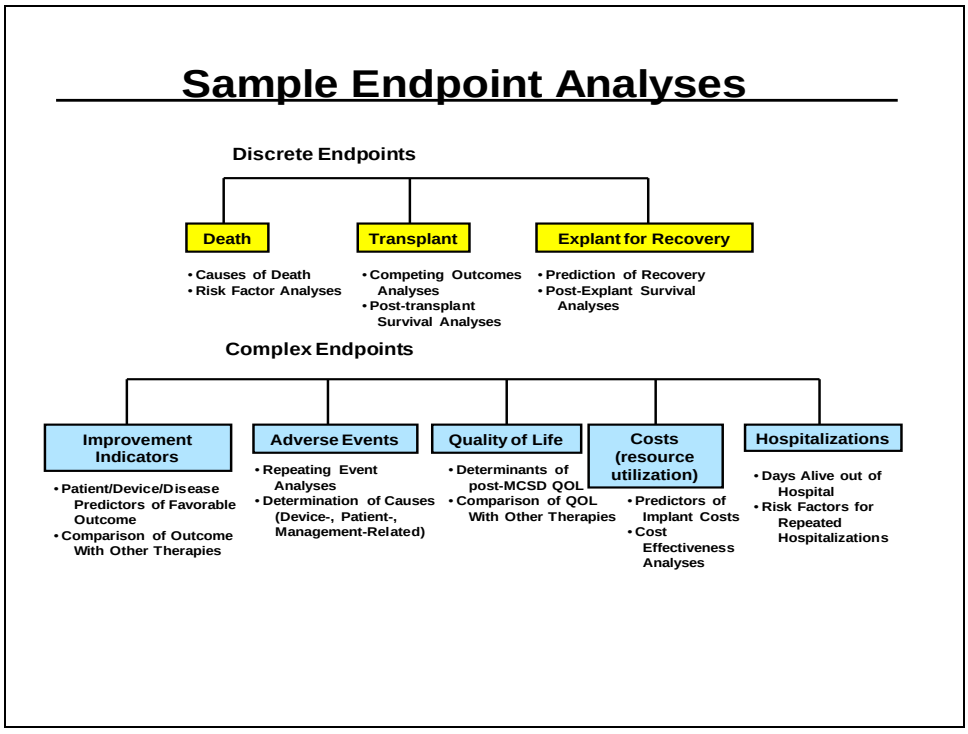
- Summarize the characteristics of the patients *who* are receiving MCSDs, *when* (in relation to progression of disease) they are receiving MCSDs and *why* (bridge to transplant, bridge to recovery, rescue therapy, or bridge to decision), and outcomes of the therapy
- Summarize the characteristics of MCSDs that are being implanted
- Describe post-implant adverse events and estimate their time-related distribution
- Determine risk factors (patient-related, facility-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 Planned Analyses

Patient Characteristics

Pediatric 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 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 representatives from participating device manufacturers will assist the Executive Committee 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 under Analytic Methods in Section 10 of the MOP. 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 in Section 10 of the MOP 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 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 center 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.5.6 Other Analyses

The Pedimacs process for investigator requests to utilize de-identified datasets to further study this patient population in summary is detailed in the MOP and can also be found on the Intermacs® website at www.intermacs.org under the "Research" tab at the top of the webpage.

The registry utilizes a separate process for requests to further study this patient population in summary within the Intermacs® organization, which permits the use of datasets with the minimal necessary PHI for evaluation purposes. Evaluations may include linking a Pedimacs dataset with datasets from other sources (e.g., the OPTN, PHTS and SRTR databases for transplant recipients; CMS databases; FDA and other health agency medical device safety databases, and other registries). These evaluations may be used to:

- Inform the practice of care, but not directly impact patient care by virtue of registry participation;
- Revise the data elements collected on the patient populations;
- Develop resources to support the practice of care, but which are independent of participation in the registry;
- Detect emerging MCSD adverse event patterns.

All Executive Committee members and their respective institutional officials are required to sign a contractual instrument, which holds them to the same standards regarding the protection of PHI as UAB and the NHLBI (refer to Section B.4.2).

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 Reports will include an overall summary of Intermacs® patient characteristics, implant characteristics, center 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 will receive copies of the NHLBI Quarterly Statistical Reports and ad hoc reports, if requested.

B.6.4 Industry

Quarterly reports will be provided to each participating MCSD manufacturer summarizing their device data entered into Pedimacs. 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 Centers

Quarterly reports will be provided to each participating center. A specific center will not receive identified information about any other center. These reports have two components. The first component is a quality assurance report that summarizes and compares the results at the individual center with the entire Pedimacs registry. These benchmark comparisons allow the center to evaluate the patients and outcomes as compared to the aggregate data of the other participating centers. The second component focuses on patient-specific data and the quality of the center data. A dashboard is available for centers to view a patient's chronological history of major implant-related events, as well as real-time access to the center's completed data forms for quality improvement purposes.

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 produce periodic data reports. The focus will be on completeness of MCSD capture as well as periodic follow-up and also on identifying impossible or improbable combinations of variables. Questionable data points will be verified.

B.7.2 Data Checks for Inconsistencies

The database will be subject to analytical QA audits following the completion of data entry. This activity will include obtaining copies of Pedimacs-participating centers' MCSD implant logs (redacted). Depending on the types of discrepancies identified, the DCC 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 the majority of previously

submitted data at any time. Additionally, summary screens and reports of patients and devices, current patient status, most recent reported event and other data will be available to the member centers to assist the center 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. Refer to Section B.8.4 for additional information on the audit process.

B.7.3 Major Adverse Events

Major adverse events entered into the Pedimacs database are **not** adjudicated; however, the events may be reviewed periodically by the Executive Committee to inform changes to adverse event definitions, as well as to provide guidance to the DCC for:

- evaluating the *quality* of the major adverse event data being entered.
- developing strategies for electronically identifying duplicate events and questionable events.
- categorizing device malfunction.
- auditing the correct capture of major adverse events.

All data identified as questionable are resolved via direct interactions between the nurse monitors and the local center. Refer to Section B.8.4 for further detail on the auditing process.

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

B.8.1 Requirements for Centers

Each participating center shall:

(1) provide dated proof of initial IRB/EB review and,
   a) where the IRB/EB has exempted Intermacs®, documentation of the exemption,
   b) where the IRB/EB has *not* exempted Intermacs®, documentation of initial and annual IRB/EB approval, and as applicable, proof of FWA Number and CLIA certification;

(2) provide current personnel roster, Financial Disclosure and Conflict of Interest form, and proof of Privacy Awareness Training for all center staff;

(3) have at least one person complete training;

(4) enter complete baseline, implant, and follow-up data on all patients at specified time points;

(5) provide redacted MCSD implant logs upon request (refer to Section B.8.4);

(6) submit to regular and “for cause” data audits; and

(7) 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 Users' Guide** will provide step-by-step instructions for using the system and will include definitions for all fields collected in the system. The Site Users' 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 Intermacs® centers involves multiple interactions between the DCC and center staff. In general, an on-site visit will be conducted when "For Cause" audits are required. Routine audits will be conducted remotely and require source documentation (with patient identifying information redacted) to be sent to the DCC via secure fax or email 30 days in advance of the routine audit. Redacted source documents comprise any items listed by the nurse monitors (including but not limited to MCSD implant logs) so that they can verify legally utilized MSCDs have been entered into the database. Routine audits will involve a review of the data entered into the database for completeness, duplicate entries, and questionable entries, as well as discussion with center staff via telephone and/or WebEx.

Centers are notified up to 60 days prior to a routine audit via email or telephone. Audited data include key data fields, as determined by Intermacs®.

The Intermacs® monitor contacts the center by phone for a pre-audit review approximately 2 weeks before the scheduled audit. During the call, the monitor reviews center-specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explant inconsistencies and any other noted discrepancies. The centers are requested to make corrections and to provide additional 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 center performance and recommends actions to reestablish compliance. All “For Cause” audit results will be reported to the Executive Committee.

The audit process will identify member centers 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 centers will be retrained on proper data collection methods with the goal of identifying and overcoming obstacles to submission. Continued non-compliance will result in the center’s being deactivated until the center has implemented corrective actions to re-establish compliance.