**Interagency Registry for Mechanically Assisted Circulatory Support**

# Manual of Operations and Procedures

**Sponsored by the National Heart, Lung, and Blood Institute**

**Data and Clinical Coordinating Center:** University of Alabama at Birmingham

**Version 5.0**

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| 6MWT | Six-minute Walk Test |
| CLIA | Clinical Laboratory Improvement Amendment(s) |
| CMS | Centers for Medicare and Medicaid Services |
| CPX | Cardiopulmonary Exercise |
| DAAP | Data Access, Analysis, and Publications Committee |
| DCC | Data and Clinical Coordinating Center |
| DT | Destination Therapy |
| EB | Ethics Board or Body (for MCSD-implanting centers outside the US) |
| EC | Executive Committee |
| EQ-5D | EuroQoL Questionnaire |
| FDA | United States Food and Drug Administration |
| FWA | Federal Wide Assurance |
| HHS | Health and Human Services |
| HICN | Health Insurance Claim Number |
| HIPAA | Health Insurance Portability and Accountability Act |
| Intermacs® | Interagency Registry for Mechanical Assisted Circulatory Support |
| IRB | Institutional Review Board |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| LVAD | Left Ventricular Assist Device |
| MCSD | Mechanical Circulatory Support Device |
| MOP | Manual of Operations and Procedures (Registry-specific) |
| MRS | Modified Rankin Scale |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIHSS | National Institutes of Health Stroke Scale |
| 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 |
| PHTS | Pediatric Heart Transplant Study |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QoL | Quality of Life |
| RVAD | Right Ventricular Assist Device |
| SIN | Social Insurance Number |
| SRTR | Scientific Registry of Transplant Recipients |
| SSN | Social Security Number |
| TAH | Total Artificial Heart |
| UAB | University of Alabama at Birmingham |
| VADQoL | Ventricular Assist Device Quality of Life instrument |

# 1 Overview

The **Inte**ragency **R**egistry of **M**echanically **A**ssisted **C**irculatory **S**upport (Intermacs®) is a registry of adult and pediatric patients receiving a mechanical circulatory support device (MCSD) to treat heart failure. With data collected since 2006, Intermacs® now serves as the national quality improvement system to assess the characteristics, treatments, and outcomes of patients receiving legally utilized MCSDs. The registry also includes MCSD-implanting centers outside the United States (US), including 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 Intermacs® registry for pediatric patients is also referred to as Pedimacs and was launched on September 19, 2012. While Intermacs® has always included durable devices implanted in pediatric patients, Pedimacs has been developed to focus on capturing data elements unique to pediatric patients. Pedimacs evaluates special issues in the pediatric population receiving MCSD therapy, differences in available devices, and the particular pediatric population for whom this therapy may be most effective. Unless otherwise noted in this document, reference to Intermacs®, includes Pedimacs.

Data reports from Intermacs® are shared with the NHLBI, the 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 clinical center performance measures (as compared to national benchmarks) are supplied to every participating center each quarter, along with a description of the benchmarking methodology, 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, clinical centers, and devices. Most of these data are collected through chart review by trained clinicians at the clinical centers. Standard of care data on Quality of Life (QoL) and functional capacity are collected for adults and pediatric patients through administration of instruments and tests. Additionally, standard of care neurocognitive data are collected for adults. **No data beyond the data gathered in the course of routine care will be collected for this registry.**

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, the Intermacs® DCC works closely with the member centers.

***Additionally, clinical centers are required to submit medical device reports to the FDA in accordance with 21 CFR 803.10. Refer to Appendix R for center responsibilities and timelines for reporting.***

# 2 Registry Synopsis

**Title:**
Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs®)

**Contract Number:**
HHSN268201100025C

**Objectives:**
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.

**Registry Design:**
Intermacs® is a registry for both adults (Intermacs® - Adults, or Intermacs®) and children (Intermacs® - Pediatrics, or Pedimacs) in which data are collected primarily 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 at defined intervals.

| **Number of Subjects:** | **Number of Sites:** |
|---|---|
| Any patient receiving a legally utilized MCSD at an Intermacs®-participating center is eligible to participate. | Any medical center that has an active MCSD program and meets Intemacs® enrollment and activation criteria is eligible to participate. |

**Period of Evaluation:**
Patients are followed for the life of the legally utilized 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. If the patient is transplanted, then he/she will no longer be followed in Intermacs® but will be followed in the Organ Procurement and Transplant Network (OPTN).

**Major Endpoints**:
Discrete
1. Death
2. Transplant
3. Explant for Recovery

Complex
1. Adverse Events
2. Improvement Indicators
3. Quality of Life
4. Costs
5. Hospitalizations

**Statistical Considerations:**
Because this registry is observational in nature, analyses will be on-going for descriptive variables. More specific analyses for hypothesis generation will be determined as appropriate.

**Title:**
Intermacs - Adults (Intermacs®)

**Registry Design Following Implant:**
Post implant follow-up data are collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that for as long as an MCSD is utilized and up to 1 year after device removal/turn off. 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) and Kansas City Cardiomyopathy Questionnaire (KCCQ) for quality of life assessment and the Trail Making Neurocognitive Test, Part B, for neurocognitive assessment. **No data beyond the data gathered in the course of routine care will be collected for this registry.**

**Criteria for Inclusion:**
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 **Appendix K** for a list of legally utilized adult MCSDs currently accepted by Intermacs®.

**Criteria for Exclusion:**
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).

| |
|---|
| **Title:**<br>Intermacs - Pediatrics (Pedimacs) |
| **Registry Design Following Implant:**<br>Post implant follow-up data is collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that for as long as an MCSD is utilized and up to 1 year after device removal/turn off. Physical examination and functional capacity 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. Neurocognitive assessments will **not** be performed in Pedimacs. **No data beyond the data gathered in the course of routine care will be collected for this registry.**<br>Of note, once a patient is entered as a pediatric patient, the patient will remain in pediatric status until the device is turned off or removed. |
| **Criteria for Inclusion:**<br>All patients <19 years of age who receive a legally utilized MCSD* implanted at a Intermacs®-activated center.(NOTE: Patients implanted before the center activation date are not eligible for participation in Pedimacs.)<br>*Refer to **Appendix K** for a list of legally utilized pediatric MCSDs currently accepted by Pedimacs. |
| **Criteria for Exclusion:**<br>1. Patients who receive an MCSD, which is ***not*** legally utilized.<br>2. Patients who are ≥ 19 years of age at time of implant (NOTE: These patients should be enrolled into Intermacs®.)<br>3. Patients who are incarcerated persons (prisoners). |

# 3 Registry Organization and Responsibilities

Intermacs® represents an interagency partnership with the NHLBI, FDA, and CMS that works collaboratively with participating centers, and industry. 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. These collaborations are coordinated by the DCC.

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
NHLBI, its designated partners and assigns

Officials from the institutions within the Intermacs® organization are required to sign a contractual instrument, which holds them to the same high standards regarding protected health information (PHI) in accordance with Federal regulations.

The overall structure of Intermacs® is described below.

### 3.1 NHLBI, National Institutes of Health

As the primary funding agency, NHLBI, located in Bethesda, Maryland is the major partner of the registry. In addition to its oversight role, the NHLBI has been involved with many of the day-to-day activities of Intermacs®, including the role of ensuring scientific and regulatory integrity and participant protection. NHLBI staff includes:

- Contracting Officer's Representative (COR): Marissa A. Miller, DVM, MPH;
- Alternate COR: J. Timothy Baldwin, PhD
- Clinical Trials/Regulatory Specialist: Wendy C. Taddei-Peters, PhD
- Program Analyst: Catherine Burke, MA
- Contract Officer: Joanne Deshler

### 3.2 Investigators

The team of investigators, working in collaboration with the NHLBI to oversee registry activities, includes:

- Principal Investigator: James K. Kirklin, MD, University of Alabama at Birmingham (UAB)
- Study Chair: James B. Young, MD, Cleveland Clinic Lerner College of Medicine
- Co-Investigators:
    - Elizabeth D. Blume, MD, Boston Children's Hospital
    - Robert L. Kormos, MD, University of Pittsburgh Medical Center
    - Francis D, Pagani, MD, PhD, University of Michigan Medical School
    - Lynne Warner Stevenson, MD, Brigham & Women's Hospital

Additional information on each of the investigators may be found at www.intermacs.org.

### 3.3 Data and Clinical Coordinating Center (DCC)

The DCC located in the Cardiac Research Group within the Department of Surgery, UAB 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. The DCC is organized into multiple functional groups and headed by the Director who reports directly to the PI.

DCC staff includes:

- Director: S. Craig Collum, MPH
- Administrative and Fiscal Oversight

    - Claire Finley, Director
    - Jeanne Anne Love, Pedimacs Manager
- Clinical Affairs
    - Kathryn Hollifield, BSN, RN, Director
    - Tammy Davis, RN, Nurse Monitor
    - Janella Miller, BSN, RN, Nurse Monitor
    - Monica Henderson, Audit Support Specialist
- Data Management and Quality Control
    - Susan L. Myers, Director
    - David Helms, Lead Data Analyst
    - John Pennington, Data Analyst
    - Grant Studdard, Research Manager
- Information Technology and Security
    - Robert Kasco, Director
    - Chase Lenderman, Web Developer/Graphic Designer
- Legal Affairs
    - M. Allison Landrum, JD, Director
- Regulatory Affairs
    - Mary Lynne Clark, Director
    - Jeanne Anne Love, Manager
    - David Baldwin, Coordinator
    - Jennifer Gunther, Coordinator
    - Zachary Lindsay, Coordinator
    - DeAnna Beckham, Administrative Manager
    - Sherita Brown, Administrative Support Specialist
- Statistical Reporting
    - Ryan Cantor, MSPH, Director
    - Maceo Cleggett, Programming Specialist
    - Devin Koehl, Research Programming/Statistical Reviewer

Contact information for DCC staff is found in **Appendix L** of this MOP.

## 3.4 Committees

Intermacs® Committees and Subcommittees are described below. Contact information for Committee chairs is located in **Appendix L**.

### 3.4.1 Executive Committee

The Executive Committee (EC), led by Study Chair James Young and comprised of the PI (J. Kirklin), DCC Director (C. Collum), Co-Is (R. Kormos, F. Pagani, L. Warner Stevenson, and E. Blume), and the NHLBI COR (M. Miller) and Alternate COR (T. Baldwin), provides direction, oversight and approval to the registry's design, architecture, refinement, policies, procedures, data collection forms and other functional components. As the driving force behind the entire registry, the EC reviews and formalizes all major decisions and initiatives of the registry,

including linkage of the Intermacs® database to other databases (e.g., the Organ Procurement and Transplant Network, Scientific Registry of Transplant Recipients, Pediatric Heart Transplant Study, CMS, FDA or other health agency medical device safety databases).

The EC may periodically review major adverse events to inform changes to definitions and descriptors following MCSD therapy, promote consensus from its stakeholders about the precise definitions of these events, and propose data elements that will aid in differentiating the underlying causes of adverse events as device-related, patient-related, and management-related. In addition, the EC works closely with the DCC to provide guidance for monitoring and auditing activities. However, major adverse events entered into the Intermacs® database are **not** adjudicated.

All EC 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. The EC convenes weekly via conference calls.

### 3.4.2 Data Access, Analysis, and Publications Committees

Two Data Access, Analysis, and Publications (DAAP) Committees have been established:

- Intermacs®-Adults, chaired by Co-I F. Pagani
- Intermacs®-Pediatrics/Pedimacs, chaired by David Rosenthal, MD, Lucile Salter Packard Children's Hospital at Stanford University

The DAAP Committees address issues of: access to registry data by investigators, proposed analyses which feature Intermacs® data, collaborations, publications, and overall prioritization of such activities. Proposals are reviewed and scored by the DAAP Committees. The DAAP Committees meet quarterly via conference call and may convene more frequently as needed.

### 3.4.3 Hospital Standards Committee

The Hospital Standards Committee, led by the Study Chair and comprised of the EC, as well as additional representatives from the NHLBI and DCC, sets the criteria that participating centers must meet to become members of the Intermacs® registry. It also establishes policies and procedures to ensure satisfactory performance from participating centers. Oversight is provided for staff training of participating centers in registry methods of data collection such that eligible centers can be certified to participate in the registry. This Committee reviews centers that fail to meet or maintain performance standards and develops remedial or educational efforts to reestablish compliance. The Hospital Standards Committee works with the DCC Clinical Affairs group to ensure efficient resolution and holds conference calls as needed.

### 3.4.4 Quality (QoL) Subcommittee

The QoL Subcommittee, chaired by Kathleen L. Grady, PhD, Northwestern University Feinberg School of Medicine, assesses current QoL instruments in patients with advanced heart failure. This Committee advises the EC on the utilization of these questionnaires, is instrumental in the analysis of the data, including QoL outcomes and identification of risk factors for worsening QoL, as well as direct dissemination of results via abstracts, publications and other forms of media. The QoL Subcommittee holds quarterly conference calls.

### 3.4.5 Pediatrics Committee

The Pediatrics Committee, chaired by Co-I E. Blume, oversees Pedimacs and evaluates special issues in the pediatric population receiving MCSD therapy, differences in available devices, and the particular pediatric population for whom this therapy may be most effective. They provide expertise on the unique aspects of infants, children, and teenagers receiving MCSD therapy. This committee is instrumental in the analysis of pediatric data and direct dissemination of results via abstracts, publications and other forms of media. They also investigate merging relationships with other registries and/or databases, e.g., the Pediatric Heart Transplant Study (PHTS), to gain a greater understanding of the effects of pediatric MCSD therapy. The Pediatrics Committee members also participate in other committees. This Committee meets via conference calls on a monthly basis.

### 3.4.6 Conflict of Interest Subcommittee

The Conflict of Interest Subcommittee, chaired by PI J. Kirklin, is responsible for establishing and maintaining oversight of any perceived or real conflicts arising directly or indirectly from Intermacs® members. Specific charges of this Subcommittee include:

- Conducting an assessment of all annual Conflict of Interest Disclosures related to Intermacs® activities;
- Reporting to the Executive Committee the nature of the conflict of interest and the action taken by the Subcommittee;
- Approving or disapproving plans to manage perceived or real conflicts of interest, where appropriate, and recommending any corrective actions as necessary to assure that the approved management plan is followed; and
- Maintaining an awareness of financial conflict of interest policies and guidelines issues by financial sponsors such as the Public Health Service (PHS) and Food and Drug Administration (FDA).

In addition to the PI, this Subcommittee is currently composed of the Study Chair J. Young, NHLBI COR M. Miller, and the DCC Director of Regulatory Affairs M.L. Clark. The Conflict of Interest Subcommittee meets as needed.

### 3.4.7 Business Advisory Committee

The Business Advisory Committee, chaired by DCC Director C. Collum, provides guidance to the EC concerning the sustainability of the registry. This Committee is responsible for implementing and maintaining a public-private collaboration, as well as ensuring that private financial support is provided on an increasing scale, thereby allowing the registry to be maintained in the future when funding by the NHLBI is reduced. In addition to the Chair, the Business Advisory Committee is comprised of representatives from the EC (the PI, Study Chair, and NHLBI COR), participating centers and industry (i.e., MCSD manufacturers). This committee meets annually via conference calls and more frequently as needed.

# 4 Communication

The Intermacs® DCC conducts all aspects of administrative guidance, oversight, and support. The DCC is also responsible for clinical site coordination; data collection, management, and analyses; developing and negotiating legal agreements; and preparation of regulatory packages (including protocol amendments, protocol revision records, and corresponding memos and templates) in support of the registry. Communication, both method and frequency, between the entities of the DCC, Clinical Sites EC, and additional Subcommittees, as well as the government and industry collaborators are outlined below.

## 4.1 Specific Lines of Communication

The DCC facilitates all Intermacs® in-person meetings and teleconferences between stakeholders, which include the participating clinical center clinicians and administrators; participating MCSD manufacturers; Federal collaborators (NHLBI, FDA, and CMS); and the Intermacs® PI and Co-investigators.

Additionally, stakeholders may contact DCC staff directly via email or telephone. For a complete listing of DCC staff with contact information, refer to **Appendix L**. Key DCC staff may also be found on the Intermacs® website and contacted through the general DCC email address at: intermacs@uab.edu.

## 4.2 Intermacs® Website

In addition to specific lines of communication between the DCC and all stakeholders, a comprehensive public website (www.intermacs.org) has been created to enhance overall registry organization and flow. This website contains:

- Special sections designated for general information regarding registry organization, history, and activities;
- Guidance for MCSD implanting centers who wish to participate in the registry (refer to “Participation”);

- Information for MCSD implanting center staff already participating in the registry, including the current protocol and MOP;
- Information for researchers who may wish to request data sets for analysis or collaborate with Intermacs® investigators ("Data Requests");
- "FAQ – Frequently Asked Questions" that can be used as a resource for Intermacs® clinicians;
- A listing of Intermacs® publications and abstracts;
- Intermacs® presentations and statistical summaries; and
- Links to stakeholder websites.

To access the Intermacs® website, click on the following link: www.intermacs.org.

### 4.3 ClinicalTrials.gov

The ClinicalTrials.gov Identifier for Intermacs® is NCT00119834. Please contact the DCC at intermacs@uab.edu with any identified errors or updates. The posting can be accessed through the link below:

http://clinicaltrials.gov/ct2/show/NCT00119834?term=NCT00119834&rank=1

## 5 Registry Design

Intermacs® 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 turned off or explanted. Physical examination is a routine portion of the care for these patients. For adults, the interview consists of survey questions from the EuroQoL (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ) QoL, as well as the Trail Making Neurocognitive Test, Part B, instruments (refer to **Appendices F-H, and M**). For children, the interview consists of survey questions from the Pediatric Quality of Life Inventory (PedsQL) and Ventricular Assist Device Quality of Life (VADQoL) instruments (see **Appendices F and N**). Functional capacity for adults and children is also measured (refer to **Appendices M and N**, respectively).

Intermacs® does not require informed consent. This is a registry for quality improvement. **No data beyond the data gathered in the course of routine care will be collected for this registry.**

# 6 Registry Procedures

## 6.1 Site Registration and Activation

Any medical center in the United States and outside the United States (e.g., Canada) that has an active MCSD program is eligible to participate in Intermacs®. The program must provide personnel and facilities to record and transmit Intermacs®-required data into the web-based electronic database.

Registration and activation of a new center in Intermacs® involves meeting a series of requirements, which are as follows:

1. Complete the online enrollment forms, which include the **Hospital Information** and **Personnel Contact Information** forms, located at: www.intermacs.org. Refer to the "Join Intermacs" button on the left side of the main web page.
    - A local PI representing the center's MCSD program and a Site Administrator as a primary contact for the registry must be identified and their contact information entered into the Intermacs® on-line form during the registration process.
        - The local PI will be responsible for oversight of data submissions and regulatory compliance.
        - The Site Administrator will serve as the "point person" for data related inquiries, receipt and distribution of reports and other materials, and audit coordination.
    - An Intermacs® regulatory staff member will review the information entered in the form and provide additional enrollment guidance to the Site Administrator, as needed.
    - An email notification regarding application status will be sent to the Site Administrator after the forms are submitted.

2. Download the documents needed for IRB/EB submission, which are located at www.intermacs.org under the "Intermacs Documents" tab at the top of the web page. These documents include:
    - Protocol Version 5.0
    - Protocol Version 5.0 Record of Revisions
    - Request for Waiver of Consent and Authorization (refer to **Appendix C**)

3. Follow local policies regarding additional IRB/EB requirements (e.g., submission of the Users' Guides, data collection forms, and other required documents). IRB/EB Guidelines are located in **Appendix B**. Data collection forms for Intermacs® (patients ≥ 19 years of age) are located in **Appendix P** and for Pedimacs (patients < 19 years of age) in **Appendix Q**.

4. Complete the following agreements and disclosures, which must be submitted as part of the Enrollment Package (described below in item 5):

- The Participation Agreement is an agreement between the local center and The Board of Trustees of the University of Alabama on behalf of Intermacs® outlining the responsibilities of the center and of Intermacs®. The agreement must be signed and dated by a clinical center official and submitted to Intermacs®. The Participation Agreement template is located in **Appendix D**.
- The Business Associates Agreement is an agreement between the local center and The Board of Trustees of the University of Alabama on behalf of Intermacs® that describes the applicable Health Insurance Portability and Accountability Act (HIPAA) requirements for sharing protected health information (PHI) and allows Intermacs® to perform quality improvement services on behalf of the local clinical center. The agreement must be signed and dated by a clinical center official and submitted to Intermacs®. This template is also located in **Appendix D**.
- Financial Disclosure and Conflict of Interest forms must be completed for all site personnel participating in Intermacs® and submitted to the Intermacs® DCC. This form must be updated on an annual basis and is located in **Appendix E**.

5. Submit the Enrollment Package to the INTERMACS® DCC at intermacs@uab.edu. This package includes the following documents:
    - Documentation of IRB/EB review of the protocol and waiver of informed consent and authorization.
        - In the event that your IRB/EB indicates that this Quality Improvement Registry no longer falls under their purview, then request that your IRB provide a letter stating that they have reviewed the protocol and do not believe that it falls under their purview; therefore, they cannot grant approval.
        - In the event that a waiver is obtained but the IRB/EB continues to require annual review, then provide the IRB/EB's written decision to the Intermacs® DCC.
        - In the event that a waiver cannot be obtained, then the IRB/EB approval letter and approved informed consent and patient authorization form(s), as well as any other related correspondence must be submitted to the Intermacs® DCC.
            - Instructions and updated consent and authorization templates are located in **Appendix C**.
            - Follow local policies regarding additional IRB/EB requirements (e.g., submission of Users' Guides [**Appendix M-Adults and N-Pediatrics**]).
    - Current Federal Wide Assurance Number (FWA), as applicable;
    - Current Clinical Laboratory Improvement Amendments (CLIA) Certificate;
    - Documentation of the NIH's Privacy Awareness Training (refer to Section 8.1 for further instruction).
    - Signed Participation Agreement, which requires a participation fee in order to activate the site.
    - Signed Business Associates Agreement; and

- Completed Financial Disclosure and Conflict of Interest forms

The submission process takes *approximately 2 months*. Sufficient time is needed for IRB/EB review, completion of agreements and disclosures, and staff training on Privacy Awareness.

6. After submission of the Enrollment Package, Intermacs® staff will:
   - Review the package to verify that all documents have been submitted in accordance with Intermacs® requirements.
   - Provide an invoice for the participation fee, which is invoiced annually thereafter.

   Verification and processing of the documents by the DCC takes approximately 2-3 weeks after receipt of the Enrollment Package.

7. Site training will occur after acceptance of the Enrollment Package and payment of the participation fee.
   - The enrolling site will be contacted by Intermacs® staff to schedule a live web-based training session to be held via conference call and Cisco Web-Ex.
   - Training sessions run approximately 2 hours. At least one team member from the site is required to receive training.
   - During this session, the trainer will review the protocol requirements, QoL and Neurocognitive assessments, and other relevant procedures. In addition, site staff will be trained on data entry.

8. The site is normally activated within 24-72 hours of training. A secure phone call or email notification with a username and password will be provided to each designated member at the activated site.

### 6.2 Annual Re-certification

Once activated, Intermacs® requires annual submission of regulatory documents and the participation fee to continue participation in the registry. 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 the protocol and Users' Guide (**Appendix M** for adults and **Appendix N** for pediatrics).

NOTE: Provide documentation that site staff has taken Privacy Awareness refresher training per local IRB requirements or every 2 years, whichever comes first. Refer to Section 8.1 for details.

### 6.3 Screening and Eligibility

All patients receiving MCSDs will be screened according to the inclusion and exclusion criteria provided in Section 2 and in the protocol (Sections A.1.1 and B.1.1). Procedural guidance for the two inclusion criteria are as follows:

1. The device brand lists of legally utilized devices accepted by Intermacs® for adults and for pediatrics (< 19 years of age) may be found in **Appendix K**.

2. Patients receiving an MCSD must be at an Intermacs®-activated center. The center is considered to be activated once it has received DCC approval and has gained access to the Intermacs® database.

For patients who do not meet the eligibility criteria, the following information will be recorded on the screening log:

- gender,
- race,
- ethnicity,
- age decade,
- device type (LVAD, RVAD, Both, TAH),
- device brand,
- date of implant,
- whether the MCSD is investigational,
- whether the patient is in an MCSD clinical study, and
- death should it occur within 2 days of implant

Refer to Section 2.1 of the Users' Guide-**Appendix M** for adults and **Appendix N** for pediatrics. 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.

For patients who meet the eligibility criteria, additional data are requested for those individuals with congenital diagnoses. For adult (non-congenital) patients, these data elements are not visible.

## 6.4 Enrollment and Assignment of Registry Identification Number

During the time that the patient is being consented for implant of their MCSD or as soon as possible after implant in emergent cases, a copy of the patient information summary may be provided. **The information sheet is provided as a courtesy and is not a requirement of Intermacs®.** Patient information sheets, one specific for adult and another specific for pediatric patients are provided in **Appendix C**.

For those sites where a Waiver of Consent and Authorization has not been granted, patients will be required to sign an IRB/EB-approved informed consent and HIPAA authorization. Refer to **Appendix C** for instructions and templates.

All data will be entered electronically through the Intermacs® web-based data entry system (Intermacs® application). In order to begin entering patient data, go to www.intermacs.org, click on the "Intermacs Login" or "Pedimacs Login" button on the left side of the webpage, and enter your user name and password. The instructions for data entry beginning with the Screening Log are located in the Users' Guide-**Appendix M** for adults and **Appendix N** for pediatrics).

The Screening Log records the results of the inclusion/exclusion criteria and must be completed at the time of patient enrollment. Once the patient has met the eligibility criteria listed on the screening log, you will automatically be directed to the data entry system.

A registry identification number, which is generated by the Intermacs® application, will be assigned to each patient at the time of initial data entry into Intermacs®. This identification number will be used as the primary patient identifier between the clinical center, Intermacs®, MCSD manufacturers, and government agencies.

## 6.5 Follow-up

For all patients entered into the registry, follow-up will occur at select time points (i.e.,1 week, 1 month, 3 months, 6 months and every 6 months thereafter) for as long as an MCSD is in place, and for up to 1 year, if a patient has an MCSD removed/turned off and is not transplanted. Vital status, including transplantation and survival, will be determined during this 1-year follow-up period.

The following table provides the acceptable clinic visit windows for each time point.

**Follow-up Visit Windows**

| Expected Clinic Visit | Acceptable Time Window for Clinic Visit |
|---|---|
| 1 week | +/- 3 days |
| 1 month | +/- 7days |
| 3 month | +/- 30 days |
| 6 month | +/- 60 days |
| 12 month | +/- 60 days |
| 18 month | +/- 60 days |
| 24 month | +/- 60 days |
| 30 month | +/- 60 days |
| 36 month | +/- 60 days |

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 OPTN database and will be followed by that database. A patient undergoing transplantation more than 1 year after VAD explantation will be included in Intermacs® for the first year after explant, and then will be followed through the OPTN at the time of transplantation.

## 6.6 Transfer

If a patient transfers his/her care to another center, the patient is deactivated at the implanting center at the time of transfer. The patient is re-activated at the new center, provided the new center is an Intermacs®-participating center.

The following steps must be completed for a patient transfer:

1. The original (implanting) center must complete any required event forms before the official date of transfer.

2. The original (implanting) center must complete the **Patient Transfer (formerly Registry Status) Form** in the Intermacs® application indicating that the patient is no longer receiving care.

3. The new center must have the patient complete the **Patient Authorization for Intermacs® to Release Information Form**. In the event that the IRB/EB did not

grant a waiver of consent at the new center, then the patient must also sign the local IRB/EB-approved Informed Consent Form.

4. The new center must provide the DCC with the patient's date of birth, gender, race and implant date ***before the patient can be transferred to the new site***.

5. If a patient is transferred to a site that uses a unique identifier in place of the patient's name or partial social security/insurance number, the following steps must be taken:
   - Ask the original (implanting) center to edit the name and partial social security/insurance number by using a code appropriate for the new (receiving) center. (The original center may require IRB/EB approval prior to revising the identifiers.)

   - If a patient is transferred to a center that does not collect the partial social security/insurance number, then replace the number with "99999" as shown in the example below for patient "John Doe".

   Example:

| | |
|---|---|
| Old Identifiers: | Name - John Doe |
| | Partial SS# - 56789 |
| New Code: | Name - Jo Do |
| | SS# Code - 99999 |

   The registry-assigned ID number will remain the same.

6. The DCC will re-activate the patient once all submitted documentation has been verified as complete and accurate.

Once the transfer has been completed, the original (implanting) center will have "read only" access to pre-transfer Intermacs® data and will no longer be able to review or make any changes to patient records after the transfer date. The new (receiving) center will have "read only" access to all forms prior to and up to the transfer date. Once the transfer has been completed, any follow-up entries automatically generated past the transfer, will be completed by the new center.

*[Note: Since the transfer process involves participant Protected Health Information (PHI), only send PHI through secure e-mail. Access to the Intermacs® secure e-mail is available by contacting Intermacs® at intermacs@uab.edu.]*

## 6.7 Data Collection

### 6.7.1 Web-based Data Entry

The Intermacs® Application, which is a web-based data entry system, is comprised of a series of forms. The data to be collected are divided into forms

that correspond to the clinical time course of the patient. It is critical that each site stay current with Intermacs® data entry. Data that are submitted late will have an adverse effect on many of the internal Intermacs® calculations, including survival estimates, incidence of adverse events, and rates of transplant. Forms should generally be completed within 7 days of an event, but always within 30 days of an event/clinic visit as described in Section 9.1. Forms entered beyond the 30-day window will be flagged as late and used as a criterion for site compliance as described in Section 9.1.

Instructions for entering data along with the Data Dictionary for these forms are located in the Users' Guide (**Appendix M** for adults and **Appendix N** for pediatrics, Section 2.0). Listed below are the clinical data forms requiring data entry along with the timing of data entry, if applicable, for each form. Specific instructions are located in the Intermacs® and Pedimacs Users' Guides in the specific sections listed next to each data entry form below.

**Demographics (Section 2.2 of Users' Guides)**

- To be completed prior to implant and as close to implant as possible
- Collects the following data for each participant:

| | | |
|---|---|---|
| Name | Gender | Employment status – adults only |
| Medical record # | Ethnicity | Work level (e.g., full-time, part-time, disability) - adults only |
| Last 5 digits of SSN/SIN | Race | Participation in VAD study |
| Health Insurance Claim Number (HICN) - adults only | Marital status – adults only | Surgeon/Operator first, middle and last name |
| Date of birth | Education level – adults only | Surgeon/Operator national provider identifier (NPI) for US centers |

**Pre-implant (Section 2.3 of Users' Guides)**

- To be collected at the time of implant or closest to the implant date and within 60 days of pre-implant, but not to be collected in the operating room; the Quality of Life surveys need to be collected within 30 days pre-implant.
- Collects the following information for each participant:

| | | |
|---|---|---|
| Height | Known cardiac biopsy – adults | Concurrent ICD or CRT |
| Weight | Prior cardiac surgeries | Metalozone/thiazide therapy – adults |
| Blood type | Admitting diagnosis | Phosphodiesterase inhibitors – adults |

| | | |
|---|---|---|
| Device strategy | Hospital clinical events & interventions pre-implant | Laboratory values |
| Co-morbidities | Inotrope therapy | Medical condition – NYHA Class for patients ≥ 2 years, Ross Class for patients < 2 years |
| Time since first cardiac diagnosis | Intermacs® / Pedimacs profile at time of primary implant | Functional capacity (exercise function) |
| # of cardiac hospitalizations in last 12 months – adults | Primary & secondary reasons for implant – pediatrics | QoL |
| Primary cardiac diagnosis | Hemodynamic parameters pre-implant | Neurocognitive function – adults |
| Secondary cardiac diagnosis – adults | Concurrent medications – adults | |

**Implant (Section 2.4 of Users' Guides)**

- To be completed within 1 week of post implant
- Collects information on:

| | | |
|---|---|---|
| Additional indication for VAD | LVAD inflow cannula parameters | RVAD pump size – pediatrics |
| Device type | LVAD outflow cannula parameters | Total artificial heart (TAH) serial number |
| Device brand | LVAD pump size – pediatrics | Associated findings (surgical observations or intraoperative TEE) |
| Implant date | RVAD serial number | Concomitant surgery |
| LVAD serial number | RVAD inflow cannula parameters | Total cardiopulmonary bypass and cross clamp times |
| Surgical approach | RVAD outflow cannula parameters | Total surgery time |

**1 Week and 1 Month Follow-up (Section 2.5 of Users' Guides)**

- To be collected 1 week ± 3 days ***and*** 1 month ± 7 days post-implant date
- When doing medical chart abstraction, use the clinic visit closest to the follow-up period.
- Collects information on:

| | | |
|---|---|---|
| Hemodynamic parameters | Transfusion – pediatrics | Functional capacity and Excursions – pediatrics |
| Concurrent medications | Laboratory values | Zones (hemolysis and |

| | | |
|---|---|---|
| | | right heart failure zones) |
| Pump change | Medical condition - NYHA Class patients ≥ 2 years, Ross Class for patients < 2 years | Adverse events |

**3 Month and 6 Month Follow-Up (Section 2.6 of Users' Guides)**

- To be collected 3 months ± 30 days, 6 months ± 60 days, and every 6 ± 60 days post-implant perpetually
- When doing medical chart abstraction, use the clinic visit closest to the follow-up period.
- Collects information on:

| | | |
|---|---|---|
| Hemodynamic parameters | Device parameters | Zones (hemolysis and right heart failure zones) |
| Concurrent medications | Device inspection | Neurologic status (adults) |
| Pump change | Functional capacity (exercise function) | QoL |
| Transfusion - pediatrics | Medical condition – NYHA Class patients ≥ 2 years, Ross Class for patients < 2 years | Neurocognitive function – adults |
| Laboratory values | Patient status | Major outcomes & adverse events |
| Device function | Functional capacity (qualitative) and excursions – pediatrics | |

**Implant Discharge (Section 2.7 of Users' Guides)**

- Collects information about a patient from the device implant to one of the following occurrences during the implant hospitalization:
  - Patient is discharged from the center with a device in place;
  - Patient receives a transplant during the implant hospitalization (date of transplant is considered the date of discharge);
  - Patient dies during the implant hospitalization (date of death is considered to be the date of discharge); or
  - Patient has the device(s) explanted due to recovery (date of device(s) explant is considered to be the date of discharge).
  - Patient has device exchange (excluding RVAD exchange).
- Information collected includes functional capacity, transfusions, pump change, major outcomes and adverse events.

**Listing Date for Transplant (Section 2.8 of Users' Guides)**

- If the patient was NOT listed for transplant at the time of implant, then the list date for transplant, if applicable to the patient, is collected on this form.

**Re-hospitalization (Section 2.9 of Users' Guides)**

- To be collected within 1 week from re-hospitalization discharge; this form is intended to collect information about a patient from the date of re-hospitalization to one of the following occurrences:
  - Patient is discharged from the center with a device in place;
  - Patient receives a transplant during the re-hospitalization (date of transplant is considered date of discharge);
  - Patient dies during the re-hospitalization (date of death is considered date of discharge);
  - Patient has the device(s) explanted due to recovery during the re-hospitalization (date of explant is considered date of discharge).

**Adverse Events (Section 2.10 of Users' Guides)**

- Four forms are associated with the 4 major adverse events that are to be collected at the time of the event; they include: Major Infection, Neurological Dysfunction, Device Malfunction/Failure and/or Pump Thrombus, and Major Bleeding.
- For patients who experience a neurologic event post-implant, the modified Rankin Scale (MRS) and/or National Institutes of Health Stroke Scale (NIHSS) must be administered and the resultant scores recorded at the time of the event and at follow-up visits as part of the patient's routine care (Refer to Section 6.7.4 and **Appendix I**). Event reminders for all other adverse events listed in **Appendix A** are prompted during each follow-up visit and re-hospitalization.
  - The following events are considered "trigger events", which are captured within the database based on the relevant data entered for follow-up and re-hospitalization:
    - hemolysis
    - hypertension
    - right heart failure

**Death (Section 2.11 of Users' Guides)**

- To be collected at the time of death
- Collects data related to the patient's death, including date, time, place, cause, whether device was functioning normally, if expected or unexpected

**Explant for Device Exchange, Recovery or Transplant (Section 2.12 of Users' Guides)**

- To be collected at the time of explant, transplant or both; this includes devices that are "turned off" AND left in place
- Collects data related to the explant, including device type, explant date, and reason for explant

Note: If the patient is transplanted, that patient will no longer be followed in the Intermacs® Registry, but will be followed in the OPTN database. If the patient is

explanted due to ventricular recovery or an MCSD is no longer utilized (e.g., removed or turned off), Intermacs® will continue a 1 year follow-up for this patient for death and/or transplant.

**Patient Transfer/Withdrawal Forms [formerly Patient Registry Status (Section 2.13 of Users' Guides)]**

- To be completed when a patient transfers their care to another center as discussed in Section 6.6;
- If the receiving center is not an Intermacs® center, then patient records are 'stopped' at time of transfer.

**Quality of Life (Section 2.14 of Users' Guides)**

- QoL questionnaires are to be administered pre-implant and post-implant (3 months, 6 months, and every 6 months thereafter) as part of the patient's routine care.
- All adult patients should complete the EuroQoL (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ), which are located in **Appendix F** and **Appendix H**, respectively, and discussed below in Section 6.7.2.
- All pediatric patients should complete the Pediatric Quality of Life Inventory (PedsQL) and Ventricular Assist Device Quality of Life (VADQoL) instruments, which are located in **Appendix F** and discussed below in Section 6.7.2.

**Neurocognitive Function Test (Section 2.15 Intermacs® Users' Guide only)**

- The Trail Making B test is to be administered pre-implant and post-implant (3 months, 6 months and every 6 months thereafter) as part of the patient's routine care.
- All adult patients should complete the Trail-Making Part B test, which is located in **Appendix G** and discussed below in Section 6.7.4.

### 6.7.2 Quality of Life Evaluation

**Adult Patients**

QoL will be measured by the EQ-5D and the KCCQ instruments in adult patients as part of the patient's routine care. If these assessments are not considered standard of care at your site, Intermacs® does not require the data. The EQ-5D and KCCQ are located in **Appendix F** and **Appendix H**, respectively.

The EQ-5D and KCCQ may be printed for the patient to complete. The EQ-5D and the KCCQ are available in English, Spanish, and French. It is anticipated that completing these instruments will take the patient 20 minutes per instrument. Administering the instrument and entering the data into the registry will require approximately 30 minutes of clinical staff 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).

The EQ-5D and KCCQ are provided to patients by trained clinical staff as designated by each participating medical center. The patient is to complete both instruments via self-report independently. If the patient is unable to complete these instruments, the trained clinician or a family member is to read the questions to the patient and complete both questionnaires documenting the patient's responses. Indicate on the instruments that the EQ-5D and KCCQ were self-administered or administered verbally by another. NOTE: There should be no coaching regarding responses.

The patient is to complete the EQ-5D and KCCQ *before MCSD implant and at the return clinic visits closest to the appropriate data collection time points* (assuming the patient has been discharged prior to the data collection time points). Otherwise, the questionnaires are to be administered during hospitalization at the appropriate data collection time points. **Pre-implant assessment of quality of life is essential in evaluating MCSD therapy.** Every effort should be made to obtain this information at each time point as part of the patient's routine care.

The EQ-5D and KCCQ are to be reviewed for missing or unclear data at the time of instrument completion. Corrections must be made with the patient at that time. Enter the patient's answers from the paper form into the database through www.intermacs.org.

For patients who do not complete the EQ-5D or KCCQ, enter reason as to why these questionnaires were not completed.

Refer to the Users' Guide (**Appendix M**) for additional data entry instructions.

**Pediatric Patients**
In pediatric patients, QoL will be measured by the PedsQL and VADQoL instruments as part of the patient's routine care. If these assessments are not considered standard of care at your center, Intermacs® does not require the data. The PedsQL and VADQoL may be printed for the patient/parent to complete.

The following PedsQL instruments are located in **Appendix F** in English, Spanish, and French:

- Parent Report for Toddlers (Ages 2-4 years)
- Young Child Report (Ages 5-7 years)
- Parent Report for Young Children (Ages 5-7 years)
- Child Report (Ages 8-12 years)
- Parent Report for Children (Ages 8-12 years)
- Teen Report (Ages 13-18 years)
- Parent Report for Teens (13-18 years)

The following VADQoL instruments are also located in **Appendix F** in English only:

- Parent Report for Children Ages < 2 years
- Parent Report for Children Ages ≥ 2 years
- Child Report for Children Ages > 8 years

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 clinical staff 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) as part of the patient's routine care.

The PedsQL and VADQoL are provided to patients/parents by trained clinical staff as designated by each participating medical center. The patient/parent is to complete the PedsQL and VADQoL instruments via self-report independently. If the patient/parent is unable to complete the instruments, the trained clinician or a family member is to read the questions to the patient/parent and complete the instruments documenting the patient's/parent's responses. Indicate on the instruments that the PedsQL and VADQoL were self-administered or administered verbally by another. NOTE: There should be no coaching regarding responses.

The patient/parent is to complete the PedsQL and VADQoL *before MCSD implant and at the return clinic visits closest to the appropriate data collection time points* (assuming the patient has been discharged prior to the data collection time points). Otherwise, the questionnaires are to be administered during hospitalization at the appropriate data collection time points. **Pre-implant assessment of quality of life is essential in evaluating MCSD therapy.** Every effort should be made to obtain this information at each time point as part of the patient's routine care.

The PedsQL and VADQoL are to be reviewed for missing or unclear data at the time of instrument completion. Corrections must be made with the patient/parent at that time. Enter the patient's/parent's answers from the paper form into the database through www.intermacs.org.

For patients who do not complete the PedsQL and VADQoL, enter reason as to why these instruments were not completed.

Refer to the Users' Guide (**Appendix N**) for additional data entry instructions.

### 6.7.3 Functional Capacity Evaluation

**Adult Patients**
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 (6MWT), gait speed, and cardiopulmonary exercise indices.

All patients should be encouraged to attempt to complete these functional capacity measurements especially for those patients classified as Intermacs® patient profile levels 4-7:

- **6MWT**: The 6MWT should be performed along a long, straight, quiet 30-meter corridor. The turnaround points can be marked with tape or a cone (such as a bright orange traffic cone). The subject's usual medications should be continued. Subjects should not have exercised vigorously for at least 2 hours prior to the walk test. Exercise can be done after a light meal.

  The patient should sit in a chair near the start line for at least 5 minutes before the test starts. Resting heart rate and blood pressure should be checked to ensure that the patient is not too ill to undergo the test (e.g., patients with unstable angina, a heart rate >120 bpm, or systolic BP < 80 mm Hg should not undergo the walk test). The patient should then stand at the starting line.

  Set the lap counter to zero and stopwatch to 6 minutes.

  The following script may be used to instruct the patient:
  "The object of the test is to walk as far as possible in 6 minutes. You will walk back and forth in this hallway to the designated markers. You will be exerting yourself and you may get exhausted or short of breath. You are permitted to slow down and stop if you need to rest. You may lean against the wall while resting but should resume walking as soon as you are able. You should make sharp turns around the markers and continue back and forth without hesitation. I will use a counter to keep track of your laps and click it each time you reach the starting line.

  REMEMBER THE OBJECT OF THE TEST IS TO WALK AS FAR AS POSSIBLE IN 6 MINUTES BUT DON'T RUN OR JOG.

  During the test I will tell you how much time has elapsed. I will let you know when there is only 15 seconds remaining. At the end of 6 minutes, I will tell you to stop. Please stay where you are and I will come to you.

  Let me know when you are ready to start."

The staff member performing the test should not walk with the patient but should stand *behind* the patient to avoid undue influence on pace. He/she should use an even tone of voice and standard phrases of encouragement. He/she should not tell or signal to the patient to speed up or hurry. The staff member should report the time remaining to the patient. Use phrases like – "Keep up the good work. You have x minutes remaining." "Good job, you're halfway through." "You are doing well, x minutes remain."

All efforts should be made to perform the 6MWT for any patient able to walk more than a few steps. A distance as short as 3 feet may be recorded. If the test is not done, the reason must be indicated as "Not done: too sick" or "Not done: other", for which an example might be a patient needing to remain supine after a groin puncture for routine catheterization. Any musculoskeletal limitation to walking should be recorded as "Not done: too sick". If it is unknown whether the test was performed, select "Unknown".

- **Gait Speed (First 15-foot walk)**: Record the time in seconds required for the patient to walk 15 feet. The "starting" line and the 15-foot line should be clearly marked. Record the time from the first footfall at 0 feet to the first footfall at 15 feet in the nearest 0.1 seconds with a stopwatch. NOTE: You may use the time from the first 15 feet of the 6MWT for the Gait Speed test.

  All efforts should be made to perform the Gait Speed test for any patient able to walk more than a few steps. If the test is not done, the reason must be indicated as "Not done: too sick", "Not done: other" or "Unknown".

- **Maximum volume of oxygen the body can consume during exercise (Peak $VO_2$ Max) is measured in mL/kg/min**: Peak $VO_2$ Max is measured during symptom-limited cardiopulmonary exercise (CPX) either on a bicycle or treadmill. The values recorded during bicycle CPX are usually 1-2 mL/min lower than for the treadmill; however, it is assumed that most institutions will use only one instrument. If both are available, the bicycle is preferable as the mode easiest to standardize. If CPX is not done, the reason must be indicated as "Not done: too sick", "Not done: other" or "Unknown".

- **R Value at Peak**: R Value at Peak is the respiratory quotient of carbon dioxide production divided by oxygen consumption and is used as an index of how vigorously the patient exercised. A value above 1.05 is generally considered to represent an adequate effort. If CPX is not done, the reason must be indicated as "Not done or "Unknown".

Refer to the Users' Guide (**Appendix M**) for additional data entry instructions.

**Pediatric Patients**
Functional capacity measures for pediatric patients ages ≥ 10 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: 6MWT, gait speed, and cardiopulmonary exercise indices as described above for adults. All patients ≥ 10 years of age at the time of implant should be encouraged to attempt to complete these functional capacity measurements especially for those patients classified as Pedimacs patient profile levels 4-7:

- **6MWT**: If the test is not done, the reason must be indicated as "Not done: too sick", "Not done: other", or "Not done: age inappropriate".

- **Gait Speed test**: If the test is not done, the reason must be indicated as "Not done: too sick", "Not done: other", or "Not done: age inappropriate".

- **Peak $VO_2$ Max**: If CPX is not done, the reason must be indicated as "Not done: too sick", "Not done: other", or "Not done: age inappropriate".

- **R Value at Peak**: If CPX is not done, the reason must be indicated as "Not done: too sick", "Not done: other", or "Not done: age inappropriate".

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).

Refer to the Users' Guide (**Appendix N**) for additional data entry instructions.

### 6.7.4 Neurocognitive Evaluation

**Trail Making Neurocognitive Test, Part B**
Neurocognitive function will be measured by the Trail Making Neurocognitive Test, Part B in adults only as part of routine care. If this assessment is not considered standard of care at your center, Intermacs® does not require the data to be entered into the web-based electronic database. The test is located in **Appendix G** and must be printed for the patient to complete. 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.

The Trail Making Test, Part B, requires the patient to draw in ascending order and alternating sequentially between circled numbers (1-13) and alphabet letters (A-L) without lifting the pencil. The test is timed (measured in seconds), with the faster times (seconds) being better. Lifting the pencil and wrong direction with the examiner prompting constitutes errors.

The test is to be administered **pre-implant** and **post-implant** (at 3 months, 6 months, and every 6 months thereafter) as part of the patient's routine care.

After the subject completes Part B, take the test sheet and record the time in seconds. Errors contribute to the evaluation of the performance principally by increasing the total performance time. If the patient completes the test, but the test is considered invalid, select "completed but invalid (score not entered)". ***Do not allow patient to retake the test.***

Steps in administering the test are as follows:

1. Let the patient practice with the Trail Making Sample B. The following script may be used to instruct the patient (refer to italicized text):

   "*On this page are some numbers and letters. Begin at 1* (point to the number 1) *and draw a line from 1 to A*" (point to A) "*A to 2*,"(point to 2), "*2 to B*" (point to B), "*B to 3*" (point to 3), "*3 to C*" (point to C), "*and so on, in order, until you reach the end*" (point to the circle marked "end").

   "*Remember, first you have a number*" (point to 1), "*then a letter*" (point to A), "*then a number*" (point to 2), "*then a letter*" (point to B), "*and so on. Draw the lines as fast as you can. Ready--- Begin!*"

   If the subject completes the sample B correctly say: *"Good! Let's try the next one."* Proceed immediately to the test as described in step 2 below.

   **If the subject makes a mistake on sample B, point out the error and explain why it is incorrect.** The following explanations of mistakes serve as illustrations:

   *"You started with the wrong circle. This is where you start* (point to 2). "*You skipped this circle"* (point to the circle the subject omitted). "*You should go from 1"* (point to 1) *"to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"and so on until you reach the circle marked end"* (point to the circle marked "end").

   **If the subject cannot complete Sample B**, take his/her hand and guide the pencil, <u>using the eraser end</u>, through the circles. Then say:

*"Now you try it. Remember, you begin at number 1"* (point to the number 1), *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"and so on until you reach the circle marked 'end'."* (point to this word), *"Ready --- Begin!"*

2. Ask patient to complete the actual Trail Making Test, Part B.

   After the subject has correctly completed the sample, turn the paper over to Part B and say:

   *"On this page, there are both numbers and letters. Do this the same way. Begin at number 1"* (point to 1), *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"3 to C"* (point to C), *"and so on, in order, until you reach the end"* (point to the circle marked "end"*). "Remember, first you have a number"* (point to 1), *"then a letter"* (point to A), "*then a number"* (point to 2), *"then a letter"* (point to B), *"and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready ---Begin!"*

   Using a stopwatch, start timing as soon as the subject is told to begin. Remember to be alert for mistakes. If the subject makes an error, DO NOT STOP TIMING. Point it out immediately, return the subject to the last correct circle and say, *"Now, are you looking for a number or a letter?"* Continue the test from that point. DO NOT STOP TIMING.

   After the subject completes Part B, take the test sheet and record the time in seconds. Errors contribute to the evaluation of the performance principally by increasing the total performance time. If the patient completes the test, but the test is considered invalid, select "**Other, specify**" and, specify the reason you are not entering a score. ***Do not allow patient to retake the test.***

Refer to the Users' Guide (**Appendix M**) to enter the Trail Making Data results. Status (e.g., completed, completed but invalid, attempted but not completed, not attempted) and the time it required to complete the test (in seconds) must be entered.

**Modified Rankin Scale (MRS) Score**
For patients who experience a neurological event post-implant, the MRS score (refer to **Appendix I** for this form**)** must be recorded unless the NIHSS is considered the standard of care at your center. The MRS is a scale commonly used for measuring the degree of disability or dependence in the daily activities of individuals who have suffered a stroke. The MRS is administered at the time of the event and at follow-up visits after the event. The assessment requires approximately 5 minutes to complete.

The scale runs from 0-6, running from perfect health without symptoms to death:

- 0 - No symptoms
- 1 - No significant disability despite symptoms; able to carry out all usual duties and activities.
- 2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
- 3 - Moderate disability; requires some help, but able to walk unassisted.
- 4 - Moderately severe disability; unable to walk unassisted and unable to attend to own bodily needs without assistance.
- 5 - Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
- 6 - Dead

Only clinical staff trained to administer the test may do so. Training may be obtained at the following website: *http://www.rankinscale.org/.*

**National Institutes of Health Stroke Scale (NIHSS) Score**
For patients who experience a neurological event post-implant, the NIHSS score (refer to **Appendix I** for this form**)** can be recorded in addition to or instead of the MRS score depending whether these assessments are considered standard of care at your center.

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The scale was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. However, the NIHSS is now widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome.

The NIHSS is an 11-item neurologic examination stroke scale; each item scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

| Stroke[1] | Stroke Severity |
|---|---|
| 0 | No Stroke Symptoms |
| 1-4 | Minor Stroke |
| 5-15 | Moderate Stroke |
| 16-20 | Moderate to Severe Stroke |
| 21-42 | Severe Stroke |

[1] http://emedicine.medscape.com/article/2172609-overview

The single patient assessment requires less than 10 minutes to complete. Throughout the assessment, it is important that the examiner does not coach or help with the assigned task. The examiner may demonstrate the commands to patients that are unable to comprehend verbal instructions; however, the score should reflect the patient's own ability. It is acceptable for the examiner to physically help the patient get into position to begin the test, but the examiner must not provide further assistance while the patient is attempting to complete the task. For each item, the examiner should score the patient's first effort and repeated attempts should not affect the patient's score. An exception to this rule is the language assessment (Item 9) in which the patient's best effort should be scored. Some of the items contain "Default Coma Scores", these scores are automatically assigned to patients that scored a 3 in item 1a.

Only clinical staff trained to administer the test may do so. Training may be obtained on-line at several websites (e.g., https://learn.heart.org/nihss.aspx). Alternatively, the NIH Stroke Scale Training DVD (version 2.0) may be obtained via the National Institute of Neurologic Disorders and Stroke at: https://catalog.ninds.nih.gov/ninds/product/NIH-Stroke-Scale-Training-DVD-version-2-0-/NDS-511.

# 7 Informed Consent and Release of Medical Records

Intermacs® does not require informed consent because it 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. **No data beyond the data gathered in the course of routine care are required for this registry.**

## 7.1 Waiver of Consent and Authorization

For centers who have been granted a Waiver of Consent and Authorization, a written summary describing Intermacs® is available in **Appendix C** and may be provided to the patient (or patient's parents), e.g., at the time that the patient/parent is completing the routine MCSD surgical consent form. Patient Information Sheets, one for adult patients and one for pediatric patients, may be provided as a courtesy but are not a requirement of Intermacs®. **NOTE: Before providing the Patient Information Sheet to the patient/parent, insert the name of your institution in the first paragraph and the appropriate contact information at the bottom of the page to ensure that all patients have access to qualified staff for any questions they may have regarding Intermacs®.**

## 7.2 Informed Consent Process

In the event that Waiver of Consent and Authorization is not granted by the IRB/EB, then participating centers should follow their local IRB/EB policies in regard to obtaining informed consent. Informed consent templates for adult and pediatric patients are provided in **Appendix C**. Because participation in this Registry is considered minimal risk, the IRB/EB may approve a consent that does not include or alters some of the elements. A list of informed consent elements is also provided in **Appendix C**.

- **Adult Templates Available**
  - Informed Consent for Participation in Intermacs®
  - Patient Authorization for Intermacs® to Release Information (for patient transfers)
  - Revoke Authorization (for patient withdrawal)

- **Pediatric Templates Available**
  - Informed Consent for Participation in Pedimacs
  - Patient Authorization for Pedimacs to Release Information (for patient transfers)
  - Revoke Authorization (for patient withdrawal)

The templates may be customized with specific requirements designated by your center. The draft consent form must be provided to the DCC for review prior to IRB/EB submission. For any questions during the submission process, contact the DCC at intermacs@uab.edu.

In some cases, the local IRB/EB may grant a waiver of consent and authorization for the overall registry but require written consent for a particular evaluation (e.g., Trail Making Test, Part B). Each center should work with their local IRB/EB to develop consent forms for specific evaluations as required. The DCC is available to provide assistance as needed. Note that Intermacs® does ***not*** require any evaluations, which are not considered standard of care at your institution.

**Consent Process**
Obtaining informed consent and timing for the informed consent process must be consistent with the clinical center's institutional IRB/EB and privacy policies. The investigator or a designated individual will provide a thorough explanation of the objective, patient responsibilities, risks and benefits of the registry, and will fully address concerns raised by the patient and/or family. The consent process (and its documentation) must begin prior to all data collection and protocol procedures. This is to ensure that all potential study participants are given adequate time to review the informed consent document and consider participation in the registry.

A patient should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time.

A signed copy of the consent form must be given to the study participant. All signed consent forms, including the initial consent and any re-consents must be available for audits (e.g., by Intermacs® and/or local IRB/EB).

The consent process must be documented in the study participant's record according to the institutional requirements. The investigator or his/her designee must:

- Document any questions addressed with the patient and/or family during the informed consent process in the medical chart;
- Confirm that all signatures on the informed consent are complete and dated;
- File the original signed informed consent with study participant's research documents.

**Non-English Speaking or Hearing Impaired Subjects**

Clinical centers must abide by local institutional guidelines when approaching a non-English speaking or hearing impaired subjects during the informed consent process. Local IRBs/EBs will have guidelines in place that must be followed. For all consented non-English speaking or hearing impaired participants, the clinical center must document the information noted in the Consent Process section above but also specify such information as:

- A brief description of local policy on consenting a non-English or hearing impaired patient;
- A brief description of how the policy was followed in the consent process for these patients;
- The name of the translator and/or anyone else present at the time of consent; and
- A statement that the patient was given the opportunity to ask questions and to receive answers about the study in his/her native/sign language.

**Visually Impaired or Low Literacy Level Subjects**

Clinical centers must abide by local institutional guidelines in the informed consent process for visually impaired or low literacy level subjects. As with consenting non-English speaking and hearing impaired patients, the clinical centers must document the information noted in the Consent Process section above but also specify such information as:

- A brief description of the local policy on consenting patients with visual impairments or literacy challenges;
- A brief description of how this policy was followed in the consent process for this patient;
- The name of the person reading the consent form to the patient and/or anyone else present at the time of the consent; and
- A statement that the patient was given the opportunity to ask questions and to receive answers about the informed consent document as it was read to him/her.

### 7.3 HIPAA and Release of Medical Records

In the event that Waiver of Authorization is not granted, each center is required to follow their institutional policy for HIPAA Authorization and Release of Medical Information. Consent to authorize release of medical records to the trial investigators, monitors, government agencies (NHLBI, FDA, CMS), device manufacturers, and the members of the Intermacs® organization must be obtained for registry participation. Sample (adult and pediatric) HIPAA Authorization templates are provided in **Appendix C**. Customize these templates per local institutional policy before submitting to your IRB/EB. For any questions during the submission process, contact the DCC at intermacs@uab.edu.

## 8 Training

### 8.1 Privacy Awareness Training

Center staff who are Intermacs® members must complete Privacy Awareness Training offered by the NIH. The NIH training modules can be accessed via the following link: http://irtsectraining.nih.gov/.

Follow the steps below to access the Privacy Awareness Training module:
1. Click on “Public Access to NIH Courses Enter Here” (bottom left hand corner)
2. Click on “Enter Training”
3. Click on “Entire Privacy Awareness Course”
4. Upon completion of the course print or save the certificate of training completion.
5. Submit the “Privacy Awareness Course” certificate of completion to the DCC as part of the enrollment package.

Once activated, Intermacs® requires evidence of current training to remain a Member in Good Standing. Intermacs® members must complete refresher training in accordance with local IRB/EB policy or every 2 years, whichever comes first, and submit the certificate of refresher training to the DCC. The NIH Privacy Refresher Course can currently be accessed at: http://irtsectraining.nih.gov/.

Follow the steps below to access the refresher training module:
1. Click on “Public Access to NIH Courses Enter Here” (bottom left hand corner)
2. Click on “Enter Training”
3. Click on “*[Current Year]* NIH Annual Privacy Refresher”
4. Upon completion of the course print or save the certificate of completion.
5. Submit the “Privacy Refresher” certificate of completion to the DCC as part of the re-certification package (as outlined in Section 6.2).

### 8.2 Web-based Data Entry System (Intermacs® Application) Training

Training for participating clinical centers on the Intermacs® Application will occur immediately prior to center activation as stated in Section 6.1. Additional training occurs

periodically after major changes are made to the system (e.g., with a protocol amendment) and on an as needed basis (e.g., for new center staff or staff having a specific issue with the system).

Web-based interactive software is used to conduct training. 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 and are able to ask questions and receive answers during the training.

In addition to training, a comprehensive **Intermacs® Site User's Guide** provides step-by-step instructions for entering data into the Intermacs® Application and will include definitions for all fields collected in the system. The Users' Guide will also identify main processes in the application and explain standard procedures for data collection. Refer to **Appendix M and N**, respectively, for adult and pediatric patients.

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

# 9 Quality Assurance

## 9.1 Overview

Clinical Center performance as it pertains to the data entry process into Intermacs® will be closely and regularly monitored for compliance, completeness, and accuracy by the DCC. The focus of monitoring is on:

- completeness of the data entered into the Intermacs® Application during the index hospitalization, re-hospitalizations, and follow-up evaluations; and
- identification of impossible or improbable combinations of variables utilizing edit checks.

**Data Completeness**
As stated in Section 6.7.1, forms should generally be completed within 7 days of an event or clinic visit, but always within 30 days. Forms entered beyond the 30-day window will be flagged as late. On a quarterly basis, the proportion of late forms will be calculated and used as a criterion for center compliance. This approach will also allow evaluation of follow-up forms that are not completed.

Summary screens as well as reports of patients and devices entered, current patient status, most recently reported event(s), and other data will be available to the member institutions to assist the institution in assessing the completeness of data entry. When missing data are identified by either the DCC or clinical center, the DCC will work with the center to either obtain the missing data or determine that the data cannot be

obtained because evaluations could not be done. The latter information must be noted in the Intermacs® Application (e.g., not done: too sick).

**Data Accuracy**
At the end of each quarter, data submitted by the centers are checked for internal consistency by the DCC. For example, heights and weights will be compared to identify patients with improbable or impossible combinations. These checks will result in lists of possible errors that will be sent to the centers. Centers with a high proportion of impossible data will be flagged. In addition to quarterly data checks for internal consistency, center staff are required to provide Intermacs® with a list of MCSDs that were implanted during the previous quarter at their institution, but were not entered into Intermacs®. This list will only include the type of device, brand of device, implant date, and reason for not entering into Intermacs®. As a check on the total implants at an institution, MCSD manufacturers will provide a tally of all implants at each institution by calendar periods.

All questionable data points entered into the Intermacs® Application will be verified with the center. 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. Participating centers will be able to review and modify previously submitted data at any time. Resolution of the noted discrepancies and deficiencies will be tracked by the DCC.

## 9.2 Data Audits

In addition to the remote monitoring performed by the DCC as described in the previous Section, Intermacs® monitors conduct in-depth data audits to ensure the highest possible quality of the data. 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 (Refer to Section 9.3). 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 site 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. The audit process helps to identify member institutions that perform poorly in data submission compliance.

## 9.3 Hospital Standards Committee Review

To assist the Hospital Standards Committee in overseeing center compliance, the DCC maintains score cards for each participating center based on several measures such as meeting institutional requirements, timely submission of regulatory documents to the DCC (e.g., Conflict of Interest Disclosure, training certificates, IRB reviews where applicable), accounting for all MCSDs, timely submission of complete data, and quality of submitted data. The score card serves as the primary tool to evaluate center performance.

Periodically, the Hospital Standards Committee, which reviews center performance and recommends actions to reestablish compliance, will objectively review these score cards. For centers performing below acceptable metrics, the Committee will require "for cause" audits to be conducted by the Intermacs® monitors. Centers will be notified of a "for cause" audit up to 30 days prior to the on-site audit via email and/or telephone. The monitors may require source documentation (with patient identifying information redacted) to be sent to the DCC via secure fax or email within 5 to 10 working days of notification. Centers that do not submit to the "for cause" audit in a timely manner will be deactivated, and the Joint Commission will be notified of this action ***within 24 hours***.

All audit results will be reported to the Hospital Standards Committee, which includes the Executive Committee members, as well as additional members from the NHLBI and DCC. The Intermacs® monitors, in collaboration with the Hospital Standards Committee, will work with underperforming centers 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 compliance. Continued non-compliance will result in the center being deactivated until the center has implemented corrective actions to re-establish compliance. The Joint Commission will be notified of the center's deactivation ***within 24 hours*** of this action.

## 9.4 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 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 adverse events.

All data identified as questionable are resolved via direct interactions between the nurse monitors and the local center.

## 9.5 Observational Study Monitoring Board Oversight

To further evaluate Intermacs® and provide an independent expert perspective, an NHLBI-appointed (independent) Observational Study Monitoring Board (OSMB) was established in 2006 and meets, at a minimum, annually.

The principal role of the OSMB is to regularly monitor the data from the registry, review and assess the performance of its operations, assure patient safety, and make recommendations, as appropriate, to the NHLBI and Intermacs® co-investigators with respect to:

- the performance of individual centers (including possible recommendation on actions to be taken regarding any centers that perform unsatisfactorily);
- issues related to maintenance of patient confidentiality;
- adequacy of registry processes in terms of:
  - the number of patients enrolled into Intermacs® and the number of MCSDs that were implanted
  - quality control
  - data completeness
  - data analysis, and
  - publications
- issues pertaining to patient burden;
- impact of proposed ancillary studies and sub-studies on patient burden and overall achievement on the main registry goals;
- possible modifications in the registry protocol; and
- overall scientific direction of the registry

The OSMB is composed of a Chair and members with expertise in biostatistics, clinical trials, bioethics, heart failure, cardiac surgery, bioengineering, and device complications. Ad hoc members may be added to the OSMB to have greater representation of expertise in a relevant biomedical field. All standing members of an OSMB may vote. Ad hoc members have the same voting rights as standing members when reviewing the protocol.

The DCC will prepare and distribute data reports at least 10 working days prior to an OSMB meeting/conference call. The basic format for the presentation of ongoing data and the need to provide these data within a certain time frame was established at the initial OSMB meeting.

During the meeting, the OSMB discusses the registry's overall performance, data quality, and subject burden. The DCC, in consultation with the Executive Committee, is responsible for preparing the meeting materials. Meeting materials are distributed by the

DCC to the Board members approximately 10 days prior to the meeting. The NHLBI Executive Secretary facilitates the meetings in conjunction with the Chair and prepares minutes for approval by the Chair and NHLBI Office of the Director.

The NHLBI policy on its Monitoring Boards is located at: http://www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm.

# 10 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.

# 11 Data Access

All Intermacs® stakeholders have the ability to request data and/or submit proposals for DCC data analysis (refer to the Intermacs® website at www.intermacs.org for instructions regarding submission of proposals and data requests). Intermacs® also maintains open communication channels with its federal partners (NIH, FDA, and CMS). Additionally, device manufacturers have access to data specific to their devices. The types of data that Intermacs® releases are dependent on the specific request, which can include:

- De-identified data sets (currently provided in Statistical Analysis System (SAS) format);
- Device manufacturer-specific data sets with limited PHI, as required by law, for safety purposes (requested by the device manufacturer and/or the FDA); or
- Select items in Excel format to participating centers directly from the web-based data entry system.

The policy for data access and/or analysis is outlined in the protocol and detailed **in Appendix J**. Request forms are located in **Appendix J**.

Intermacs® also makes data and analytical resources available to the MCSD community for research purposes, in order to fulfill its goal of disseminating rigorously analyzed scientific information to the large community of physicians and other professionals interested in MCSDs for advanced heart failure. Publications originate from four general sources: (a) governmental initiatives, (b) investigator initiatives from within the Executive Committee, (c) investigator initiatives from participating Intermacs® centers, and (d) investigator initiatives from the medical and scientific community. The Intermacs® publication guidelines are located at: www.intermacs.org under the "Research" tab at the top of the home page.

# 12 Standard Quality Improvement Reports

The DCC prepares standard reports for its stakeholders at specific points during the year. These reports include:

- Public Reports (also referred to as Quarterly Statistical Reports):
  On a quarterly basis, Intermacs® produces a cumulative statistical report that is available to the public. This report is intended to give a current status of the Registry and contains de-identified data analyses so that no participating center can be identified nor can a specific device. Public reports may be accessed at: www.intermacs.org under the "Reports" tab.

- Center-specific Reports:
  - On a quarterly basis, reports containing center-specific information are sent individually to the Site Administrator of each participating center via secure email. The information contained in these reports includes a quality assurance component that compares the results of the individual center with the entire Intermacs® registry;
  - Approved users can download all data entered by their site into the Intermacs® database. Key features include:
    - Instantaneous download of the data entered into Intermacs® by form;
    - Data, which can be downloaded in several formats – MS Excel, PDF, CSV (comma delimited), MHTML (web archive) and TIFF;
    - PowerPoint tutorials providing useful examples for creating high quality tables and charts from the Excel data.

- Manufacturer-specific Reports:
  On a quarterly basis, reports containing the following information are sent via secure email to the appropriate manufacturer:
  - Statistical summaries of patient demographics and clinical characteristics at the time of implant are provided to the individual manufacturers of MCSDs that are entered into Intermacs®. Additionally, adverse event rates, including death and explant, are calculated. Of note, a specific manufacturer will not receive identifiable information about any MCSDs from other manufacturers.
  - Manufacturers also receive redacted source documentation for adjudication of serious adverse events, as required by law. The Intermacs®-assigned identification number is used as the primary patient identifier between the center, Intermacs®, and the MCSD manufacturer on all source documentation.

- OSMB Reports: On at least an annual basis, the OSMB receives a comprehensive report that includes:
  - Responses to previous OSMB recommendations and comments;
  - Registry progress updates on center activity, monitoring and compliance, serious adverse events, reports to stakeholders, requested analyses and reports, publications, protocol amendments, and other regulatory activities;
  - Additional activities such as updates on Annual Investigator Meetings, other registries under the OSMB's purview, and regular teleconference calls with stakeholders; and
  - Copies of standard reports sent to stakeholders

  The OSMB meets within 30 days of receiving this report to review with Intermacs® investigators and provide recommendations. Refer to Section 9.5 for additional details on OSMB oversight.