Medamacs

SUPPORTING HEARTS THROUGH KNOWLEDGE

Date: November 16, 2012

Re: **Administrative Change for Protocol, Version Date 11/08/2011**

To: Sites participating in the Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support (MedaMACS)

NCT#: NCT01932294

From: Mary Lynne Clark
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The following administrative change impacts the MedaMACS Protocol, Version Date 11/8/2011. This letter must be submitted with your initial IRB submission. In the event you have already submitted the initial IRB application, please forward this letter to your Institutional Review Board (IRB) as soon as possible. IRB acknowledgment must be forwarded to the MedaMACS Data Coordinating Center.

Please file this letter with all copies of the protocol. Please file this letter and any IRB correspondence in your regulatory file and other pertinent files.

List of Changes to the MedaMACS Protocol, Version Date 11/8/2011:

- ***The following text, Section 2, Specific Aims, Aim 4 has been removed from the protocol:***

  "To develop and advance a team of emerging clinical investigators who will increase awareness of mechanical circulatory support and serve as role models for other young investigators.

  Hypothesis: Focused mentorship of early career investigators will foster the next generation of leaders in the clinical care of patients with advanced heart disease.

  4.1.1 Junior investigators will take the lead in designing and analyzing research questions of their own with the mentorship of a more senior investigator at each clinical site. Presentation of MedaMACS data at national meetings and manuscript development will be the responsibility of junior investigators. A centralized publications committee with ensure equitable distribution of topics of interest so there is synergy across centers and appropriate extramural mentorship is available.

  4.1.2 Survey will be made among the young investigators for VAD-related publications, progression to independent research status, and affiliation to clinical VAD programs at 5 years after initiation of MedaMACS enrollment."

MedaMACS continues to develop and advance a team of emerging clinical investigators to increase awareness of mechanical circulatory support and serve as role models for young investigators. However, we feel that this can best be addressed in a separate format and should not be included in the study protocol.

Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support (Medamacs) Study

Version 11/8/2011

1. INTRODUCTION

Despite widespread use of evidence-based medical therapies, including neurohormonal blockers and biventricular pacing, mortality and morbidity from systolic heart failure remain high.[1] Breakthroughs in mechanical circulatory support technology have extended survival and improved quality in advanced heart failure patients awaiting cardiac transplantation and in inotrope-dependent patients who are ineligible for transplant.[2-4] The INTERMACS Registry (Interagency Registry of Mechanical Assist Circulatory Support) has facilitated the refinement of patient selection for this therapy by analysis of those patients who have received devices[5, 6]

Integral to the original intent of INTERMACS was comparison to ambulatory patients living with advanced heart failure who were not currently receiving mechanical circulatory support devices. As the first years of INTERMACS were dominated by INTERMACS profiles 1-2 with medical survival of hours to weeks, comparison to outcomes for ambulatory patients without devices was initially of limited relevance. However, the lack of information on outcomes with continued medical therapy has limited the ability to define and advance indications in the "less sick" despite INTERMACS-documented progress that should attract ambulatory patients, who currently make up fewer than 20% of all patients receiving mechanical support.[6] (Figure 1)

The development of a contemporary parallel population of ambulatory patients with heart failure is necessary in order to meet the commitment defined for INTERMACS at its inception in 2005 and re-emphasized for the renewal beginning 2010, for INTERMACS to 1). Facilitate the refinement of patient selection to maximize outcomes with current devices within approved indications, and to 2). Guide and expedite clinical trials for new indications and/or new devices. This is true both for survival outcomes and for outcomes beyond survival, measured in terms of quality of life, functional capacity, and satisfaction with the chosen strategy of care.

The future impact of mechanical circulatory support on public health will be experienced by ambulatory heart failure patients in whom support can be employed electively for long-term benefit with diminishing operative risk. At present, the size and clinical characteristics of the population with advanced ambulatory heart failure despite optimal contemporary medical therapy remain unknown since few such patients have been enrolled in clinical trials. Patients with less severe heart failure can clearly identify thresholds for consideration of a ventricular assist device, or VAD.[7] A better understanding of this population and their unique priorities is vital in order to anticipate the optimal expansion of mechanical circulatory support into the less critically ill population.

These needs will be addressed in the Medical Arm for Mechanically Assisted Circulatory Support (MedaMACS) Pilot Study. MedaMACS will characterize the types of patients who are not receiving an LVAD currently due to the intersection of relative contra-indications, to their own preferences, or to their characterization as "less sick" either by perception or by absolute criteria as currently defined for lifetime VAD support. The nature of contemporary "optimal" medical therapy will be reported, and the major risk scores for heart failure will be calculated and challenged. MedaMACS will incorporate specific consideration of frailty as measured by gait speed, the proposed new "geriatric vital sign". In relation to the characteristics at baseline and over time, MedaMACS will provide information on medical outcomes in terms of timed endpoints of VAD, transplant, or death. There will also be determination of adverse events of stroke and hospitalizations for comparison to those experienced after VAD. Of equal weight will be the determination of functional capacity, quality of life, and satisfaction with therapy. For many ambulatory patients with chronic heart failure, the magnitude and predictability of expected improvement in functional status with a VAD will likely influence their VAD decisions more than the margin of survival benefit. These are pivotal components of decision-making for advanced heart

failure in order to progress toward the 21st century goal of patient-centered care. The MedaMACS program will provide landmark data from which to refine selection for mechanical circulatory support from the ambulatory heart failure population within which the greatest benefit of mechanical support is anticipated.

Since INTERMACS was originally conceived, penetration of this technology has advanced steadily but increasingly requires expanded expertise and commitment beyond the original investigators. The presence and influence of a vital young academic cardiology cadre will be crucial to maintain skill and focus on clinical application during rapid evolution of mechanical support technology. MedaMACS has been designed to meet the scientific goals required for progress while fostering the development of a core group of emerging heart failure cardiology investigators at key sites. This group will provide leadership in the identification and follow-up of the cascading sequence of changing populations for mechanical support.

2. SPECIFIC AIMS

Aim 1: **To identify prospectively a population of ambulatory patients followed on optimal medical therapy for whom chronic heart failure limits both function and survival to a range where elective implantation of left ventricular assist devices should offer meaningful benefit.**
Hypothesis: It will be possible to define baseline characteristics that predict a one year mortality of ≥35±5% for patients on medical therapy and ≤25±5% in patients who have had VAD.

1.1 Characterize ambulatory patients with advanced heart failure by baseline variables and interval change, including functional capacity, frailty, and interest in technical intervention. There will be two baseline measurements one month a part (used to predict early stability) and a repeated set at 1 year (used to predict outcome between 1 and 2 years). These outcomes will include: a). All clinical parameters required for current risk score models and prediction, b). Follow-up values and changes from baseline to 1 month and baseline to 1 year as additional variables from which to predict outcomes on medical therapy, c). Functional capacity, quality of life, and patient preferences at baseline and after time.

1.2 Distinguish between risk factors that predict mortality whether therapy is medical or mechanical, and those risk factors that predict outcomes with different impact depending on whether therapy is medical or VAD. This will be stratified by whether patient is eligible for transplant or not.

1.3 Record outcomes for ambulatory patients with advanced heart failure for comparison to VAD, to include a). Hospitalizations, VAD, transplant, survival without VAD or transplant, b). Major adverse events leading to hospitalization, including infection, neurologic or bleeding, c). Functional capacity and quality of life, d). Eligibility for transplant, e). Changes in resuscitation status and enrollment in hospice.

Aim 2: To design an integrated endpoint of survival and objective functional assessment that provides more discrimination between chronic ambulatory heart failure and current device outcomes than survival alone.
Hypothesis: It will be possible to identify a composite endpoint of survival and function that will show a 30% difference between outcomes on medical therapy and outcome with initial VAD.

2.1 Compare survival and functional outcomes for MedaMACS patients and recipients of single LVAD. Within each Profile 4-7, comparisons will be made for a). Clinical characteristics, b). Outcomes, and c). Outcomes for populations from INTERMACS and MedaMACS defined by other baseline variables and risk scores.

2.2 Define changes in 6 minute walk between baselines and 12 and 24 months after enrollment, to determine timing, frequency and degree of improvement for Profiles 4-7 after entry for medical therapy, and compare to INTERMACS results.

2.3 Define changes in quality of life as assessed by Euroqol-5D and Kansas City Cardiomyopathy Questionnaire.

2.4 Analyze distribution of integrated functional survival endpoints to a). Inform individual patient decisions between VAD and medical therapy, b). Provide basis of evidence Level B for VAD guidelines, and c). Estimate sample sizes for pivotal randomized trials.

Aim 3: To evaluate patient perceptions about their cardiac condition, ventricular assist device technology, preferences for their care, and thresholds for considering device implant.
Hypothesis: The likelihood of patients expressing preference for a VAD will increase with their functional limitation and with their predicted risk of 1 year mortality.

3.1 Patient functional capacity by questionnaire and 6 minute walk will be assessed twice at baseline and again at 1 year and 2 years. These will be compared to their expressed willingness to consider VAD at their own level of function and from a series of hypothetically worse states.

3.2 Available relevant mortality prediction models will be used to estimate 1 year survival from baseline and from the one-year re-evaluation. These will be compared to patients' expressed willingness to consider VAD at their own anticipated level of survival and from a series of hypothetically worse states.

Aim 4: To develop and advance a team of emerging clinical investigators who will increase awareness of mechanical circulatory support and serve as role models for other young investigators.
Hypothesis: Focused mentorship of early career investigators will foster the next generation of leaders in the clinical care of patients with advanced heart disease.

4.2 Junior investigators will take the lead in designing and analyzing research questions of their own with the mentorship of a more senior investigator at each clinical site. Presentation of MedaMACS data at national meetings and manuscript development will be the responsibility of junior investigators. A centralized publications committee with ensure equitable distribution of topics of interest so there is synergy across centers and appropriate extramural mentorship is available.

4.3 Survey will be made among the young investigators for VAD-related publications, progression to independent research status, and affiliation to clinical VAD programs at 5 years after initiation of MedaMACS enrollment.

3. BACKGROUND - Gaps in Current Medical Trial Data

Survival Prediction

The available information from the randomized trials of REMATCH, INTREPID, and the combined experiences of other inotrope-dependent patients provides a boundary of approximately 75% one-year mortality on medical therapies.[2,8] On the other side are the experiences in ambulatory outpatients with advanced heart failure, in which one-year mortality is no more than 20% in trial of beta blockers, aldosterone antagonists, and cardiac resynchronization. These medical trial populations thus cannot be aligned with experiences with approved VADs, in whom the one-year mortality was in the range of 30% as reported specifically in the HeartMate II device trial.[4] The one-year mortality in the broader experience of approved devices for destination therapy is declining toward 20% in INTERMACS when outcomes are isolated for LVAD without right ventricular support.[6] These sets of medical data thus leave unaddressed the wide chasm of one year medical mortality between 25 and 75%, within which falls the largest anticipated target population of ambulatory patients for current implantable VADs.

This chasm cannot be crossed by community registry populations which describe overall one-year mortality of 30-50%, but an average age is 75.[9,10] with prevalence of co-morbidities such as chronic pulmonary disease and peripheral vascular disease in the range of 30%, with dementia, stroke, cancer each in the range of 10-20%.[10] Multiple risk scores exist from these populations for the identification of patients at high risk for death from heart failure,[11-13] but they do not fully address the challenge of identifying ambulatory patients both sick enough and well enough to benefit from VADs. On the other end, scores developed from low-ejection fraction HF outpatient trials depict a young population with one-year survival rates in the range of 80-90%. In the pyramid of risk for death during heart failure, the largest level is the bed of risk at the base, in which the patient remains regardless of therapy received, with such risks as intrinsic liver and lung disease, and the intermediate levels where malnutrition and renal dysfunction compromise peri-operative outcomes and offer uncertain potential for improvement. (Figure 2) Potential for benefit is reflected best at the top of the pyramid with risk factors such as hemodynamics and biomarkers that are addressed directly by VAD (or transplant). The robust Seattle Heart Failure Score versions, derived from disparate trial populations, have been used to identify very low risk patients and patients with heart failure severity unlikely to benefit from ICD therapy.[11] This score will provide the central screen for the ongoing REVIVE-IT trial in ambulatory heart failure. The MedaMACS population is designed to surround the 50 patients on medical therapy in the REVIVE it trial, by including patients deemed sicker by recent hospitalization, but also less sick patients who have a Seattle score below the 1.5 threshold. The accuracy of current criteria to select this spectrum of patients has been shown in analysis of the first140 patients of the MedaMACS screening pilot. (Figure 3)

Functional Capacity Prediction

As we look toward the “less sick” populations, it has been shown that patient interest in VAD is heavily influenced by the degree of functional limitation. The increasing focus on shared decision-making in advanced heart failure requires that patients be given adequate information to choose among available options. This requires better understanding of the expected functional outcome on medical therapy as well as with VADs. Current reports of those patients providing serial information on quality of life through Kansas City questionnaires indicate improvement in the range of 40 points after VAD, which exceeds that demonstrated with any other therapy thus far. However, these are from baseline levels substantially worse than anticipated for most ambulatory

heart failure.[14] Similarly, 6 minute walk distances show major improvement but the majority of patients were unable to perform them at baseline.[14] Contemporary information about the trajectory of quality of life and functional capacity over 12-24 months for patients ambulatory at baseline will be crucial to understanding and communicating expected benefits from VAD.

Benefit Emphasized Over Risk

MedaMACS outcomes will accelerate the progress of mechanical circulatory support into the ambulatory population. Outcomes will include the rate of progression to transplant or VAD after enrollment for 2 years. For those patients remaining alive on medical therapy, information will include key adverse events and functional capacity in detail for one year and general life satisfaction at one and 2 years. Taken in conjunction with INTERMACS data, the MedaMACS baseline and outcome data will facilitate the important evolution from risk scores to "Benefit Scores", which reflect both the anticipated risk without MCS and the likelihood of good outcomes with MCS. This will be used both for overall survival, survival without major events, and adjusted scores that include quality of life and functional capacity in survivors.

4. PRELIMINARY DATA

INTERMACS Provides the Framework

INTERMACS has established the key questions in the potential VAD populations along with the data field framework upon which to answer them for ambulatory patients on medical therapy. INTERMACS has validated clinical patient profiles and has established new branch points for decisions regarding transplant.[15] Outcome fields for specific adverse events, re-hospitalization, cardiac function, systemic markers of disease, and functional capacity are designed to capture not only endpoints but the crucial midpoints that allow an integration of function and survival over time. The architecture for INTERMACS has been designed from its inception to favor entry of parallel information for patients receiving contemporary medical therapies. The experience from INTERMACS will illuminate the establishment of MedaMACS.

MedaMACS Screening Pilot Confirms Feasibility

A MedaMACS Screening Pilot study has completed enrollment at 10 JCAHO-certified mechanical circulatory support programs across the United States. Using similar entry criteria as outlined below, 168 patients with advanced ambulatory systolic heart failure and recurrent hospitalizations were enrolled over 7 months. Comprehensive baseline data of usual care practices was recorded along with a 14 item patient questionnaire and the Euroqol-5D instrument. Rapid enrollment confirmed that a population of advanced ambulatory heart failure patients could be readily identified and enrolled in an observational study. Data from the screening pilot suggests that there may be a cohort of patients who may benefit from LVAD therapy who are not yet being considered for mechanical support.[16] (Figure 4) In addition, the patient survey instrument successfully provided information on patient perception of VAD technology, thresholds for implant, and goals of therapy.[17] The screening pilot is also being used to field test telephone administered outcome measures at 6 and 12 months after enrollment. Baseline entry criteria, data elements and survey items have been refined based on collaborative feedback from the screening pilot effort. The successful design and implementation of the screening pilot over a short time-line demonstrates that such an effort can be led by junior investigators committed to clinical research in advanced heart disease.

5. STUDY DESIGN AND POPULATION

Screening and Determination of Eligibility

The MedaMACS Pilot Study is a prospective, observational study of ambulatory patients with advanced heart failure. The study will enroll patients who have not yet received an LVAD but who receive their care at a hospital with a JCAHO-certified mechanical circulatory support program.

Participants will be screened for this study if they are between 18 and 80 years old with low ejection fraction history and hospitalization for heart failure within the past year. All subjects who have been admitted to the heart failure service will be screened and recruited for study participation, either as an inpatient or during their first outpatient follow-up appointment by the investigator and research staff caring for patients in the advanced heart failure program of the enrolling center. Eligibility for enrollment will be based only upon information that is clinically available at the time of screening. The history of prior hospitalizations will be available from clinical records. Routine evaluation and triage of ambulatory patients with advanced heart disease includes echocardiography and functional assessment with peak oxygen consumption and frequently 6 minute walk distance, The elements of information required for estimation of the Seattle Heart Failure Risk score will be gleaned from laboratory data, or imputed as described in the Seattle score literature. The research coordinator will enter this data onto a currently available website for calculation of the Seattle score.

Eligibility will be determined by the inclusion and exclusion criteria listed below. The inclusion criteria will be checked individually for "all that apply, with numeric values where indicated. The exclusion criteria will be verified by individual checkboxes. After determination of eligibility, a member of the study research team will approach individual subjects who are potential candidates for participation and for whom the subject's primary physician has given permission to approach. No group of persons will be excluded without a good scientific or ethical reason to do so. Incarcerated prisoners have been excluded by this protocol. For patients who meet inclusion criteria but who have an exclusion criteria related to non-cardiac conditions (Exclusion Criterion #2, #3, or #9) and for eligible patients not providing informed consent, a screening log will be kept that includes their age, ejection fraction, race and gender. This basic information is necessary to assess completeness of patient capture and possible bias in the screening process and in the process to obtain informed consent. No further information will be collected on patients who do not meet the inclusion criteria. This screening log will help determine the total number of advanced ambulatory heart failure patients eligible for MedaMACS participation at each study center.

We anticipate a total of 350 patients enrolled from 12 centers in the United States over a 12 month period. The screening pilot enrolled 168 patients at 10 sites during a 7 month period. Once all sites are activated with enrollment of approximately 3 patients per month per site, enrollment should be complete by 12 months.

Inclusion Criteria

1. Age 18-80 years
2. NYHA class III-IV heart failure for 45 of the last 60 days
3. Left ventricular ejection fraction $\leq 35\%$
4. Heart failure diagnosis or typical symptoms for 12 months
5. Use of evidence based oral medications (beta-blockers, ACE-inhibitors/ARBs, aldosterone antagonist) for at least 3 months prior to enrollment or documented medication contraindication or intolerance.

6. Hospitalization for heart failure within the previous 12 months (other than for elective procedure)
7. Informed consent given

In addition, they must have at least one of the following:

A. An additional unplanned hospitalization during the previous 12 months for a total of at least 2 inpatient hospitalizations lasting >24 hours with heart failure as the primary or secondary diagnosis within the previous 12 months

OR

B.
1) Peak oxygen uptake (VO2) <55% of age- and sex-predicted (using Wasserman equation) OR a peak VO2 ≤16 ml/kg/min for men and ≤14 ml/kg/min for women in a test with an RER >1.08 on cardiopulmonary exercise testing.
2) 6-minute walk distance <300 meters without non-cardiac limitation.
3) Serum BNP > 1000 (NT-proBNP > 4000 pg/ml) as outpatient or at hospital discharge.

OR

C. Seattle Heart Failure Model Score ≥ 1.5.

Available information will be obtained on all of these inclusion criteria for comparison regardless of which meets eligibility.

Exclusion Criteria

1. Age >80 years or <18 years
2. Non-cardiac diagnosis anticipated to limit 2-year survival (≥30-50% mortality within 2 years from non-cardiac diagnosis)
3. Primary functional limitation from non-cardiac diagnosis even if not likely to limit survival
4. QRS > 120msec and planned biventricular pacemaker implant or biventricular pacemaker implantation within past 90 days
5. Current home intravenous inotrope therapy
6. Chronic hemodialysis or peritoneal dialysis
7. Scheduled for non-ventricular assist device cardiac surgery on current hospital admission
8. Obvious anatomical or other major contra-indication to any cardiac surgery in the future (e.g. previous pneumonectomy, advanced connective tissue disease)
9. Actively listed for heart transplant as UNOS Status 1 or 2
10. History of cardiac amyloidosis
11. Dominant lesion of at least moderate aortic or mitral stenosis or congenital structural heart defect.

Informed Consent

Informed consent is mandatory and will be obtained from all subjects prior to participation in this clinical study. Informed consent will be obtained in accordance with IRB policies and procedures. Prior to inclusion in the study, it will be the responsibility of the Investigator to give each subject full and adequate verbal and written information about the objectives and the

procedures of the study and the possible risks involved. Each subject will be informed of their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. When a potential subject is the investigator's own patient, it will be made clear to the potential subject that participation in the study is entirely voluntary and that their decision will not affect their care now or in the future.

Furthermore, it will be the responsibility of the Investigator to obtain a signed Informed Consent form from each subject prior to administering any questionnaires, recording data into the Registry, or performing a 6 minute walk at a time other than when customarily performed in their routine clinical care. Informed consent documents will be written in language understandable to the subject or subject's legally authorized representative. One copy of the signed Informed Consent form will be given to the subject and another retained by the Investigator.

6. PROCEDURES AND ASSESSMENTS

Clinical, Demographic and Laboratory Data

It has been verified that the requested data is normally acquired in the routine care of these types of patients at the referral centers for the primary investigators. Laboratory data will be obtained from routine blood draws as clinically indicated. Peak VO2 and echocardiographic parameters will be measured once during the baseline period and once at the one-year visit as clinically indicated. In those centers selected for MedaMACS, as in most centers with high volume advanced heart disease evaluation, peak VO2 and echocardiographic assessment are routine components of regular and serial evaluation. Medications, cardiac imaging, and exercise testing will occur at the discretion of the physicians caring for each study participant. Patient therapies and testing will conform to standards of care and published clinical guidelines for heart failure management.[18, 19] Subjects will have additional functional assessment of both endurance (6 minute walk) and frailty (gait speed) one month after consent to measure early stability. Registry data will be obtained by chart review from both the electronic medical record and paper charts. Note all dates for baseline data will be by intervals rather than calendar dates. There will be a total of six data collection time points, four with face to face clinical encounters and another two by telephone: (Figure 5).

- Baseline A – at consent (face to face encounter)
- Baseline B – 3-6 weeks after consent (face to face encounter)
- 6 month telephone call by study site personnel
- 12 month follow-up – 10-14 months after consent (face to face encounter)
- 18 month telephone call by study site personnel
- 24 month follow-up – 22-26 months after consent (face to face encounter; study close)

Patient Survey

The patient survey instrument patient will assess quality of life, health-related stress, along with impression of and thresholds for consideration of VAD therapy . All survey responses are for research only and as such will be kept confidential and not be shared with members of the medical team. This written survey will be administered at Baseline A, Baseline B, the 12 month visit and again at the 24 month study close-out visit. Patients will receive the Kansas City Cardiomyopathy Questionnaire to determine disease specific quality of life and with the Euroqol-5D questionnaire including the thermometer. There will also be a brief instrument on health-related stress identical to

the tool being used in INTERMACS. The quality of life instruments will be completed independently by the patients in a single session.

After quality of life instruments have been completed, study coordinators will read a description of a VAD and provide a simple picture. The description of a VAD will include information on implantation, anticipated benefits and potential risks. The surveys will only be administered at face-to-face visits to allow a study nurse to assist with the VAD portion of the instrument. Patients will complete the VAD portion of the survey after receiving this standard information and a study nurse will be present to answer any queries about the VAD items. Similar VAD survey items were administered in the screening pilot with excellent response rates.[17] Any patient who fails to complete a survey will have a missing data form filled outlining why the self-reported instruments were not completed. In all, there are 40 questions for the patients to answer in a written format, which should take approximately 35-40 minutes for most subjects. Original copies of the written survey instruments will be kept on site by study investigators and the data will be entered electronically by the coordinators or their data assistants on site (Appendix A).

Follow-up Telephone Contact at 6 and 18 Months

A telephone call will be made by local site investigators or their study staff to patients at 6 and 18 months after study enrollment, but can be replaced by face-to-face visits if occurring as part of their routine care. The major purpose of this telephone call is to assess patient vital status and important interval events such as transplantation, placement of VAD, or other major procedures. The second purpose is to estimate the number of hospitalizations after study enrollment and the frequency of other major adverse events as recalled by patients. Any major endpoint or adverse event will be confirmed or amended by review of the interim medical record by site investigators. At the time of each study follow-up visit, the records will be reviewed for evidence of any major events leading to hospitalization that might have been missed in the intervening phone interviews.

Patients will be asked the questions determining functional class and profile. They will be asked a small subset of questions from the baseline questionnaire related to preferences for resuscitation and for VAD. They will be asked to bring their medications to the telephone to list them with doses.

Clinical Assessment at 12 months

It is anticipated that patients will be seen at some time between 10 and 14 months after the baseline study. Clinical information including routine laboratory values, physical examination, and symptoms will be reported. An echocardiogram and peak oxygen consumption will be recorded if obtained for clinical indications, as is routine practice for patients with this severity of illness followed at major centers. The six minute walk functional test will be repeated along with 5 meter gait speed to assess frailty. Patients will be re-administered the questionnaires regarding functional status, quality of life, and preferences for VAD as at baseline.

End of study at 24 months

A final face to face encounter at 24 months (between 22-26 months) will be completed and the study will end at that point. Routine clinical assessment components and other study data elements will be recorded as available from the clinical record, including results of imaging and exercise testing for measurement of peak oxygen consumption, if performed at or after the 18 month time point. The six minute walk functional test will be repeated along with 5 meter gait speed to assess frailty. Patients will be re-administered the questionnaires regarding functional status, quality of life, and preferences for VAD as at baseline. Finally, at 24 months each patient

will receive the VAD survey and questionnaire to assess quality of life and perception of VAD technology. After the two year face to face visit, study participation will end.

Data Elements

A full list of data elements to be collected along with collection times may be found in Appendix B. All data will be recorded in a web based data entry system.

7. DATA SAFETY AND MONITORING

Data Safety and Coordination

Data and safety monitoring, including guarding the rights, safety and welfare of subjects, will be the responsibility of the individual site investigators. The data coordinating center for the study will be the University of Alabama Birmingham (UAB). All information collected in this registry will be held confidential to the extent permitted by law. No published or unpublished report or visual or speaking presentation about this study will include any material that will identify the subject as a participant in this study. No specimens will be collected. Subjects may withdraw consent from the study at any time. Data will not be used by collaborators for any purposes other than those described in this protocol.

Data will be transferred to the coordinating center electronically for all data. Datasets containing de-identified individual data and summary data will be available to the INTERMACS and MedaMACS investigators and industry partners. All of the data systems feature multiple levels of security, which protect patient data by the most stringent requirements. All are fully compliant with the Health Insurance Portability and Accountability Act (HIPPA) and are certified by the Health Resources and Services Administration (HRSA). Any plans for data to be shared with outside entities as part of contractual arrangements will be within the conditions specified in the patient consent form and detailed in contracts to be reviewed separately.

Study Monitoring

The Principal Investigator and UAB study staff will regularly monitor the data from the registry, review and assess the performance of its operation, and make recommendations, as appropriate, to participating institutions with respect to:

- Enrollment and data timeliness and completeness from individual enrolling sites
- Issues related to participant safety and informed consents
- Adequacy of study progress in terms of recruitment, quality control, and data analysis
- Issues pertaining to participant burden
- Achievement on the main study goals
- Possible modifications in the study protocol
- Overall scientific direction of the registry

8. ANALYSIS PLAN

Planned Analysis

The prospective data analysis is planned to be descriptive and correlative, with primary hypothesis outlined in the specific aims. Data collected are designed to generate future hypotheses.

Actuarial survival curves will be generated and compared to known risk models, such as the Seattle Heart Failure Score and the Heart Failure Survival Score, for both heart failure populations and VAD populations from INTERMACS.[19, 20] In addition, new models will be developed to allow comparison of anticipated outcomes after VADs using INTERMACS data. It is fully recognized that these comparisons will be inevitably limited through confounding by indication. The intent is to identify a range of baseline profiles for which anticipated outcome with medical survival can be projected. From this information, hypotheses can be generated for target populations in whom VAD therapy might be expected to yield better outcomes.

"Primary" Endpoint and Power

As this is a registry designed to determine outcomes for particular groups of patients, there will be more than one "primary" endpoint depending on the level of severity of illness. Knowing that survival in isolated VAD patients dominated by Profile I and II has reached 70% at one year, it is reasonable to assume that survival will be at least as good or better with VAD in less sick patients. We hypothesize that it will be possible to define baseline characteristics that predict a one year mortality of $\geq 35 \pm 5\%$ for patients on medical therapy and $\leq 25 \pm 5\%$ in patients who have had VAD. Seeking a confidence interval of approximately $\pm 5\%$, this could be accomplished initially with approximately 350 patients if they have similar risk. We anticipate that some patients will have better survival and some may have worse survival than this, such that there will be overlapping groups, and a small proportion of patients will have other events ending their medical history, such as transplant and deterioration to worse INTERMACS profiles for which they receive VADs.

For groups within which survival is > 60% at 1 year on medical therapy, a composite of survival and function will be the most important for comparison to VAD therapy. We hypothesize that it will be possible to identify a composite endpoint of survival and function that will show a 30% difference between outcomes on medical therapy and outcome with initial VAD. The nature of these survival-function endpoints will be explored during the first year of MEDAMACS data. The two simplest will be done with the endpoints of days alive out of hospital, and quality-adjusted life years according to the Euroqol. However, more complex endpoints will be tested for survival and functional scores at specific intervals. (Figure 5)

Information will be collected regarding the major adverse events that lead to hospitalization both with and without mechanical circulatory support, as listed in the data appendix: neurologic event, non-CNS bleeding, sepsis, ventricular tachyarrhythmia or ICD firing. The hospitalizations, adverse events and deaths will be attributed on site by the investigators in drop-down menus. There will be no independent adjudication of causes of hospitalizations or deaths. The general categories of causality are broad and not the focus of the primary hypotheses. Thus, the lack of formal adjudication should not compromise the data for the endpoints of death, transplant, and VAD, which are objectively determined. The secondary endpoints that relate to functional capacity and to quality of life will also be specifically determined.

Statistical Methods

Baseline data between different patient groups will be compared using student's t-test for normally distributed continuous variables and Wilcoxon Rank Sum for non-normally continuous variables. Kaplan-Meier curves will be constructed for time to death, VAD or transplant for the two-year study period. Event rates including cause-specific hospitalizations will be generated for different groups of patients and analyzed. Analysis plans for specific research questions will be developed under guidance of the DCC after approval by the Research and Publication Committee.

All summary statistics and subsequent analysis will be performed using SAS statistical software (Cary, NC).

Publications

Publications will be authored by the primary investigators at the participating sites. The senior site investigators will be offered inclusion as authors for the manuscripts on which they supervise the efforts of the investigator from their own site as first author. Options may become available for research coordinators to author manuscripts on secondary analyses of topics of their special interest.

9. MATURATION OF MEDAMACS

The launching of MedaMACS will focus on the ambulatory population closely proximal to the common threshold for implementation of mechanical circulatory support. The foundation of the 10 sites entering patients for the MedaMACS screening pilot will allow rapid initiation of the new protocol, with the additional 2 sites. The fastidious definition of entry criteria offers a fine-tuning knob to dial up or down disease acuity of patients enrolled, as this becomes necessary. However, the general approach to baseline data collection, risk profiling, assessment of adverse events and outcomes, is planned for cascading applications to progressively "more well" populations to keep pace with those enrolling into INTERMACS. The next promising target population will be the population of patients waiting at home after listing for transplant. As the improving outcomes of implantable VADs are demonstrated by INTERMACS to advance beyond a bridge to transplant, past even the current focus on the transplant-ineligible population, MedaMACS will prepare the field on which mechanical circulatory support will finally compete with cardiac transplantation as primary therapy to improve quality life for a substantial proportion of the patients currently suffering from advanced heart failure.

10. PARTICIPATING CENTERS

Study protocol and informed consent forms will be approved by local institutional review board prior to study enrollment. Participating centers will include:

- Brigham and Women's Hospital (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Cedars Sinai Hospital (Los Angeles, CA)
- Duke University Hospital (Durham, NC)
- Hospital of the University of Pennsylvania (Philadelphia, PA)
- University of Alabama, Birmingham (Birmingham, AL)
- University of Colorado (Denver, CO)
- University of Iowa Hospitals (Iowa City, IA)
- University of Michigan Hospital (Ann Arbor, MI)
- University of Pittsburgh Medical Center (Pittsburgh, PA)
- University of South Florida, (Tampa FL)
- University of Texas Southwestern Medical Center (Dallas, TX)

It is anticipated that sites will begin to be activated early in 2012 such that several will have some initial experience prior to the first investigators' meeting. (Figure 6) This meeting is planned for March 2012 to include both investigators and a research nurse, with one plenary session for general trial structure and goals, followed by split sessions for the investigators and the research nurses. The focus of the investigator sessions will be review of the hypotheses, primary and secondary endpoints, initial timetable for publications of baseline data, and primary endpoint data after completion of one year of follow-up for all patients enrolled within year 1. The research nurses will receive orientation and instruction regarding the informed consent procedures and documentation, conduct of the study, and electronic data entry.

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FIGURE 1:

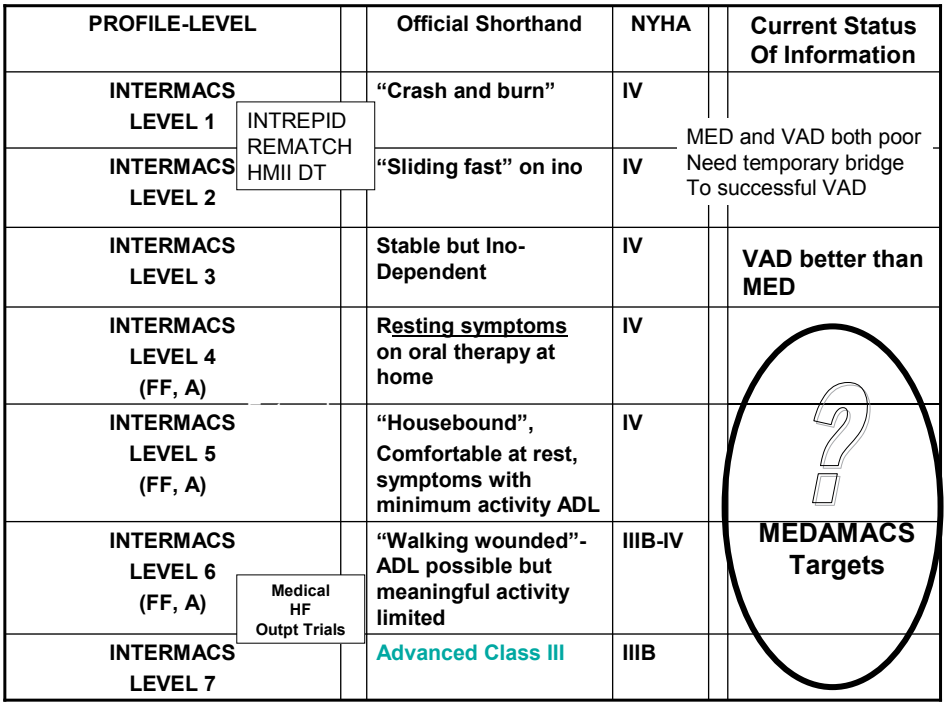
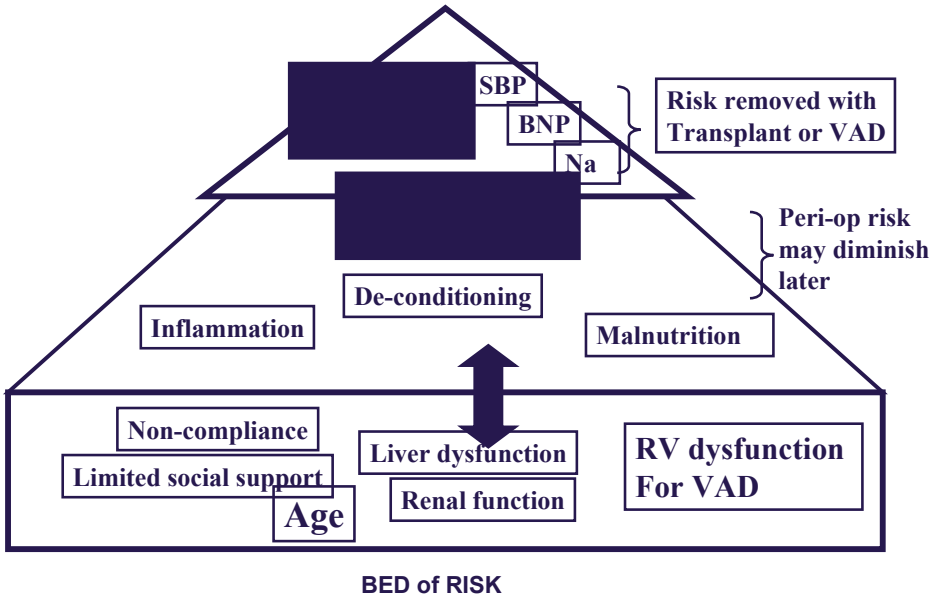

PROFILE-LEVEL
Official Shorthand
NYHA
Current Status Of Information
INTERMACS LEVEL 1
"Crash and burn"
IV
INTREPID
REMATCH
HMII DT
INTERMACS LEVEL 2
"Sliding fast" on ino
IV
MED and VAD both poor
Need temporary bridge
To successful VAD
INTERMACS LEVEL 3
Stable but Ino-Dependent
IV
VAD better than MED
INTERMACS LEVEL 4 (FF, A)
Resting symptoms on oral therapy at home
IV
INTERMACS LEVEL 5 (FF, A)
"Housebound", Comfortable at rest, symptoms with minimum activity ADL
IV
?
INTERMACS LEVEL 6 (FF, A)
"Walking wounded"- ADL possible but meaningful activity limited
IIIB-IV
MEDAMACS Targets
Medical HF Outpt Trials
INTERMACS LEVEL 7
Advanced Class III
IIIB

FIGURE 2:



Pyramid of Risk Factors for HF Death

FIGURE 3:

Profiles in Ongoing MEDAMACS Screening Pilot

	SHFM < 1.5	SHFM 1.5-2.5	SHFM > 2.5
Total N =140	N=90	N=39	N=11
EF	0.18	0.16	0.18
NYHA IV IIIB IIIA	6% 43% 51%	18% 41% 41%	55% 36% 9%
INTERMACS 4 (resting symptoms) 5 6 7	 17% 33% 34% 16%	 31% 23% 39% 8%	 46% 46% 9%
Mod-Sev RV Dysfn	34%	56%	64%
Cardiac Index (72% pts)	2.2	2.0	2.0
No Eval Yet for either Tranplant or VAD	57%	44%	27%

EF, ejection fraction; SHFM, Seattle Heart Failure Model Score;
RV, right ventricle; VAD, ventricular assist device

FIGURE 4:

Level of Illness in MEDAMACS Screening Pilot

	MEDAMACS N=140	REMATCH[2]	HMII-DT[3]
Peak VO_2, ml/kg/min	**13.1 (4.1)**	**---**	**---**
6 minute walk test, m	**253 (134)**	**---**	**182 (140)**
LV ejection fraction, %	**17 (6)**	**17 (5)**	**15 (6)**
Inotrope use	**20%** (within 6 mo)	**71%** (at implant)	**79%** (at implant)
Systolic blood pressure, mmHg	**112 (18)**	**101 (15)**	**104 (14)**
RA pressure, mmHg	**13 (7)**	**----**	**13 (6)**
Wedge pressure, mmHg	**22 (9)**	**25 (10)**	**24 (8)**
Cardiac index, L/min*m^2	**2.1 (0.5)**	**1.9 (1.0)**	**2.0 (0.6)**

Continuous variables, mean (SD)

Adapted from Cowger et al.[16]

FIGURE 5:

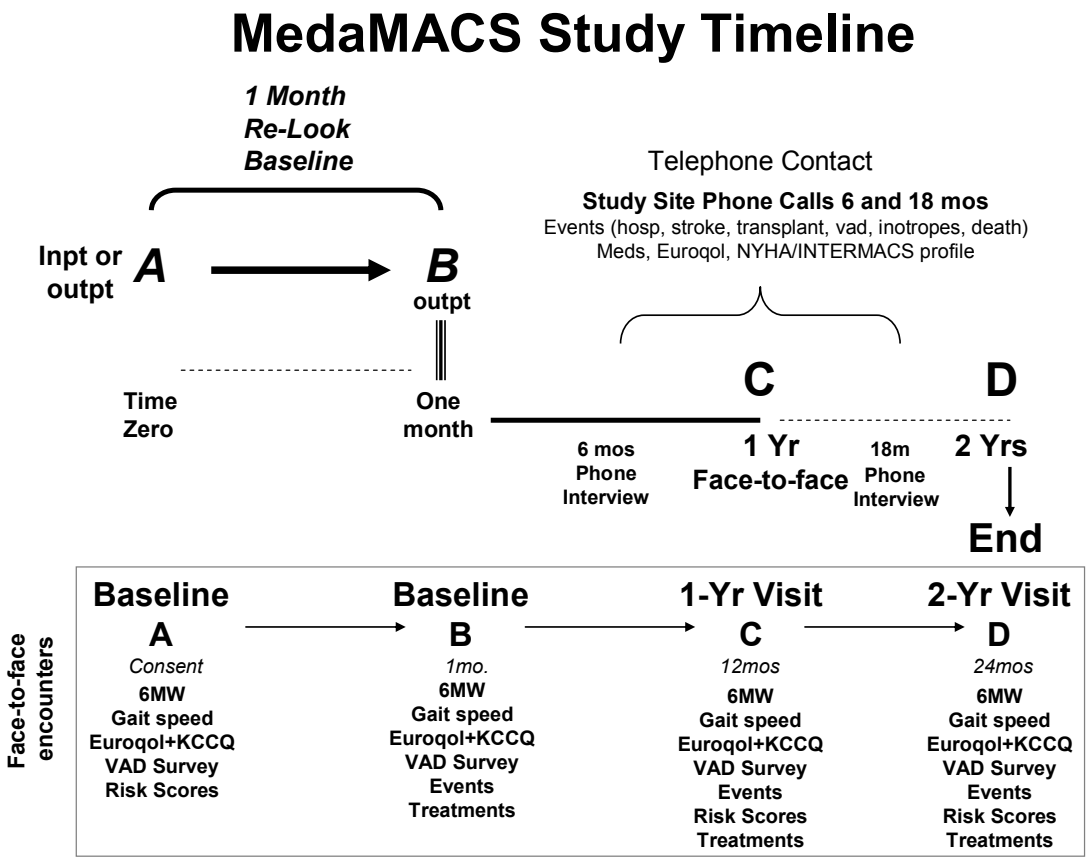
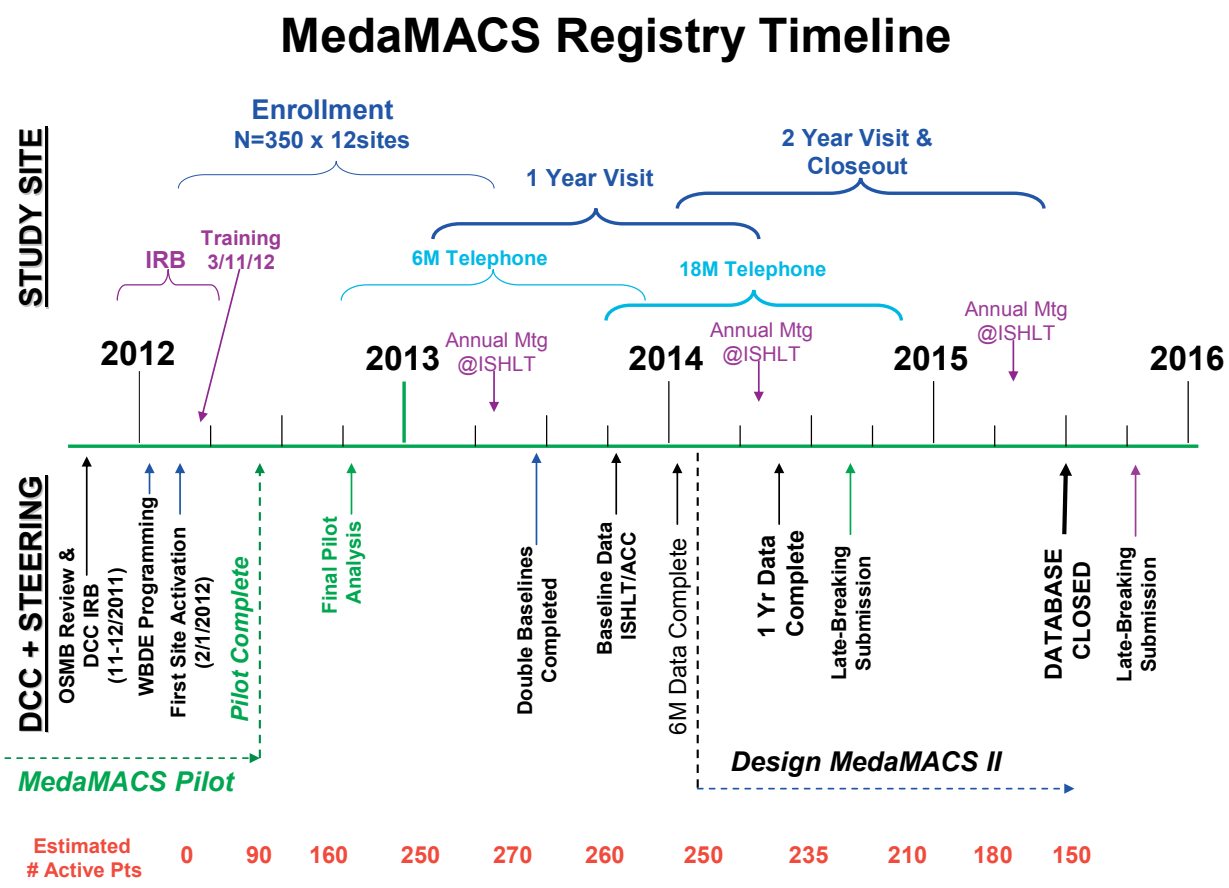

MedaMACS Study Timeline
1 Month
Re-Look
Baseline
Telephone Contact
Study Site Phone Calls 6 and 18 mos
Events (hosp, stroke, transplant, vad, inotropes, death)
Meds, Euroqol, NYHA/INTERMACS profile
Inpt or outpt
A
B
outpt
Time Zero
One month
C
D
6 mos Phone Interview
1 Yr Face-to-face
18m Phone Interview
2 Yrs
End
Face-to-face encounters
Baseline
A
Consent
6MW
Gait speed
Euroqol+KCCQ
VAD Survey
Risk Scores
Baseline
B
1mo.
6MW
Gait speed
Euroqol+KCCQ
VAD Survey
Events
Treatments
1-Yr Visit
C
12mos
6MW
Gait speed
Euroqol+KCCQ
VAD Survey
Events
Risk Scores
Treatments
2-Yr Visit
D
24mos
6MW
Gait speed
Euroqol+KCCQ
VAD Survey
Events
Risk Scores
Treatments

FIGURE 6:


MedaMACS Registry Timeline
STUDY SITE
Enrollment
N=350 x 12sites
1 Year Visit
2 Year Visit &
Closeout
IRB
Training
3/11/12
6M Telephone
18M Telephone
2012
2013
Annual Mtg
@ISHLT
2014
Annual Mtg
@ISHLT
2015
Annual Mtg
@ISHLT
2016
DCC + STEERING
OSMB Review &
DCC IRB
(11-12/2011)
WBDE Programming
First Site Activation
(2/1/2012)
Pilot Complete
Final Pilot
Analysis
Double Baselines
Completed
Baseline Data
ISHLT/ACC
6M Data Complete
1 Yr Data
Complete
Late-Breaking
Submission
DATABASE
CLOSED
Late-Breaking
Submission
MedaMACS Pilot
Design MedaMACS II
Estimated
Active Pts
0
90
160
250
270
260
250
235
210
180
150

APPENDIX A: SURVEY INSTRUMENTS

Part I: Physician Questionnaire:

Baseline A only

1. How long has patient been under care of your heart failure program?

   A. < 3 months
   B. 3-12 months
   C. 1-2 years
   D. > 2 years

2. If <3 months, which best describes the route of presentation: (as a drop-down from A in previous)

   A. New onset event or diagnosis within your institution
   B. Unspecified evaluation of severe heart failure
   C. Cardiac transplant and/or VAD evaluation

3. If a referral (B or C above), who referred the patient? (as a drop-down from B/C in previous)

   A. Local internist
   B. Local cardiologist
   C. Cardiac Surgeon
   D. Self-referral
   E. Unsure
   F. Other

Baseline A, B, 12 months and 24 months: (face to face encounters)

4. What is your best estimate of the likelihood of becoming sick enough to warrant urgent Stage D intervention within one year? This includes home inotropes, hospice, VAD, and urgent transplant.

   A. Highly LIKELY
   B. Moderately LIKELY
   C. Uncertain
   D. Moderately UNLIKELY
   E. Highly UNLIKELY

5. If it became medically indicated, what is likelihood that this patient would be eligible for transplant?

   A. Highly LIKELY
   B. Moderately LIKELY
   C. Uncertain
   D. Moderately UNLIKELY
   E. Highly UNLIKELY

6. If a VAD became medically indicated, what is the likelihood that they would require biventricular mechanical support rather than LVAD alone?
(answer only if C, D, E in question 5)

A. Definitely need Biventricular support
B. Probably need Biventricular support
C. Uncertain
D. Probably LVAD only
E. Definitely LVAD only

7. If not likely to be a transplant candidate and mechanical support became medically indicated, what is likelihood the patient would be eligible for destination LVAD alone as lifetime support?
(answer only if C, D, E above)

A. Highly LIKELY
B. Moderately LIKELY
C. Uncertain
D. Moderately UNLIKELY
E. Highly UNLIKELY

Part II: Patient Quality of Life Questionnaires

Baseline A, B, 12 months, and 24 months

1. Which of the following best describes your main activity?

Actively working	Full Time ☐ Part Time ☐
Student	Full Time ☐ Part Time ☐
Seeking work	Full Time ☐ Part Time ☐
Too sick to work (disabled)	☐
Retired	☐
Keeping house	☐
Other (please specify)	_____

2. How many of your close friends or relatives do you see in person, speak to on the telephone, or contact via the internet at least once a month? _____ (please count each person 1 time)

3. How much stress do you feel you've been under during the past 1 month, related to your health issues?

1 2 3 4 5 6 7 8 9 10
No stress Very much stress

4. How well do you feel you've been coping with or handling your stress during the past 1 month, related to your health issues?

1 2 3 4 5 6 7 8 9 10
Coping very poorly Coping very well

5. How confident are you that you can do the tasks and activities needed to manage your heart failure so as to reduce how much having heart failure affects your everyday life?

1 2 3 4 5 6 7 8 9 10
Not at all confident Totally confident

6. How satisfied are you with the results of your therapy for heart failure during the past 6 months? Please circle a number from 1 to 10, with 1 meaning that you're not satisfied at all, and 10 meaning that you're very satisfied.

1 2 3 4 5 6 7 8 9 10
Not satisfied Very satisfied

EUROQOL – 5D + Thremometer

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

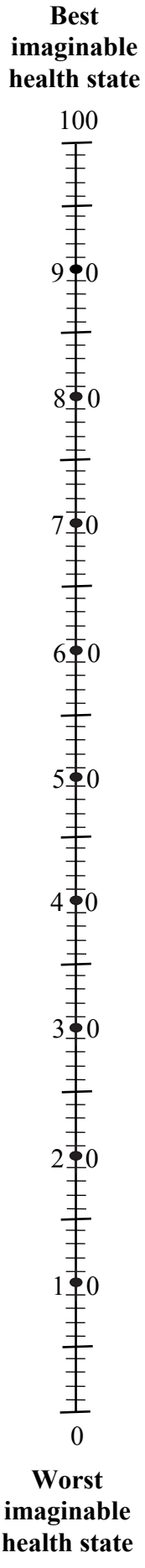
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

Heart Failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an X in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yard work, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

1. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed? My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

3. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you? It has been…

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

4. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
□	□	□	□	□	□	□

5. Over the <u>past 2 weeks</u>, how much has your **fatigue** bothered you?
It has been…

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
□	□	□	□	□	□

6. Over the <u>past 2 weeks</u>, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
□	□	□	□	□	□	□

7. Over the <u>past 2 weeks</u>, how much has your <u>shortness of breath</u> bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
□	□	□	□	□	□

8. Over the <u>past 2 weeks</u>, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
□	□	□	□	□

9**. Heart Failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
□	□	□	□	□

10. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
□	□	□	□	□

11. Over the <u>past 2 weeks</u>, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my	It has limited my enjoyment	It has **moderately**	It has **slightly** limited my	It has **not limited** my enjoyment of life

enjoyment of life	of life **quite a bit**	limited my enjoyment of life	enjoyment of life	at all
☐	☐	☐	☐	☐

12. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

13. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

14. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks?

Please place an X in one box on each line

Activity or did	**Severely**	Limited	**Moderately**	**Slightly**	**Did not**	Does not apply
reasons	limited	**quite a bit**	limited	limited	limit at all	not do for other
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐

Developed by John Spertus et al., Mid America Heart Institute, Saint Luke's Hospital, Kansas City, MO.

Part III: MedaMACS VAD Survey

Thank you for taking the time to fill out this short survey. We will be asking you several questions about your heart failure and a new therapy for heart failure. This survey should take no more than 15 minutes of your time. Your responses will remain confidential.

1. Based on how you feel today and what you know about your heart failure, what is your best estimate of how much longer you have to live? (choose one)

A. Less than 6 months

B. Between 6 months to 2 year

C. Between 2 to 5 years

D. More than 5 years

Ventricular Assist Device

There are many effective medical therapies available to treat congestive heart failure. Sometimes the heart can become too weak to pump enough blood to the body. At that stage, drugs may not be enough to treat heart failure.

Mechanical heart pumps called ventricular assist devices, or VADs, are a way to improve the circulation of blood throughout the body. These pumps do not replace the heart. They only assist the heart in pumping blood to the body. Once blood flow is improved, many patients have more energy and breathe easier. Clinical studies show that select patients with severe heart failure live longer with an assist device than with drug treatments alone.

Placement of a VAD requires major open heart surgery. The pump is placed inside the chest and abdomen and is connected to the heart. The VAD also has a power line that leaves the body through the skin in the front of the abdomen and is attached to a power supply outside the body. On average patients will remain in the hospital for about one month after surgery. Once discharged from the hospital, most patients are able to return home and live independently.

2. Based on how you feel <u>right now</u> and knowing only the above information above, which statement best describes how you would feel about having an assist device placed?

A. I would DEFINITELY want it

B. I would PROBABLY want it

C. I don't know if I would want it or not

D. I would PROBABLY NOT want it.

E. I would DEFINITELY NOT want it

3. Suppose that your doctor told you with certainty that you only had a limited about of time to live. The next series of questions will ask you to imagine different scenarios where you only have a certain amount of time left to live.
(Check one box)

Would you want a ventricular assist device if you had:	**Probably YES**	**Unsure**	**Probably NOT**
A. Less than 1 month to live?	**o**	**o**	**o**
B. Less than 6 months to live?	**o**	**o**	**o**
C. Less than 2 years to live?	**o**	**o**	**o**
D. Less than 5 years to live?	**o**	**o**	**o**

4. The next series of questions asks to imagine that you are experiencing various degrees of illness related to your heart failure. Please consider each scenario in terms of how limited you might feel and whether or not you would want an assist device to feel better. (Check one box)

Would you want an assist device if:	**Probably YES**	**Unsure**	**Probably NOT**
1. In the intensive care unit with hours or days to live.	**O**	**O**	**O**
2. In the hospital on intravenous medicines to keep you alive, with only days or weeks to live.	**O**	**O**	**O**
3. At home requiring continuous medicine through an intravenous 24 hours a day with weeks to months to live.	**O**	**O**	**O**
4. At home and always breathless at rest and with light activities such as dressing or bathing.	**O**	**O**	**O**
5. At home, comfortable at rest but breathless when walking around the house.	**O**	**O**	**O**
6. At home but breathless after walking more than one block or more than one flight of stairs	**O**	**O**	**O**
7. Not breathless during daily activities at home or after walking several blocks, but breathless with all other activities	**O**	**O**	**O**

5. Prior to this survey, have you heard about a ventricular assist device (VAD)?

A. Yes

B. No

C. Don't know

6. If you have heard about an assist device before, how did you first hear about a VAD?

A. Television/Radio

B. Newspaper/Magazine

C. Your health care provider

D. Family members or friends

E. The Internet

7. Knowing what you know now about different treatments for severe heart failure, which of these therapies would you rather have?

A. Ventricular Assist Device

B. Heart Transplant

C. Don't know

8. Do you have a designated health care proxy or durable power of attorney for health care?

A. Don't know

B. Yes

C. No

The next series of questions focuses on treatment choices near the end of life. Once again, all responses are confidential and will not be shared with your medical team. Please let us know if you wish to discuss any of these matters with your physicians.

9. Many life-sustaining therapies are available near the end of the life. These include dialysis, breathing machines, tubes for feeing, and whether or not you would wish to be resuscitated if your breathing or heart stops beating. Has your physician talked about your wishes regarding such life-sustaining therapies?

A. Yes

B. No

C. Don't know

10. At this time, if there are any life-sustaining therapies you **do not want**, please circle them below:

A. Chest compressions

B. Being placed on a breathing machine

C. Kidney dialysis

D. Transfer to the Intensive Care Unit (ICU)

E. Feeding tube if unable to eat

Part IV: Missing Data Form

Check one response regarding WHY "self-report instruments" were not completed by the PATIENT:

_____ too sick

_____ too tired

_____ too stressed, anxious, and / or depressed

_____can't concentrate

_____ no time / too busy

_____ too much trouble / don't want to be bothered / not interested

_____ unwilling to complete instruments, no reason given

_____ unable to read English and / or illiterate

_____ administrative (check specific reason below)

_____No time, coordinator too busy to administer self-report instruments

_____Coordinator forgot to administer self-report instruments

_____Unable to contact patient face-to-face or per telephone

_____Patient did not return mailed self-report instruments within the window for instrument completion

_____ other reason

(describe)_____

Part V: Supplemental Questions:

1. In general, how comfortable would you be if your life depended on interacting with technology every day? Please draw an "X" on the line below that best describes how you feel.

Highly Uncomfortable — Very Comfortable

2. Treatments for heart disease can range from pills to pacemakers and even major heart surgeries. Some patients are willing to undergo more aggressive treatment to survive, while others are reluctant to consider more aggressive therapies and wish to focus on comfort alone. Based on how you feel today, please draw an "X" on the line below to indicate how you feel about medical treatments for your heart failure.

Focus on Comfort Only — Do Anything to Survive

APPENDIX B: DATA ELEMENTS

DEMOGRAPHICS	Baseline A	Baseline B	6m	12m	18m	24m
Name	X					
Social security number	X					
Date of birth	X					
Gender	X					
Ethnicity	X					
Race	X					
Marital status	X			X		
Highest education level	X					
Working for income	X			X		
Height	X	X				
Weight	X	X	X	X	X	X
Blood type	X					
Inpatient/Outpatient status	X	X				
Context of referral*	X					

CLINICAL	Baseline A	Baseline B	6m	12m	18m	24m
Time since first cardiac diagnosis	X			X		X
Heart failure hospitalizations in last 12mos	X			X		X
Primary cardiac diagnosis	X					
Cancer	X					
Congenital heart disease	X					
Coronary artery disease	X					
Dilated cardiomyopathy	X					
Adriamycin	X					
Toxic/Alcoholic	X					
Familial	X					
Idiopathic	X					
Ischemic	X					
Myocarditis	X					
Other	X					
Post-partum	X					
Viral	X					
Hypertrophic	X					

Sarcoidosis	X					
Other	X					
Previous cardiac operations	X			X		X
None	X			X		X
CABG	X			X		X
Aortic valve repair/replacement	X			X		X
Mitral valve repair/replacement	X			X		X
Congenital card surg	X			X		X
Aneurysmectomy	X			X		X
Other	X			X		X
INTERMACS patient profile	X	X	X	X	X	X
Modifiers: A, FF, none	X	X	X	X	X	X
Current NYHA class	X	X	X	X	X	X
Prior heart transplant evaluation	X	X		X		X
Eval outcome: accept, reject, defer	X	X		X		X
Prior DT VAD evaluation	X	X		X		X
Eval outcome: accept, reject, defer	X	X		X		X
Diabetes	X	X		X		X
Home oxygen	X	X		X		X
Previous renal replacement	X	X		X		X
Any dialysis	X	X		X		X
Any ultrafiltration	X	X		X		X
Recent intubation	X	X		X		X
Recent intraaortic counterpulsation (within 6m)	X	X		X		X
Inotrope Use in last 6 months	X	X		X		X
Timing; which drugs	X	X		X		X
Length of time followed by program	X					
Referral source	X					
Reason for referral	X					

COMORBID CONCERNS	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Advanced age	X			X		X
Patient refuses transplant	X			X		X
Frailty	X			X		X
Contraindication to immunotherapy	X			X		X
Malnutrition/cachexia	X			X		X
Large body mass index	X			X		X
Musculoskeletal limitations	X			X		X
History of solid organ cancer	X			X		X
History lymphoma, leukemia	X			X		X
Major stroke	X			X		X
Other cerebrovascular disease	X			X		X
Renal dysfunction	X			X		X
Pulmonary disease	X			X		X
Severe diabetes	X			X		X
Peripheral vascular disease	X			X		X
Risk of recurrent infection	X			X		X
Pulmonary hypertension	X			X		X
Recent pulmonary embolus	X			X		X

Allosensitization	X			X		X
Heparin-induced thrombocytopenia	X			X		X
Current infection	X			X		X
Limited cognition/understanding	X			X		X
Limited social support	X			X		X
History of illicit drug use	X			X		X
History of alcohol abuse	X			X		X
History of smoking	X			X		X
Currently smoking	X			X		X
Severe depression	X			X		X
Other major psychiatric disorder	X			X		X
Repeated non-compliance	X			X		X
More than one prior sternotomy	X			X		X
Mediastinal radiation	X			X		X
Thoracic aortic disease	X			X		X
History of hepatitis	X			X		X
Chronic coagulopathy	X			X		X
History of human immunodeficiency virus or AIDS	X			X		X
History of GI ulcers	X			X		X
History of atrial arrhythmias	X			X		X
History of symptomatic ventricular tachycardia or defibrillator shocks	X			X		X
Other co-morbidity (specify)	X			X		X

PHYSICAL	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Heart rate	X	X		X		X
Blood pressure	X	X		X		X
Jugular venous pressure	X	X		X		X
S3 gallop	X	X		X		X
S4 gallop	X	X		X		X
Peripheral edema	X	X		X		X
Ascites	X	X		X		X
Hepatomegaly	X	X		X		X

EKG	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Rate	X	X		X		X
Rhythm: atria, ventricles, pacing type	X	X		X		X
QRS duration	X	X		X		X

ECHOCARDIOGRAPHY	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Date	X			X		(X)
Left ventricular (LV) ejection fraction	X			X		(X)
LV end-diastolic dimension	X			X		(X)
Right ventricular (RV) Indices	X			X		(X)
Qualitative RV Function	X			X		(X)
Qualitative RV Size	X			X		(X)
Maximum mid RV dimension	X			X		(X)

Tricuspid annular plane excursion		X		X		(X)
Tricuspid regurgitant velocity		X		X		(X)
Tricuspid regurgitation (none, mild, mod, sev)		X		X		(X)
Mitral regurgitation (none, mild, mod, sev)		X		X		(X)
Aortic stenosis (none, mild, mod, sev)		X		X		(X)
Aortic insufficiency (none, mild, mod, sev)		X		X		(X)
Inferior vena cava size		X		X		(X)
Inferior vena cava respiration variation: yes, blunted, none		X		X		(X)
Ancillary indices of RV function		X		X		(X)
RIGHT HEART CATHETERIZATION	**Baseline A**	**Baseline B**	**6m**	**12m* If avail**	**18m**	**24m**
Date	X			X		
Therapies at cath: no iv, iv, iabp	X			X		
Systolic blood pressure	X			X		
Diastolic blood pressure	X			X		
heart rate	X			X		
Right atrial pressure	X			X		
Pulmonary artery systolic pressure	X			X		
Pulmonary artery diastolic pressure	X			X		
Pulmonary capillary wedge pressure	X			X		
PA saturation	X			X		
Cardiac output	X			X		
Cardiac index	X			X		
EXERCISE TESTING	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
6 minute walk distance	X	X		X		X
15 ft walk time (gait speed/frailty)	X	X		X		X
Cardiopulmonary exercise testing		X		X		
Resting heart rate		X		X		
Peak heart rate		X		X		
Peak oxygen uptake		X		X		
Peak oxygen uptake % predicted		X		X		
Ventilatory efficiency (Ve/VCO2)		X		X		
Peak respiratory exchange ratio		X		X		
MEDICAL AND DEVICE THERAPIES	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Meds: Current/Previous/No/Unknown						
Angiotensin converting enzyme inhibitor	X	X	X	X	X	X
Angiotensin receptor blocker	X	X	X	X	X	X
Beta adrenergic blocker	X	X	X	X	X	X
Aldosterone antagonist	X	X	X	X	X	X
Potassium supplement	X	X	X	X	X	X
Long acting nitrate	X	X	X	X	X	X
Hydralazine	X	X	X	X	X	X

Phosphodiesterase inhibitor	X	X	X	X	X	X
Digoxin	X	X	X	X	X	X
Loop diuretic + daily dose	X	X	X	X	X	X
Metolazone/thiazide and frequency	X	X	X	X	X	X
Aspirin	X	X	X	X	X	X
Clopidogrel	X	X	X	X	X	X
Coumadin	X	X	X	X	X	X
Other anticoagulant	X	X	X	X	X	X
Statin	X	X	X	X	X	X
Allopurinol	X	X	X	X	X	X
Amiodarone	X	X	X	X	X	X
Other antiarrhythmic	X	X	X	X	X	X
ICD	X	X	X	X	X	X
If yes, dates of any ICD shocks	X	X	X	X	X	X
Cardiac resynchronization	X	X	X	X	X	X
If < 6 months, implant date	X	X	X	X	X	X
Home oxygen	X	X	X	X	X	X

BLOOD LABORATORIES	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Chemistry						
Sodium	X	X		X		X
Potassium	X	X		X		X
Creatinine	X	X		X		X
Blood urea nitrogen	X	X		X		X
Total bilirubin	X			X		X
Direct bilirubin	X			X		X
Aspartate aminotransferase/SGOT	X			X		X
Alanine aminotransferase/SGPT	X			X		X
B-type natriuretic peptide (BNP)	X	X		X		X
NT-pro-BNP	X	X		X		X
Metabolism						
Total cholesterol	X			X		X
Low density lipoprotein	X			X		X
High density lipoprotein	X			X		X
Triglycerides	X			X		X
Uric acid	X			X		X
C-reactive protein	X			X		X
Pre-albumin	X			X		X
Albumin	X			X		X
Hematologic	X			X		X
White blood cell	X			X		X
% lymphocytes	X			X		X
Hemoglobin	X			X		X
Hematocrit	X			X		X
Platelet	X			X		X
International normalized ratio	X			X		X
Lupus anticoagulant if available	X			X		X

QOL/PREFERENCES	Baseline A	Baseline B	6m	12m	18m	24m
EuroQoL	X	X	X	X	X	X
Thermometer	X	X	X	X	X	X
5 functional domains	X	X	X	X	X	X
Kansas City Cardiomyopathy Questionnaire	X	X		X		X
Patient VAD survey instrument	X	X		X		X
Missing data survey	X	X		X		X
EVENTS/OUTCOMES	**Baseline A**	**Baseline B**	**6m**	**12m**	**18m**	**24m**
Death		X	X	X	X	X
Primary cause of death (assigned by PI)		X	X	X	X	X
Sudden death		X	X	X	X	X
Transplant		X	X	X	X	X
Listed for Transplant		X	X	X	X	X
Listing status		X	X	X	X	X
VAD, if yes then		X	X	X	X	X
Type of circulatory support		X	X	X	X	X
Device name		X	X	X	X	X
Intended Support Strategy		X		X		X
Other Cardiac Procedure/Surgery (name)		X		X		X
Chronic inotrope infusion		X		X		X
Resuscitation (Code) Status		X		X		X
Hospice		X		X		X
Recovery of EF to ≥40%		X		X		X
Current NYHA Functional Class		X		X		X
Current INTERMACS Profile		X		X		X
Hospitalization, reason for admission		X		X		X
Heart failure with iv diuresis or inotrope		X		X		X
Neurologic event		X		X		X
Major bleeding (non CNS)		X		X		X
Transfusion		X		X		X
Psychiatric episode		X		X		X
Major infection		X		X		X
Localized infection		X		X		X
Sepsis		X		X		X
Type of Infection		X		X		X
Bacterial		X		X		X
Fungal		X		X		X
Viral		X		X		X
Protozoan		X		X		X
Unknown		X		X		X
Intervention (IV, PO, surgery, other)		X		X		X
Cardiac tachyarrhythmia		X		X		X
Syncope cause unknown		X		X		X
Fever treated with antibiotics cause unknown		X		X		X
Arterial non-CNS thromboembolism		X		X		X
Venous thromboembolic event		X		X		X

Myocardial infarction	X	X	X
Other cardiac cause (specify)	X	X	X
Non-cardiac cause (specify)	X	X	X
Elective procedure - cardiac	X	X	X
Elective procedure – noncardiac	X	X	X
Abnormal lab values	X	X	X