



**ISHLT Mechanically Assisted
Circulatory Support Registry
Protocol**

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PROTOCOL

ISHLT Mechanically Assisted Circulatory Support Registry (IMACS)

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1.0 Introduction and Description

The IMACS Registry is an international registry intended to enroll and follow patients who receive durable mechanically assisted circulatory support devices (MCSD) in all countries and hospitals that wish to participate. Durable devices are defined as those devices that are capable of allowing patient discharge with the device in place. The registry will record pre-implant patient information, device information and will track the major post implant clinical events.

The primary goal of the IMACS Registry is to create, implement and analyze a registry that contains high standards for complete enrollment of patients and complete and accurate submission of MCSD data that allows participating hospitals to engage in important outcomes research about mechanical support devices.

2.0 Rationale

1-2% of the population in the industrialized parts of the world suffer from heart failure of differing degrees of severity. The prevalence of advanced heart failure is estimated to be 0.1% of the population, amounting to roughly 300,000 persons in the U.S. The age-adjusted mortality is increasing. Heart failure is a prognostically unfavorable syndrome resembling cancer. The survival probability of the syndrome of advanced heart failure with contemporary medical therapy is 40-80%, and 10-50%, for 1 and 5 years, respectively. Different novel treatment modalities have emerged during the last two decades, including vasodilators, neurohormonal antagonists, conventional surgery, multisite pacing, partial ventriculectomy, mechanical circulatory support devices (MCSD), and cardiac transplantation. The associated costs of management of heart failure are rising. The epidemic dimension which heart failure syndrome has assumed within the last four decades, and the amount of societal resources that is consumed by advanced heart failure, requires a critical assessment of current management concepts and an innovative approach to improve pathophysiological understanding, therapeutic approaches, and the infrastructure. These initiatives have to be founded on evidence-based insights.

MCSD implantation provides a viable bridge to cardiac transplantation while waiting for scarce organs to become available. It may well prove to offer a viable alternative to cardiac transplantation or death from end-stage congestive heart failure. MCSD implantation, and soon perhaps Total Artificial Heart (TAH) implantation, will experience dramatic growth over the next 5 years, and will soon become vital programs at many cardiac care institutions.

This research proposal is part of an international project organized by the International Society for Heart and Lung Transplantation (ISHLT) aimed at implementing a continuous evidence-based mechanism in MCSD therapy. ISHLT is a non-profit medical subspecialty society, which has been in existence since 1981, and is headquartered in Addison, TX. ISHLT is a multidisciplinary, professional organization dedicated to improving the care of patients with advanced heart or lung disease through

transplantation, mechanical support and innovative therapies via research, education and advocacy. ISHLT has over 2500 members from over 45 countries, representing over 14 different disciplines involved in the management and treatment of end-stage heart and lung disease. ISHLT has recently created a registry for all recipients of mechanical circulatory support devices (MCSs) in all non-US countries and hospitals that wish to participate. The database collects data related to implantation, adverse events, and outcomes.

ISHLT has awarded a three year contract to the Division of Cardiothoracic Surgery at the University of Alabama at Birmingham (UAB). UAB will serve as the data coordinating and analysis center (DCAC). The main purposes of this contract are to create the registry, implement the registry, provide statistical summaries and provide research analyses. The programming for the web-based data entry system will be performed by the Transplant Informatics Institute (TII), in Richmond, Virginia under a subcontract to UAB. TII is a subsidiary of the United Network for Organ Sharing (UNOS), which is the contractor for the United States Government's Organ Procurement and Transplantation Network.

3.0 IMACS Purpose and Structure

3.1 Purpose

The purposes of the MCSs database are:

- To capture worldwide data relating to the implantation and outcome of patients receiving cardiac assist devices designed for and capable of use for 30 or more days
- To identify risk factors for complications
- To improve patient selection and management before and after device implantation
- To generate predictive models of outcome for given patient profiles
- To generate statistical analyses of the data that can be used as the underlying evidence/justification for government agency funded studies and clinical trials
- To identify overall and best practices with the aim of improving current practices

The primary objective of the database is scientific research, specifically the analysis of a large ongoing combined experience focusing on outcomes after device implantation and identification of associated risk factors.

This database involves a retrospective chart review of materials (data, documents, records) that have been collected or will be collected solely for non-research purposes. This database will involve all patients at various institutions worldwide who have received a cardiac assist device designed for and capable of use for 30 or more days. There are no control populations.

3.2 Study Procedures

The data elements to be collected are described in the Users' Guide. Case report forms will be available to print from the web-based data entry system for hospitals wishing to capture data on paper. Hospital motivation to participate will be encouraged by access of every participating hospital to hospital-specific data at any time. Thus, duplicate data handling in every participating hospital's patient care program is avoided.

3.3 Prospective Design

IMACS is primarily a prospective registry that will collect clinical data, including follow up, essentially as it happens. Post implant follow up data will be collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that. Major outcomes after implant, e.g. death, explant, rehospitalization and adverse events, will be entered as they occur and also as part of the defined follow-up intervals.

3.4 Additional Datasets

With cooperation between IMACS and NHLBI, patients who were part of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) may be moved into IMACS. The process for acquiring this data will be developed on a case-by-case basis.

3.5 Major End Points

IMACS will provide contemporary data to demonstrate the continued progress of outcomes, with additional insight into appropriate risk stratification and patient selection. Death, transplant, and explant will be the major discrete endpoints recorded, to provide the most fundamental outcome statistics.

Information about rehospitalizations will be vital to address the integrated endpoint of days alive out of hospital, which is particularly relevant for the patient population with advanced heart failure or with ventricular assist devices, as re-hospitalizations are common but not of the same hierarchical importance as death. In addition, the number of hospital days will be closely tracked as the major resource utilized, after the initial implant. Any subsequent surgery or implants will also be noted as additive resources in addition to the hospital days required.

Definition and recording of adverse events will be important aspects of this database. With firm denominators, the incidence and prevalence of adverse events will be made within the context of device type, management practices, patient co-morbidities, timing of implantation, surgical experience and technique; all based on the consistency of uniform adverse event definition. Each adverse event will be separately categorized as primary (the major or initiating in a series of adverse events) or secondary (a sequelae of a primary event). For each adverse event, additional variables must be included which potentially allow a determination of whether an adverse event most likely resulted from device design failure or malfunction (device-related), patient co-morbid conditions (patient-related), or errors in patient management (e.g. inadequate anti-coagulation) (management-related).

3.6 IMACS MCS Committee

An ISHLT appointed Mechanical Circulatory Support (MCS) committee has been established to evaluate the registry on an ongoing basis as to procedures, findings, and adverse events to assure participant safety, confidentiality of records, and registry integrity. The MCS committee will advise the ISHLT Board of Directors and the DCAC when and if changes should be made.

A primary role of the MCS committee is to monitor regularly the data from the registry, review and assess the performance of its operations, and make recommendations, as appropriate, to ISHLT and the DCAC with respect to:

- The performance of individual hospitals (including possible recommendation on actions to be taken regarding any hospitals that performs unsatisfactorily).
- Issues related to participant safety and informed consent including notification of and referral for abnormal findings.
- Adequacy of study progress in terms of recruitment, quality control, data analysis, and publications.
- Possible modifications in the study protocol.
- Overall scientific direction of the registry.

Additional information regarding standard operating procedures for IMACS is found in Appendix A.

4.0 Patient Eligibility

4.1 Scope

The scope of IMACS encompasses those patients receiving MCSDs for whom discharge from the hospital is feasible. These devices are defined as “durable” devices. There is no exclusion for age, gender, race, or ethnicity.

4.2 Screening

Each patient who receives a MCSD at an institution will be screened according to the inclusion and exclusion criteria listed below. For patients who do not meet the inclusion criteria, the following information will be recorded on the screening log: gender, age range, date of implant, brand of the implanted device, device type (left, right, or both sides of the heart), and death within 2 days of implant. This basic information is necessary to assess completeness of patient capture and possible bias in the screening process. No further information will be collected on patients who do not meet the inclusion criteria.

4.3 Inclusion Criteria

Patients who receive a MCSD after the hospital is activated (i.e., has received local regulatory approval and has gained access to the IMACS database).

4.4 Exclusion Criteria

Patients who receive a non-durable mechanically circulatory support device (MCS D). There is no exclusion for age, gender, race, ethnicity, or any other demographic limit.

4.5 Follow-up and Censoring

All patients will be followed as long as a MCS D is in place. If a patient has a MCS D removed and is not transplanted, then the patient will be followed for 1 year. Vital status including transplantation and survival will be determined during this year. If a patient revokes his/her consent, then the patient’s data is censored at that point in time. If a patient transfers his/her care to another hospital then the patient is censored at the time of transfer.

4.6 Study Location

The study will be conducted at the University of Alabama at Birmingham in conjunction with the ISHLT/TII/UNOS central database.

4.7 Link to ISHLT Transplant Registry

If a patient has a MCS/D removed and is transplanted, then the patient is no longer followed in IMACS. At that time, the patient becomes part of the ISHLT transplant registry and will be followed by that database. A patient undergoing transplantation more than one year after explantation will be included in IMACS for the first year, and then will re-enter follow-up through the Transplant Registry at the time of transplantation.

5.0 Site Eligibility and Enrollment

5.1 Eligibility

Any medical hospital outside the United States that has an active mechanical circulatory support device program is eligible to participate in IMACS. In addition, the program must:

- Employ experienced professionals in MCS/D therapy
- Provide personnel and facilities to record and transmit data

5.2 Registration

IMACS registration must be completed by contacting IMACS at IMACS@uab.edu. Detailed registration information and steps to register the facility and personnel in IMACS can be found at www.ishlt.org/registries. Briefly, the medical hospital must complete the Institutional Enrollment Form and the Personnel Contact Information form including staff roles.

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

- Local Principal Investigator (PI), responsible for oversight of data submissions and registry compliance
- Site Administrator, to act as the “point person” for data related inquiries, receipt of reports and audit coordination
- Contact persons must be able to communicate in English

5.3 Human Subjects Research Approval (As applicable)

The facility must follow their institution’s (country’s) policies on IMACS personnel qualifications, informed consent, etc. The hospital must submit the IMACS protocol and supporting documentation (see below) to the Ethics Review Board or appropriate local agency responsible for reviewing and approving human subjects research. If the regulatory agency approves the application for participation in this registry, documentation of that decision must be submitted to IMACS.

5.4 Informed Consent (As applicable)

The facility is responsible for obtaining and maintaining all patient consent forms and all regulatory agency documentation. Documentation of human subjects research approval status and patient consent forms are subject to IMACS audit.

5.5 Memorandum of Agreement

A Memorandum of Agreement must be signed and submitted to IMACS. The Memorandum of Agreement is provided in Appendix B. This agreement is between the local hospital and the International Society for Heart and Lung Transplantation (ISHLT). The agreement outlines responsibilities of the participating hospital, ISHLT, and the DCAC. A separate Memorandum of Agreement between the collective and the ISHLT is provided in Appendix C.

5.6 Training

At least one IMACS staff member at the institution must complete the IMACS training process. A live web-based data entry training session will be scheduled with the designated staff members at each institution. This training will be conducted in English.

5.7 Activation

Once the site has completed steps 5.2 through 5.6 then the site is enrolled into IMACS. The site will be notified of activation, i.e. able to enter data in the IMACS web-based data application. This notification will consist of an e-mail that will contain the site username and password.

5.8 Annual Re-Certification

To MAINTAIN CERTIFICATION, a site must

- Maintain and provide IMACS with the annual regulatory approval (If applicable)
- Comply with data submission requirements outlined in the study protocol
- Maintain qualified personnel

6.0 Patient Safety

6.1 Risks and Benefits

Risks

The data collected for this Registry are from medical chart abstraction. The only potential risk is the inadvertent disclosure of patient information by breach of patient confidentiality. However, ISHLT, the DCAC, and TII/UNOS have extensive precautions in place as described in section 7.0 to maintain subject confidentiality.

Benefits

Benefits to patients:

There is no guarantee of direct benefit to the heart failure patients who participate in this registry. There is the possibility that some patients will experience longer life if analysis and dissemination of results improve the performance of their particular mechanical circulatory assistance device. Some patients may benefit from the knowledge that they are helping to advance knowledge for future heart failure patients.

Benefits to ISHLT, Hospitals, Industry and MCSD research community:

- Rapid access to post market data and outcomes (particularly rapid identification and evaluation of device problems) will likely lead to improved patient selection and management.
- This database serves as a valuable source of data for assessing device performance, may potentially expedite time to market for devices, and offers assurance of a system for vigilance once a device enters the marketplace.
- This database provides an opportunity to identify device performance trends, inappropriate off-label use, and hypotheses for follow-up studies.
- This database will offer long term data on significant post-implant events and quality of care.
- A centralized database ensures confidentiality of patient and physician data and enhances data consistency, reliability, and accuracy.
- Currently, a number of devices are in use, and overall results achieved with these devices are unknown and comparisons are impossible. This database should make comparisons possible and make overall results available to all.
- This database will enable practitioners to identify the populations of patients who would benefit the most from device technology; identify the type of adverse events associated with the use of these devices and generate predictive models of outcome based on factors relating to patient selection, degree of preoperative illness, or timing of implantation.

6.2 Alternative Therapies

Since this is a non-interventional observational study, all interventions scheduled for study participants based on state-of-the-art considerations will be operative.

6.3 Compensation to Participants

Individuals participating in the database will receive no compensation from ISHLT or the Registry.

6.4 Costs to Participants

No costs will be incurred by either the participant or the institution for their participation in the database. The database is funded by the International Society for Heart and Lung Transplantation.

6.5 IRB Review and Approval

All participating hospitals will obtain regulatory approval before collecting registry data, as applicable per local regulations. Dated proof of regulatory agency approval will be sent to IMACS. IMACS will send annual reminders to the participating hospitals at least 30 days prior to expiration of regulatory approval. Lapse in providing regulatory approval to IMACS will result in immediate suspension of data entry capability.

6.6 Informed Consent Process

If required by the local regulatory agency, patients will be consented prior to case data being included in the registry. The original signed informed consent documents will be kept in a double-locked area at the participating site. Informed consent documents with patient signatures will not be sent to the Registry.

7.0 Data Collection

7.1 Web-based data entry and Systems Security

All data will be entered through the IMACS web-based data entry system. Complete documentation and the Site User's Guide are contained at the data entry website (www.isHLT.org).

This system is prospective, i.e. the forms should be filled out as the implant and follow-up events occur (within specific time windows). We have attempted to make the data entry strategy as straight forward and intuitive as possible. The data are divided into forms that correspond to the clinical time course of the patient.

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

Systems security is deployed with third party software and hardware, strict adherence to policy, and regular verification and auditing. The servers that host the web applications are built within the Windows 2003 framework. They follow Microsoft's best security practices and group policy recommendations from the National Institution for Standards in Technology (NIST).

Each server is monitored 24x7 for both intrusion and vulnerabilities by an integrated third-party software package.

Microsoft System Center Configuration Manager 2007 is used for deploying any system patches in accordance with security policies. The network is also protected by an automated anti-virus retrieval and deployment system. Firewall software prevents hacking, virus, and other security risks from the outside. Internally, the servers reside on a segmented part of the Virtual Local Area Networks (VLAN) that is isolated from the rest of the network protecting it from any adverse internal forces. All server access requires use of second level authentication for administrative access. Regular internal and external penetration and vulnerability tests are conducted by third-party contractors to determine any weaknesses in the network.

Access to the data entry process and to an institution's data is available only to TII/UNOS personnel and to personnel designated in writing by the hospital. All approved access is via a protected password login. Each hospital controls which of its personnel receives a login and password. TII/UNOS personnel are exposed to various levels of sensitive data related to transplantation. They routinely handle hospital and patient specific data. In conjunction with their government contract to support the Organ Procurement and Transplantation Network, each TII/UNOS employee must pass a sensitive data clearance administered by the Department of Health and Human Services. For employees that have modification rights to transplant data, this clearance may involve a 10-year background check.

Additional security coded into the ISHLT system includes a requirement for registry assigned user names and passwords to access data. Access to the web applications will be controlled by the Hospital's designated program director. To obtain additional logins, a written request from the program director on letterhead must be submitted to the TII/UNOS and DCAC coordinator. Analytical results will be reported on the database as a whole. Each institution will have access to its own hospital-specific results, but these will not be published or distributed. When responding to data requests TII/UNOS will not provide hospital-specific or patient-specific information in either an identified or encrypted format, except to the hospital that submitted the data. Adherence to this policy will encourage accurate data submission and will protect the confidentiality of the patients and hospitals.

7.2 Clinical data

Clinical data will be collected by medical chart review.

Patient Demographics and Profile Prior to Implant

The standard demographics of age and gender will be recorded. Heart failure etiology, duration, and standard prognostic factors will be collected along with hemodynamic and echocardiographic parameters closest to the time of implant. Co-morbidities will be included, as they may affect the likelihood of success of MCS therapy compared to other options. The IMACS patient profiles (Data Dictionary) at the time of implant will also be collected. The IMACS profile describes the clinical severity at the time of implant, aids in risk stratification, improves patient selection, and refines the definition of future trial populations. The IMACS profile also seeks to transition away from the artificial distinction of bridge versus destination intent, by recording, before and at intervals after implant, the relative likelihood and limiting factors for transplant eligibility.

Device and Operative Details (implant)

The critical elements which characterize the device and describe the implant procedure will be recorded at the time of implant.

Designated Interval Follow-up

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

The follow-up forms will all include information on vital signs and volume status, medications, basic laboratory values, and device settings. At each time interval beginning with the 3-month follow-up re-assessment will be documented regarding current intent as bridge to recovery, transplant, likelihood of eligibility for transplant, or permanent support, with a check-list of considerations relevant to that decision. When available, echocardiographic information will be included regarding function of both

ventricles and atrioventricular valves. Invasive hemodynamic measurement regarding filling pressures, pulmonary pressures, and cardiac output will be included when available.

Adverse Events

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

- (1) The occurrence of infection, device failure, neurological event, bleeding and death trigger a separate screen which will collect relevant data elements;
- (2) Other adverse events (see Appendix D for complete list) will be identified and collected through routine data acquisition at the specified follow-up intervals.

8.0 Analyses of Registry Data

8.1 Introduction

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

8.2 Purposes

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

8.3 Patient Profiling

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

8.4 Primary Endpoints

The major categories of endpoints are death, transplant, explant, patient adverse events, rehospitalization, and device related adverse events. Each of the endpoints will be analyzed as time related events.

8.5 Transfer of Data to UAB for Analyses

The data will be maintained at the IMACS Data Collection Repository in Richmond, VA and then transported to the DCAC for data analysis. Periodic transfer of SAS data sets from TII/UNOS to the DCAC will occur via a secure mechanism. Separate files for each registry form will be sent as SAS datasets (SAS Institute, Cary, NC), created through SAS version 9. Merging of the files, based on unique patient identifiers, will occur after transfer.

8.6 Analytic Methods

Statistical analysis of the MCSDD 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 MCSDD 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.

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 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 US FDA approach

Most of the medical device guidance documents from the US 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 years 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 experiences his first event. He is then re-entered into the analysis, with a new starting time and is tracked until his 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 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.

8.7 Planned Analyses

Patient Characteristics

Patients who receive MCSDs will be summarized regarding their demographic data, medical history, and clinical status including descriptors of heart failure, pre-implant laboratory values and pre-implant hemodynamic data. Novel aspects of the registry include the establishment of 7 INTERMACS® patient

profiles that will describe the clinical severity of disease at the time of implantation. This will facilitate risk stratification for outcomes, and advance the selection of patients who have sufficient severity of disease to warrant MCSs but less severe decompensation to compromise the peri-operative outcome. (Data will be summarized by frequencies, measures of central tendencies, measures of dispersion, cumulative distribution functions, graphical displays, cross tabulations and correlations). An additional component is the ongoing evaluation of patients with regard to evolving eligibility for transplantation and explantation in order to better understand the factors leading to transplantation or explantation. Subsequent tracking of patients will allow the decision process to be continually refined for better outcomes.

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

MCS Characteristics

MCSs that are implanted will be summarized according to their physical and physiologic characteristics (e.g. size, weight, pulsatile or continuous flow, range of flow rates, etc.) and their initial flow settings. The MCS committee will assist in selecting variables for analysis that are relevant to emerging technologies.

Survival

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

Transplantation

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

Adverse Events: Patient and Device Related

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

Competing Outcomes

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

Analysis of MCS D Efficacy

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

Evaluation of Hospital Outcomes

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

9.0 Periodic Statistical Summaries

IMACS will provide summaries to the following entities:

9.1 International Society for Heart and Lung Transplantation (ISHLT) Board of Directors

Semi-Annual Reports will include:

- Documentation and summarization of all work results for the semi-annual period, specifically:
 - Each report will identify the number of patients enrolled by participating hospital, MCS Ds that were implanted, and describe significant patient outcomes
 - Status of follow-up data collection
 - Data analysis
 - Quality of data collected
 - Evaluation of performance of the hospitals
 - Form completion rates
 - Response variables and adverse events
- Brief overview of any problems that occurred during the current reporting period and their resolution or status
- Summary of activities planned for the next reporting period

A Final Report will include a summation of the work performed and results achieved for the entire contract period. The report shall be prepared in the format described for Semi-Annual Reports and be in sufficient detail to describe comprehensively the results achieved. The Final Report shall be submitted on or before the last day of the contract performance period and shall be in sufficient detail to serve as a reference document.

9.2 Individual Sites

Quarterly reports will be provided to each participating site. A specific site will receive no identified information about any other site. These reports have two components. The first component is a quality assurance report that summarizes and compares the results at the individual hospital with the entire

IMACS registry. These benchmark comparisons allow the hospital to evaluate the patients and outcomes as compared to the aggregate data of the international MCS community. The second component focuses on patient specific data and the quality of the site data. Clinical summaries for each patient are provided that contain a chronological history of the major implant related events.

9.3 ISHLT Mechanical Circulatory Support Committee

The ISHLT MCS committee will receive copies of the ISHLT Board of Directors reports along with any specific reports that they may require.

10.0 Quality Assurance

10.1 Data Quality

IMACS will examine data quality and provide periodic data reports. The focus will be on completeness of periodic follow-up and also on identifying impossible or improbable combinations of variables. All questionable data points will be verified. IMACS will not make changes to the data but will rely on the participating site to make necessary corrections. IMACS will track the corrections.

10.2 Data Monitoring and Checks for Inconsistencies

The database will be subject to analytical quality assurance (QA) audits following the completion of data entry. Depending on the types of discrepancies identified, IMACS will contact participating hospitals to resolve these issues. Resolution will be accomplished via telephone contact, e-mail or hard copy mailings. The discrepancies and their resolutions will be tracked for future reference and further review. Based on a review of the results of the analytical QA processes, additional items may be incorporated into the QA process at ISHLT's request. Participating hospitals will be able to review and modify previously submitted data at any time. Additionally, summary screens and reports of patients and devices reported, current patient status, most recent reported event and other data will be available to the member institutions to assist the institution in assessing the completeness of reporting. IMACS will employ established standard operating procedures and work instructions for all applications used to maintain the quality of IMACS data. These procedures and instructions will be used in completion of all data entry activities associated with the MCSD. Work instructions will provide step-by-step directions for processes involved in data entry, data maintenance, and internal audits which will ensure compliance with these standards and instructions.

11.0 Hospitals: Requirements, Training, Assistance and Audits

11.1 Requirements for Hospitals

Each participating hospital shall: (1) provide dated proof of initial and annual human subjects approval; (2) have at least one person complete training; (3) enter complete baseline, implant and follow-up data on all consenting patients; (4) submit to regular data audits; and, (5) correct identified errors in a timely fashion.

11.2 Training for Hospitals

Net Meeting will be used to conduct training meetings on an ongoing basis. Net Meeting is a secure, subscription-based service that allows for meetings and their related documents to be conducted in a virtual electronic environment. Net Meeting allows participants to collaborate on documents and view another participant's desktop. For example, trainers can run a Net Meeting and enable participants to view his or her desktop. Attendees can follow along as the trainer shows step-by-step instructions. These trainings will be conducted in English.

11.3 Assistance to Hospitals

A Comprehensive Site User's Guide will provide step-by-step instructions for using the system and will include definitions for all fields collected in the system. The Site User's Guide will also identify main processes in the application and explain standard procedures for data collection.

DCAC personnel will be available to provide support Monday through Friday from 9:00 a.m. to 4:00 p.m. Central Standard Time (CST). They will assist users of the system with questions and difficulties using the system. Participating hospital users can call in to report inconsistencies and ask questions concerning the data entry process. Additionally, participants can e-mail their questions and concerns 24 hours a day, seven days a week. An initial response will be made to all inquiries within two business days. Resolution of issues, not related to the application, will be completed within two business days of the initial response. Calls that require changes to IMACS may take longer to resolve. The details of each call and corresponding resolution are logged in a database and tracked. The help desk database is monitored routinely to achieve ongoing improvements in the application and to enhance participant service and satisfaction.

11.4 Audit Process for Hospitals

The audit process for IMACS will include submission of requested data from all participating hospitals to IMACS audit personnel. Audits will be conducted via telephone, e-mail, and mail. No on-site visits will be conducted. Sites will be notified 60 days prior to an audit. Audited data will include key data fields, as determined by IMACS. The IMACS nurse monitor will contact the site for a pre-audit phone evaluation approximately 2 weeks before the audit material submission deadline. During the call, the monitor will review site specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explants inconsistencies and any other noted discrepancies. The sites are requested to make corrections prior to the final submission of audit materials.

Audits will monitor data accuracy of web-based data submissions and information contained in source documents as well as participant performance and progress. Per site, five percent of the total number of patients plus 10 patients for major events will be audited. "For Cause" audit requests will be made as indicated by the MCS committee. All audit results will be reported to the MCS committee.

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

12.0 Collectives

The DCAC also supports the submission of “collective” (usually countrywide) data provided to IMACS. Institutions participating in a national collective who wish to participate in IMACS will most likely do so through the collective rather than enrolling individually in IMACS. ISHLT and the DCAC will work with representatives of the collective to obtain regulatory approval, execute the memorandum of agreement, map data elements and transfer the dataset. Each collective will be required to designate a registry director and data administrator to serve as the primary IMACS contact persons. The DCAC will communicate directly with other MCS registries being developed to foster data-sharing agreements allowing the incorporation of collective data into IMACS. If an agreement between the collective and ISHLT cannot be reached, an individual hospital may still enroll directly with IMACS and submit data via the web-based data entry system.