REVIVE-IT REGISTRY

(REVIVAL: *REGISTRY EVALUATION OF VITAL INFORMATION FOR VADs IN AMBULATORY LIFE*)

CLINICAL STUDY PROTOCOL

Sponsor: National Heart, Lung, and Blood Institute

Principal Investigators: Keith Aaronson, MD, MS
Garrick Stewart, MD

Co-Investigators:
Francis Pagani MD, PhD
Cathie Spino, ScD
Lynne Stevenson, MD
Robert Kormos, MD

Institution: University of Michigan

Version and Date: REVIVE-IT Version 7.0, 08Oct2015

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following ICH E6; 62 Federal Register 25691 (May 9, 1997).

Protocol Version 7.0

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Principal Investigator: _____

Signed: _____ Date: _____

Table of Contents

Statement of Compliance 2

Signature Page 3

Study Summary 7

1.0 Introduction 10

1.1 Rationale 10
1.2 Background 11
1.2.1 Mechanical Support in Ambulatory Advanced Heart Failure 11
1.2.2. Risk Profiling in Ambulatory Advanced Heart Failure 11
1.2.3 Ambulatory Patients Awaiting Heart Transplantation 12

2.0 Specific Objectives 12

3.0 Study Design and Population 13

3.1 Number of Clinical Sites and Subjects 13
3.2 Design 14
3.3 Subject Identification Procedures 14
3.4 Study Visit Overview 15
3.5 Participating Centers 15

4.0 Study Procedures and Assessments 15

4.1 Informed Consent Procedures 15
4.2 Six Minute Walk Test Distance (6MWT) 15
4.3 Maximal Oxygen Consumption (peak VO_2) 16
4.4 Echocardiogram 17
4.5 Directed History, Physicals and Vital Signs 18
4.6 Medication Criterion 18
4.7 Handgrip Strength (by Dynamometer) 18
4.8 Gait Speed Test 18
4.9 Demographics 18
4.10 Documentation of Concomitant Medications 18
4.11 Documentation of Study Events/Outcomes 19
4.12 Seattle Heart Failure Model (SHFM) Score 19
4.13 Heart Failure Survival Score (HFSS) 19
4.14 Health Status, Patient Perspective and Quality of Life Assessments 19
4.15 Electrocardiogram (ECG) 20
4.16 Procedures for Clinical Laboratory Samples 20
4.17 Blood for Analysis, Specimen Handling and Storage 20

5.0 Study Participation Criteria 21

5.1 Study Inclusion Criteria 21
5.2 Study Exclusion Criteria 22
5.3 Criteria for Discontinuation or Withdrawal of a Subject 22

6.0 Schedule of Observations and Procedures 23

6.1 Screening and Eligibility Assessment 23
6.2 Study Procedures and Assessments 23
6.2.1 Baseline A 23
6.2.2 Baseline B 24
6.2.3 Six (6) Month Follow up (+/- 30 days) 25

6.2.4 Twelve (12) Month Follow up (+/- 30 days) 26
6.2.5 Eighteen (18) Month Follow up (+/- 30 days) 27
6.2.6 Twenty-four (24) Month Follow up (+/- 30 days) 27

7.0 Adverse Event and Unanticipated Problems 28
7.1 Adverse Event and Unanticipated Problems Reporting Requirements 28
7.2 Adverse Event Category Definitions 28
Adverse Event 28
Serious Adverse Event 29
Unanticipated Problems (UPs) 29
7.3 Causality 29

8.0 Statistical Considerations 30
8.1 General Statistical Considerations 30
8.2 Sample Size Considerations 31
8.3 Analysis Approach 32
8.3.1 Demographic and Baseline Characteristics 32
8.3.2 Characterization of Clinical Outcomes and Other Outcomes 32
8.3.3 Modeling of Clinical Outcomes 32
8.4 Modeling of Other Outcomes 33
8.5 Health Associated Costs 33
8.6 Comparative Analyses of Outcomes 33

9.0 Data Access, Analysis and Publications 33

10.0 Benefit and Risk Assessment 34
10.1 Potential Benefit 34
10.2 Potential Risk 34

11.0 Investigator Responsibility 34

12.0 Institutional Review Board (IRB) Approval 35

13.0 Caregiver 35

14.0 Subject Data Protection 35

15.0 Protocol Deviations 36

16.0 Monitoring and Quality Control 36
16.1 Site Training 36
16.2 Monitoring of the Study 36
16.3 Independent Data Review 37
16.4 Reporting to Governing Agencies 37
16.5 Investigational Site Enrollment Suspension 37

17.0 Data Management 37
17.1 Case Report Forms 38
17.2 Laboratory Accreditation and Normal Values 38
17.3 Data Review 38
17.4 Data Ownership and Sharing Plan 39

18.0 Maintenance of Study Documentation 40

19.0 Record Retention 40

20.0 Study Oversight 40

Appendix A: Time and Event Schedule 42
Appendix B: INTERMACS® Patient Profiles 43
Appendix C: New York Heart Association (NYHA) Functional Classification 45
Appendix D: Study Specific Reportable Events/Outcomes 46

Study Summary

<table>
<tr><th colspan="2">REVIVE-IT REGISTRY (REVIVAL)</th></tr>
<tr><td colspan="2">Name of Funding Sponsor:
National Heart, Lung, and Blood Institute</td></tr>
<tr><td colspan="2">Title of Protocol:
REVIVAL: Registry Evaluation of Vital Information for VADS in Ambulatory Life</td></tr>
<tr><td colspan="2">Study Number:
NHLBI Solicitation Number: RFP NHLBI-HV-10-14
NHLBI Contract Number: HHSN268201100026C</td></tr>
<tr><td colspan="2">Study Design:
The REVIVE-IT Registry (i.e., REVIVAL) is a prospective cohort study to be conducted in up to twenty five (25) participating Clinical Sites in the USA. The study will continue until up to 400 eligible heart failure heart failure subjects have been enrolled (estimated length of accrual is 12 months).</td></tr>
<tr><td colspan="2">Objectives:
1. To characterize clinical outcomes, quality of life and functional impairment over two (2) years in a population of ambulatory patients on evidence-based therapy with advanced chronic systolic heart failure who may benefit from VAD therapy
2. To evaluate the relationship between heart failure subject’s modeled prognosis, self assessed prognosis, preferences for end of life care and thresholds for considering VAD implant
3. To evaluate caregiver burden associated with heart failure subject’s measures of heart failure severity, quality of life, functional limitations and with preferences for care and thresholds for considering device implant
4. To determine health-associated costs for heart failure subjects in the registry
5. To provide the REVIVE-IT Registry to the INTERMACS study group to be used in comparative analyses of outcomes of patients treated with medical versus VAD therapy</td></tr>
<tr><td>Number of Subjects:
Up to 400 patients will be consented into the Registry.</td><td>Number of Sites:
Up to 25 Clinical Sites in the US</td></tr>
<tr><td colspan="2">Period of Evaluation:
Patients will be followed for up to 2 years post-enrollment</td></tr>
<tr><td colspan="2">Major Criteria for Evaluation and Analyses:
1. Hospitalizations
2. Stroke
3. Mechanical Circulatory Support Device (MCSD)*
4. Transplant*
5. Death (Cardiovascular related vs. Non-cardiovascular related)*

* Outcomes of death, transplant and implants of a durable VAD will be considered study endpoints with no additional follow-up in REVIVAL. When a study endpoint has been reached, events/outcomes up through the point of the outcome will be reported on the eCRFs.</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
1. Ambulatory.
2. Chronic systolic heart failure ≥ 12 months.
3. NYHA II - IV for at least 45 of the last 60 days.
4. Last documented left ventricular ejection fraction ≤ 35% by any imaging modality.
5. Age 18 - 80 years.
6. Under the care of a cardiologist at the study site.
7. On appropriate evidenced-based heart failure medications – ACE inhibitor, ARB or</td></tr>
</table>

sacubitril/valsartan [LCZ-696]; beta blocker; aldosterone antagonist; hydralazine/long-acting nitrate [required of African-American subjects only] for ≥ 3 months absent contraindications or intolerances.

8. Has ICD or CRT-D. If CRT-D, present for ≥ 3 months.
9. Demonstrated advanced heart failure, including any one of the following*:
    i. Serum sodium ≤ 135 mEq/L (obtained as an outpatient)**
    ii. Serum BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL** (obtained as an outpatient)
    iii. Seattle Heart Failure Model (SHFM) one year predicted survival ≤ 85%**
    iv. Heart Failure Survival Score (HFSS) ≤ 7.19**
    v. Peak VO_2 ≤ 55% of predicted for age by Wasserman equation or ≤ 14 ml/kg/min, with RER ≥ 1.05***
    vi. VE/VC02 slope ≥ 40***
    vii. 6 minute walk test (6MWT) distance ≤ 350 m without significant non-cardiac limitation**
    viii. Currently listed as Heart Transplant Status II due to heart failure limitation

Or

History of one (1) hospitalization (≥ 24 hours) for acute or acute on chronic heart failure in the past year with additional history to include:

    i. Serum BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL** (obtained as an outpatient)

Or

History of two (2) hospitalizations (≥ 24 hours) for acute or acute on chronic heart failure in the past year.

* Qualifying measure must be the most recent of that type of measure obtained (i.e., a BNP ≥ 1000 obtained 2 months prior would not qualify the heart failure subject if a more recent BNP was < 1000)
**Using values obtained within the prior 90 days, except for peak VO_2 within 365 days
***Obtained within the prior 365 days

10. Willingness to continue to receive heart failure care from the enrolling advanced heart failure clinic over the next two (2) years and to come for all scheduled study visits.
11. Written Informed consent given.

Main Criteria for Exclusion:

1. Known serious medical problem other than heart failure that would be expected to limit 2-year survival (≥50% mortality within 2 years from non-heart failure diagnosis).
2. Patient is not likely to be compliant with the protocol, in the opinion of the Investigator.
3. Currently hospitalized.
4. Current use of an intravenous inotrope.
5. Primary functional limitation from non-cardiac diagnosis even if not likely to limit survival.
6. Chronic hemodialysis or peritoneal dialysis or a serum creatinine value of ≥ 3 mg/dL at time of enrollment.
7. Cardiac amyloidosis, cardiac sarcoidosis, constrictive pericardial disease, active myocarditis or congenital heart disease with significant structural abnormality.
8. Hypertrophic cardiomyopathy unless dilated LV and no outflow gradient.
9. Cardiac conditions that are amenable to surgical or percutaneous procedures (other than VAD or

transplant) that would substantially improve prognosis and for which this subject is a reasonable candidate, regardless of whether the procedure will or will not be performed.

10. Uncorrected hyperthyroidism or hypothyroidism.
11. Pregnancy.

Statistical Considerations:

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

1.0 Introduction

1.1 Rationale

Despite widespread use of evidence-based medical therapies, including neurohormonal blockers and biventricular pacing, mortality and morbidity from systolic heart failure remains high.[1] Breakthroughs in mechanical circulatory support (MCS) technology have extended survival and improved quality of life in the most advanced heart failure patients awaiting cardiac transplantation and in inotrope-dependent patients who are ineligible for transplant.[2-4] Left ventricular assist device (LVAD) therapy offers the promise of relieving heart failure symptoms in patients with less advanced stages of heart failure but comes with its own significant adverse effect burden. Future expansion of the target population for VAD therapy into ambulatory patients with less advanced heart failure requires improved prognostic tools to allow identification of those patients at greatest risk of dying without MCS and those who are most likely to have a favorable outcome with VAD therapy. Analyses of VAD clinical trial databases and of the INTERMACS Registry have greatly enhanced our knowledge of the latter question. The REVIVE-IT Registry (also referred to as REVIVAL to differentiate the stand-alone registry from the originally designed REVIVE-IT study where the registry was coupled to the trial) will address the former.

REVIVAL will establish a **prospective, observational, multicenter patient cohort** in ambulatory patients with chronic, advanced, systolic heart failure that will provide a greater understanding of their clinical trajectory (rates of hospitalizations, transplantation, MCSD use and death), and of how baseline clinical risk measures are related to prognosis. Within the broader goal of 1) improving prognostic assessment in chronic, ambulatory, advanced systolic heart failure, additional targeted goals are to 2) better inform the selection of appropriate candidates for a future study of a strategy of early LVAD therapy vs. optimal medical management in this population, and 3) determine the feasibility of identifying candidates for such a trial. Therefore, the target population will have known high-risk features for increased mortality and hospitalization (e.g., frequent hospitalization, reduced exercise capacity, elevated BNP or N-terminal proBNP, increased Seattle Heart Failure Model risk score, reduced Heart Failure Survival Score).

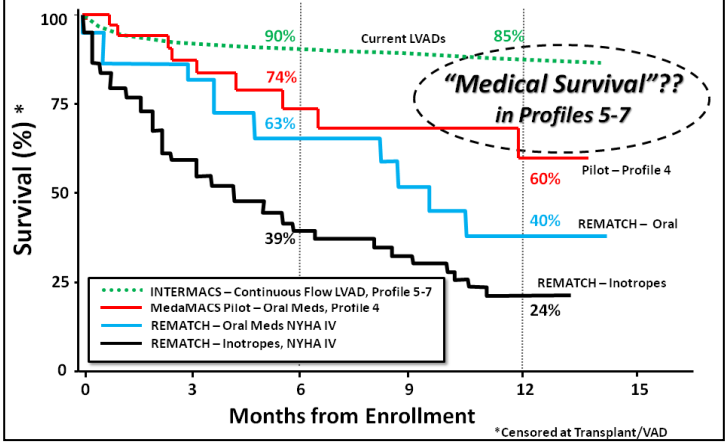
Present prognostic models have been limited by both the quality of the prognostic data and the narrowness of the outcome data (e.g., survival outcome only). The prognostic value of registry data is often limited by the restricted scope of the prognostic variables collected, poor measurement quality and missing data. Prognostic models are generally limited to predicting death or hospitalization (or both) rather than more comprehensive measures like quality adjusted life years (QALYs). REVIVAL will address this knowledge gap by creating a repository of high quality prognostic and outcome data on a cohort of patients with advanced heart failure (INTERMACS Profiles 5-7).

1.2 Background

1.2.1 Mechanical Support in Ambulatory Advanced Heart Failure

As MCS survival has increased to over 75% at one year, ambulatory patients with advanced heart failure at home on oral therapy are now being considered more often for MCS. [Figure 1] These patients with INTERMACS Profiles 4-7 still account for fewer than 20% of the over 14,000 MCS patients registered in INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support).[5] Yet in patients receiving oral heart failure therapy in Profile 4 (persistent resting symptoms at home on oral medical therapy) the contemporary event rate exceeds 50% at one year among the population screened at 11 MCS centers for feasibility of the proposed project.[6] In the screening pilot for the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS), INTERMACS profiling was shown to provide a powerful shorthand for describing ambulatory patients with heart failure at risk of death or progressive disease requiring advanced cardiac therapies, with higher patient profiles denoting lower overall risk. The largest potential public health benefit from MCS is projected to be in ambulatory patients in INTERMACS Profiles 5-7 in whom MCS can be employed electively for long-term benefit with lower complication rates and improved cost-effectiveness. For this "less sick" population in whom death is not imminent, shared decision-making about MCS requires more measured and individualized consideration of risks and benefits beyond survival.[7]

Figure 1: Survival with Ambulatory Advanced Heart Failure



1.2.2. Risk Profiling in Ambulatory Advanced Heart Failure

Identification of patients at high risk of mortality is vital for triage to advanced cardiac therapies. The only randomized trial directly comparing MCS to medical therapy was REMATCH, which followed only 61 patients on medical therapy, many on two inotropic agents.[8] The REMATCH subgroup on oral medical therapy was only 16 patients.[9] Classic scores such as the Heart Failure Survival Score from pre-transplant populations pre-date the advances of implantable defibrillators and resynchronization pacing.[10] None of the other risk scores in current use are derived from or for the advanced heart failure population in whom MCS is being considered. Data from pharmacologic trials focuses on younger patients generally with mild-moderate heart failure without recent decompensation. As a result, the prevalent Seattle Heart Failure Score amalgamated from multiple clinical trials has generally underestimated mortality in advanced heart failure.[11-13] Other risk scores derived from community populations with mean age in the mid-70s include major contributions from co-morbidities and non-cardiac mortality to overall

risk.[14] We remain limited in our ability to identify ambulatory patients who are both sick enough and well enough to derive more benefit from MCS than from contemporary medical therapy, which itself is progressing rapidly with new therapies.[15]

1.2.3 Ambulatory Patients Awaiting Heart Transplantation

The current allocation system in the United Network for Organ Sharing (UNOS) for heart transplantation prioritizes patients according to level of illness and allows listing of ambulatory patients who do not require intravenous therapies or mechanical support in UNOS Status 2. Improving survival on the waiting list, in part because of more widespread bridging with MCS, has led to increasing waiting times until transplant.[16] This ever growing waiting list coupled with a nationwide shortage of donor organs has limited transplantation in most regions to high-risk patients in UNOS Status 1A/B, priority levels that only apply to hospitalized patients or those with existing MCS.[17] As a consequence, ambulatory advanced heart failure patients awaiting transplantation in Status 2 face difficult decisions about if and when to pursue mechanical support. Patients listed in Status 2 on oral therapies must consider the tradeoffs between a major surgical intervention promising a better quality of life coupled with waitlist status upgrade versus ongoing medical therapy. REVIVAL will be the first comprehensive registry of ambulatory advanced heart failure patients to enroll UNOS Status 2 patients who have a long anticipated wait for transplant. This is another major group of patients for whom the selection of MCS versus ongoing medical therapy prior to transplant is unexplored.

2.0 Specific Objectives

Objective 1: To characterize clinical outcomes, quality of life and functional impairment over two (2) years in a population of ambulatory patients on evidence-based therapy with advanced chronic systolic heart failure who may benefit from VAD therapy

- Characterize ambulatory patients with advanced heart failure at study entry, including measures of functional capacity and (baseline peak VO_2 and serial 6 minute walk test distance), frailty, biomarkers, and quality of life, and interest in VAD therapy.

- Characterize clinical outcomes of these heart failure subjects over two (2) years of follow-up, including a) hospitalizations, Mechanical Circulatory Support Device (MCSD) implant, heart transplant, survival without MCSD or transplant; survival without MCSD, transplant or substantially impaired health utility and b) functional capacity and quality of life.

- Develop improved risk prediction tools for use in this spectrum of advanced ambulatory chronic systolic heart failure.

- Determine if a second early assessment (at two months) of clinical information provides prognostic value that is additive to that of an initial assessment alone.

- Investigate the test performance characteristics of existing classification systems to determine: a) consistency of associated clinical characteristics of a given profile within

and between sites; b) performance metrics such as calibration, discrimination and accuracy; and c) prognostic ability with respect to clinical outcomes over time.

Objective 2: To evaluate the relationship between heart failure subject's modeled prognosis, self assessed prognosis, preferences for end of life care and thresholds for considering VAD implant.

Objective 3: To evaluate caregiver burden associated with heart failure subject's measures of heart failure severity, quality of life, functional limitations and with preferences for care and thresholds for considering device implant.

- Caregiver burden will be assessed at baseline B and again at 6 months, 1 year, 18 months and 2 years to explore its global trajectory, and as a function of each subject's heart failure severity, quality of life and functional limitations, and the caregiver's health status.

- Patient preferences for care and thresholds for considering device implant will be assessed as a function of caregiver burden.

- To describe the trajectory of caregiver burden for caregivers of heart failure subjects before and after transition to VAD therapy or heart transplant.

Objective 4: To determine health-associated costs for heart failure subjects in the registry.

Objective 5: To provide the REVIVE-IT Registry to the INTERMACS study group to be used in comparative analyses of outcomes of patients treated with medical versus VAD therapy.

3.0 Study Design and Population

3.1 Number of Clinical Sites and Subjects

The REVIVE-IT Registry (i.e., REVIVAL) is a prospective cohort study to be conducted in up to twenty five (25) participating Clinical Sites in the USA. The study will continue until up to 400 eligible heart failure heart failure subjects have been enrolled (estimated length of accrual is 12 months). No single Clinical Site will enroll more than 80 heart failure subjects into the study without written approval from the Data Coordinating Center (DCC).

The REVIVE-IT Registry has been designed to provide a high likelihood of successful recruitment of the targeted 400 subjects at up to 25 study sites. The subject recruitment experience in the REVIVE-IT Trial and in MedaMACS, a registry with similar design and aims to the REVIVE-IT Registry, has informed the design of the REVIVE-IT Registry. Eligibility criteria have been expanded to no longer exclude patients who are on the heart transplant waiting list and those not yet listed who are heart transplant eligible. The pool of heart transplant listed patients alone who would be eligible for the REVIVE-IT Registry constitutes a substantial group of individuals (estimated at 30-75 per study site). These individuals may potentially benefit from

early implantation of an LVAD, so their inclusion in this registry is appropriate. Inclusion criteria have also been broadened to provide a larger pool of eligible advanced heart failure patients. For example, the REVIVE-IT Registry will enroll individuals with any of the following high-risk criteria – peak VO_2 ≤ 14 ml/min/kg, 6 minute walk distance < 350 meters, serum sodium ≤ 135 mg/dL, serum BNP ≤ 750, serum NT-proBNP ≤ 3000, HFSS ≤ 7.19 or SHFM predicted mortality ≤ 85% – whereas the REVIVE-IT trial required both a peak VO_2 ≤ 14 ml/min/kg and a 6 minute walk distance < 350 meters. In recognition of the well-described limitations of the NYHA classification system (i.e., its very poor interobserver and intraobserver variability), we have broadened the inclusion criteria to ambulatory symptomatic heart failure patients (NYHA classes II-IV), rather than NYHA class III alone, and now rely firmly on more objective and well validated criteria (as above) to identify potential subjects with advanced heart failure.

3.2 Design

All enrolled heart failure subjects will be followed and assessed for outcomes for two (2) years post enrollment. The following events will be assessed at all but the baseline A visit:

- Hospitalizations
- Stroke
- Mechanical Circulatory Support Device (MCSD)*
- Transplant*
- Death (Cardiovascular related vs. Non-cardiovascular related)*

* Outcomes of death, transplant and implants of a durable VAD will be considered study endpoints with no additional follow-up in REVIVAL. When a study endpoint has been reached, events/outcomes up through the point of the outcome will be reported on the eCRFs.

3.3 Subject Identification Procedures

Medical records should be reviewed to assess for potential enrollment into the REVIVE-IT Registry. Heart failure subjects that meet all criteria (Sections 5.1 and 5.2) should be approached to consent for this study.

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. Select data on all heart failure subjects who are approached who are ineligible (do not meet at least one inclusion or exclusion criterion) or who refuse participation in the study will be collected in a screening log. This basic information is necessary to assess completeness of heart failure subject capture and possible bias in the screening process and in the process of obtaining informed consent. No further information will be collected on heart failure subjects who do not meet the eligibility criteria or who refuse to consent to participate in the study.

3.4 Study Visit Overview

Enrolled heart failure subjects will undergo the following Schedule for Assessments.

1. Clinic visits: Baseline A, Baseline B and follow up visits at 6,12,18 and 24 months. All study visits will be in person.
2. See Schedule of Observations and Procedures (Section 6.0) and Time and Event Schedule (Appendix A) for details regarding visit specific assessments.

3.5 Participating Centers

Each of the Clinical Sites and Core Laboratories selected for REVIVAL represent experienced centers in the treatment of advanced heart failure.

4.0 Study Procedures and Assessments

4.1 Informed Consent Procedures

All REVIVAL heart failure subjects must be consented utilizing an IRB approved consent form with language that is understandable to them. Heart failure subjects must give Informed Consent to participate in the study as well as the main biomarker specimen collection, and separately may consent for genomic analysis.

All Caregivers must be consented utilizing an IRB approved consent form with language that is understandable to them. Caregiver contact details will be supplied from the heart failure subject at the first baseline visit. Consenting caregivers via mail will be permitted if this method is approved by the participating site's local IRB. Caregivers must give Informed Consent for REVIVAL prior to completion of the Caregiver Questionnaires.

If a Caregiver decides not to participate in REVIVAL, the heart failure subject will still be eligible to participate.

4.2 Six Minute Walk Test Distance (6MWT)

The 6MWT distance will be used as an eligibility criterion for potential heart failure subjects who have not had at least two heart failure related hospitalizations in the past year. The 6MWT assessment will be performed at baseline A and B and at each follow up visit. The 6MWT is a valid measurement of functional capacity and is predictive of outcomes in heart failure. The inability to walk > 350 meters is representative of poor functional class and increased morbidity and mortality in heart failure.[18] The 6MWT evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism. The 6MWT is a sub-maximal exercise test that is associated with smaller increments in heart rate, blood pressure and plasma catecholamines than maximal cardiopulmonary exercise testing, although in many ambulatory patients with advanced heart failure it may represent effort close to anaerobic threshold.[19] However, such submaximal exercise may be more reflective of

activities of daily living and has been found to more closely correlate with formal measures of Heart Failure Quality of Life (HFQOL) than peak VO_2. Despite the difference between these two functional tests, a significant correlation between 6MWT and peak VO_2 has been reported for patients. [20-22]

4.3 Maximal Oxygen Consumption (peak VO_2)

Maximal treadmill cardiopulmonary exercise tests (CPX) will be done for consented heart failure subjects at the baseline B visit. Maximal oxygen consumption (peak VO_2) during treadmill CPX is the most objective and well-validated measure of functional capacity.[23] Its depression reflects the impaired ability to increase cardiac output and is an integrated measure of the cardiac, pulmonary, vascular and muscular abnormalities that characterize heart failure. While not completely effort-dependent, the adequacy of the effort as maximal can be determined.

The reliability of peak VO_2 measurement in the setting of stable outpatients with chronic heart failure has recently been assessed in 398 subjects participating in an HF-ACTION sub-study with test-retest measurements 1-2 weeks apart.[24] The difference (mean ± SD) in peak VO_2 measurement was 0.0±1.3 ml/min/kg (10^{th},90^{th} percentile = 0.1,3.0) with nominal increases in 46% and decreases in 48% of subjects. This SD of 1.3 represented 9% of the mean peak VO_2 of these subjects. These data demonstrate the reproducibility of the peak VO_2 measurement and support the strategy of using a single measurement of peak VO_2 as an eligibility criterion in REVIVAL.

Maximal treadmill cardiopulmonary exercise testing is invaluable in the assessment of functional limitations imposed by heart failure and in predicting survival in patients referred for cardiac transplant evaluation. [19] Dr. Mancini performed the landmark study demonstrating the utility of a peak VO_2 threshold of 14 ml/min/kg for selecting heart transplant candidates.[25] At Columbia University, 396 patients age 65 years or older (mean + SD = 70±5) with systolic (80%) or diastolic heart failure (LVEF 30±15%, peak VO_2 13.9±4.4 ml/min/kg) were followed until death (35%), urgent transplantation (8.8%), LVAD (3.0%) or elective transplantation (2.3%). Overall 1-year event-free survival was 81%. As seen in Figure 2, individuals with peak VO_2 10-14 ml/min/kg and < 10 ml/min/kg had event-free survivals of ≈78% and ≈70% at 1-year and ≈60% and ≈45% at 2-years, respectively.[26]

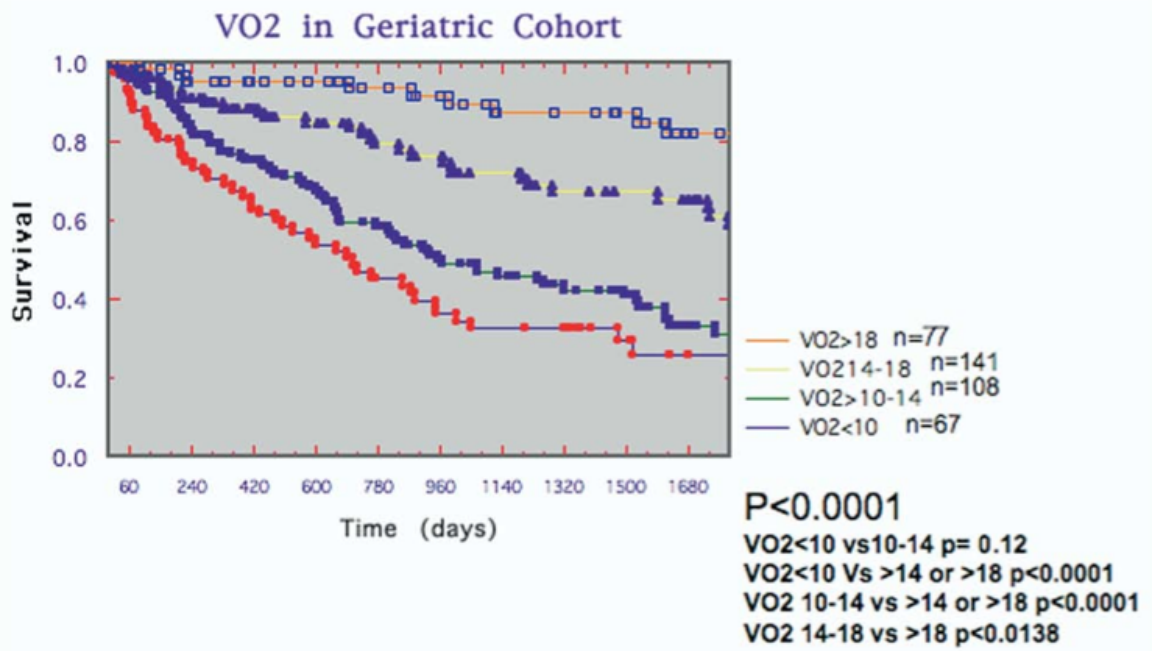


Figure 2: individuals with peak VO_2 10-14 ml/min/kg and < 10 ml/min/kg had event-free survivals of ≈78% and ≈70% at 1-year and ≈60% and ≈45% at 2-years, respectively.

4.4 Echocardiogram

At the baseline B visit, echocardiograms will be performed and DICOM data will be sent to the Echocardiography Core Lab for assessment of key elements. Details of data dissemination from the core lab to the clinical sites will be outlined in the MOP.

Rigorous echocardiographic quantification of cardiac structure and function is essential to prognosis in heart failure patients. This proposal is to demonstrate the importance of an echo core lab to quantify left ventricular (LV) and right ventricular (RV) function, along with valvular pathology and non-invasive hemodynamic measures.

The Echocardiography Core Lab will provide standardized and validated measurements of left ventricular (LV) and right ventricular (RV) function. In addition to having a proven track record with obtaining high quality routine echocardiographic measures, like ejection fraction (EF), the Echocardiography Core Lab also has extensive experience with innovations in strain imaging, using routine digital echocardiographic data, which can be immediately applied to multicenter clinical trials. An increase in as little as 5 EF units was highly statistically associated with heart failure hospitalizations in the EchoCRT randomized clinical trial.[27]

4.5 Directed History, Physicals and Vital Signs

Directed history and physicals (including NYHA and INTERMACS Patient Profile) will be performed at baseline A and B visits and at each follow up visit. Mandatory data elements pertaining to these assessments will be detailed on the study eCRFs.

INTERMACS Patient Profile classifications (refer to Appendix B) and NYHA classifications (refer to Appendix C) will be obtained for heart failure subjects at each visit for REVIVAL.

Vital signs including height (collected only at baseline A), weight, heart rate, blood pressure and temperature will be performed at every study visit.

4.6 Medication Criterion

Heart failure subjects should be receiving appropriate evidenced-based heart failure medications – ACE inhibitor, ARB or sacubitril/valsartan [LCZ-696]; beta blocker; aldosterone antagonist; hydralazine/long-acting nitrate [required of African-American subjects only] for ≥ 3 months absent contraindications or intolerances.

All heart failure therapeutics and dosages should be documented in the Case Report Forms (CRFs). Details of heart failure medications will be collected at each visit.

4.7 Handgrip Strength (by Dynamometer)

Handgrip strength will be assessed by dynamometer at each visit. Mandatory data elements pertaining to this assessment will be detailed on the study eCRFs. Instructions relevant to the assessment will be included in the MOP.

4.8 Gait Speed Test

A fifteen-foot gait speed test to measure frailty will be performed at each visit. Mandatory data elements pertaining to this assessment will be detailed on the study eCRFs. Instructions relevant to the assessment will be included in the MOP.

4.9 Demographics

Demographic information will be recorded in the study database after consent. In cases where Institutional restrictions limit reporting any component of demographic data, the DCC should be contacted to discuss reporting options. Caregiver contact information (i.e., name, address, phone and email) will be collected to allow for follow-up at the DCC. HIC numbers (if applicable for the subject) and partial social security numbers will be collected from heart failure subjects.

4.10 Documentation of Concomitant Medications

Concomitant medications will be monitored at all study visits and changes will be recorded on the eCRFs.

4.11 Documentation of Study Events/Outcomes

Adverse events related to study procedures and outcomes will be recorded on the study eCRFs. These will be recorded using data available in the medical chart as well as information gathered on patient diaries. Diaries will be provided to all heart failure subjects at the baseline A visit to provide a convenient way for the heart failure subject to capture key details about events/outcomes. Adverse event and outcomes data will be collected at all visits following the baseline A visit and in cases of early subject termination.

4.12 Seattle Heart Failure Model (SHFM) Score

The SHFM will be calculated by the Data Coordinating Center using data collected at baseline A, baseline B and the twelve (12) month follow up visit. Instructions relevant to the calculation will be included in the MOP.

4.13 Heart Failure Survival Score (HFSS)

The HFSS will be calculated by the Data Coordinating Center using data collected at baseline B. Instructions relevant to the calculation will be included in the MOP.

4.14 Health Status, Patient Perspective and Quality of Life Assessments

This study will use the following health status and QOL assessments:

a. Heart failure-related QOL (KCCQ)
b. EuroQoL (EQ-5D)
c. State-Trait Anxiety Inventory (STAI)
d. Depression (Personal Health Questionnaire [PHQ-8])
e. Patient Preferences for end of life care and thresholds for VAD implantation (MEDAMACS VAD Survey)
f. Caregiver Health QOL (EQ-5D)
g. Caregiver Oberst Caregiving Burden Scale [OCBS])
h. Caregiver Health History

QOL assessments will be provided to subjects in English. If a subject does not have proficiency in English, the subject remains eligible for the registry but should not complete the forms.

All heart failure subject QOL assessments and health utility assessment will be administered at all REVIVAL visits. The patient preference questionnaires will also be administered at all visits.

The Caregiver questionnaires will be provided to the heart failure subject's caregiver at the time of the baseline B visit and at each follow up visit. The questionnaires may be mailed to them by the DCC. Detailed instructions for completion of caregiver questionnaires are available in the MOP.

4.15 Electrocardiogram (ECG)

An ECG will be obtained at baseline A, baseline B and at the twelve (12) month visit.

If the heart failure subject has a historic ECG on file that was completed within 30 days of the assessment date, this may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic procedure is highly likely to represent the heart failure subject's current health status.

4.16 Procedures for Clinical Laboratory Samples

Laboratory samples will be taken at each REVIVAL visit. All samples will be collected in accordance with acceptable laboratory procedures.

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of a visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

4.17 Blood for Analysis, Specimen Handling and Storage

The REVIVE-IT Registry will bank samples for those heart failure subjects who consent to participate. From the developed sample bank the goals are to evaluate known biomarkers in this selected advanced heart failure sample and to develop novel biomarkers to improve the prediction of outcomes in subjects with advanced heart failure.

All heart failure subjects who consent to participate will have approximately 8 cc of blood collected for biomarker analysis at baseline B. Heart failure subjects who consent for the genomic analysis biomarkers will have an additional 13 cc collected at baseline B. These specimens will be shipped to the University of Pittsburg Biomarker Core Laboratory as specified in the MOP.

The final selection of biomarkers to be evaluated will be determined following an up to date review of the clinical literature as we approach the end of the study. The biomarkers are likely to include B-type natriuretic peptide, collagen markers (e.g., procollagen types I and III, n-terminal telopeptide, procollagen type I, c-terminal telopeptide, osteopontin, galectin-3), adiponectin, 8-isoprostane, IL-6, soluble receptor of type I alpha-TNF, ST-2, high-sensitivity CRP, CA-125 and troponin.

In addition, DNA banking and genomic analysis will be performed only for heart failure subjects with consent in place to permit the analysis. We will evaluate micro RNAs of prognostic interest in heart failure, such as miR-423-5p. We will genotype all consented heart failure subjects in REVIVAL for a core panel of 10 functional polymorphisms located in genes critical to heart failure progression including: ACE, aldosterone synthase, beta1 adrenergic receptor, alpha adrenergic receptor, NOS3, GNB3, corin (converting enzyme for BNP) and PDE5. At the completion of follow up, genomic analysis will be integrated with the clinical data set and outcomes compared by genotype. Given the role of these genes as targets for heart failure therapeutics, pharmacogenetic interactions will also be explored. In addition to the genotyping

of this core panel, DNA will be banked for analysis of future investigations of innovative genomic markers.

5.0 Study Participation Criteria

5.1 Study Inclusion Criteria

1. Ambulatory.
2. Chronic systolic heart failure ≥ 12 months.
3. NYHA II - IV for at least 45 of the last 60 days.
4. Last documented left ventricular ejection fraction ≤ 35% by any imaging modality.
5. Age 18 - 80 years.
6. Currently under the care of a cardiologist at study site.
7. On appropriate evidenced -based heart failure medications – ACE inhibitor, ARB or sacubitril/valsartan [LCZ-696]; beta blocker; aldosterone antagonist; hydralazine/long-acting nitrate [required of African-American subjects only] for ≥ 3 months absent contraindications or intolerances.
8. Has ICD or CRT-D. If CRT-D, present for ≥ 3 months.
9. Demonstrated advanced heart failure, including any of the following*:
    i. Serum sodium ≤ 135 mEq/L (obtained as an outpatient)**
    ii. Serum BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL** (obtained as an outpatient)
    iii. Seattle Heart Failure Model (SHFM) one year predicted survival ≤ 85%**
    iv. Heart Failure Survival Score (HFSS) ≤ 7.19**
    v. Peak VO_2 ≤ 55% of predicted for age by Wasserman equation or ≤ 14 ml/kg/min, with RER ≥ 1.05 ***
    vi. VE/VC02 slope ≥ 40***
    vii. 6 minute walk test (6MWT) distance ≤ 350 m without significant non-cardiac limitation**
    viii. Currently listed as Heart Transplant Status II due to heart failure limitation

Or

History of one (1) hospitalization (≥ 24 hours) for acute or acute on chronic heart failure in the past year with additional history to include:

i. Serum BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL** (obtained as an outpatient)

Or

History of two (2) hospitalizations (≥ 24 hours) for acute or acute on chronic heart failure in the past year.

* Qualifying measure must be the most recent of that type of measure obtained (i.e., a BNP ≥ 1000 obtained 2 months prior would not qualify the heart failure subject if a more recent BNP was < 1000)

**Using values obtained within the prior 90 days, except for peak VO_2 within 365 days

***Obtained within the prior 365 days

10. Willingness to continue to receive heart failure care from the enrolling advanced heart failure clinic over the next two (2) years and to come for all scheduled study visits.
11. Written Informed consent given.

5.2 Study Exclusion Criteria

1. Known serious medical problem other than heart failure that would be expected to limit 2-year survival (≥50% mortality within 2 years from non-heart failure diagnosis).
2. Patient is not likely to be compliant with the protocol, in the opinion of the Investigator. .
3. Currently hospitalized.
4. Current use of an intravenous inotrope.
5. Primary functional limitation from non-cardiac diagnosis even if not likely to limit survival.
6. Chronic hemodialysis or peritoneal dialysis or serum creatinine value of ≥ 3 mg/dL at time of enrollment.
7. Cardiac amyloidosis, cardiac sarcoidosis, constrictive pericardial disease, active myocarditis or congenital heart disease with significant structural abnormality.
8. Hypertrophic cardiomyopathy unless dilated LV and no outflow gradient.
9. Cardiac conditions that are amenable to surgical or percutaneous procedures (other than VAD or transplant) that would substantially improve prognosis and for which this subject is a reasonable candidate, regardless of whether the procedure will or will not be performed.
10. Uncorrected hyperthyroidism or hypothyroidism.
11. Pregnancy.

IMPORTANT NOTE: Patients who are currently enrolled (or may wish to enroll in the future) in additional observational studies or clinical trials are **not** excluded from REVIVAL.

5.3 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the heart failure subject from the study should be noted using the following categories.

- Lost to follow-up: The heart failure subject did not return to the clinic and attempts to contact the heart failure subject were unsuccessful. All attempts to contact the heart failure subject will be documented.
- Voluntary withdrawal: The heart failure subject (or heart failure subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, will be recorded in the electronic case report form (eCRF).
- Study termination: The sponsor, institutional review board (IRB), ethics committee (EC), or regulatory agency terminates the study.
- Other.

The clinical investigator should document in the research record each instance of a heart failure subject's withdrawal including but not limited to 1) whether the withdrawal of the heart failure

subject resulted from a decision by the subject or by the investigator and the reason(s) for the withdrawal, if known. The clinical investigator should also document whether the withdrawal was from all components of the research study or would allow follow-up for clinical outcomes at Month 24. See the Manual of Procedures (MOP) for further details.

Known events/outcomes collected for REVIVAL up to the time of termination should be reported on the study eCRFs. See the MOP for further details.

6.0 Schedule of Observations and Procedures

6.1 Screening and Eligibility Assessment

Historic data must be utilized to identify potential heart failure subjects for the REVIVE-IT Registry. Historic data utilized should be verified on the day of planned consent to ensure that the potential heart failure subject continues to meet inclusion criteria. Written informed consent must be provided by the subject prior to any study procedures being conducted, including screening labs or tests of any kind. All heart failure subjects must consent for blood storage for non-genetic biomarkers to qualify for REVIVAL. Genetic biomarker testing will have a stand-alone consent. Heart failure subjects who do not consent for the genetic biomarker testing remain eligible to participate in REVIVAL.

6.2 Study Procedures and Assessments

6.2.1 Baseline A

Initiation of baseline A will occur with the heart failure subject signing the Informed Consent document(s). Standard of Care (SOC) testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. All other procedures will be research expenses. After signing the informed consent document(s), subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. ECG [SOC]
3. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
    c. Uric Acid
    d. Total cholesterol
    e. INR
4. Handgrip strength (by dynamometer)
5. Gait Speed Test
6. 6 minute walk test
7. Quality of life and health utility questionnaires
8. Patient preference questionnaire
9. Caregiver participation overview with heart failure subject
10. Dispense patient diary

If the heart failure subject has an historic ECG on file that was completed within 30 days of the assessment date, this may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic ECG is highly likely to represent the subject's current health status.

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

Baseline A procedures should be completed within two weeks of consent. The baseline B visit should be scheduled to occur two (2) months (± 30 days) after consent.

6.2.2 Baseline B

Standard of Care [SOC] testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. For the baseline B visit, subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. ECG [SOC]
3. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
    c. Uric Acid
    d. Total cholesterol
    e. INR
4. Blood draw for Biomarker Analysis (including genetic biomarker testing ONLY if the subject consent is in place)
5. Transthoracic Echocardiogram
6. Handgrip strength (by dynamometer)
7. Gait Speed Test
8. 6 minute walk test
9. Maximal treadmill cardiopulmonary exercise test (as defined in REVIVAL MOP)
10. Quality of life and health utility questionnaires
11. Patient preference questionnaire
12. Caregiver consent (see MOP for details)
13. Obtain information needed to complete follow up eCRF
14. Outcome assessments for:
    - Hospitalizations
    - Stroke
    - MCSD
    - Transplant
    - Death (Cardiovascular related vs. Non-cardiovascular related)

If the heart failure subject has an historic ECG on file that was completed within 30 days of the assessment date, this may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic ECG is highly likely to represent the subject's current health status.

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the Baseline B assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

Core Laboratory Data Handling and Transfer (refer to MOP)

Following completion of the echocardiogram and cardiopulmonary exercise test, studies will be submitted for analysis by the Echocardiography Core Laboratory or Cardiopulmonary Exercise Core Laboratory.

Following completion of baseline B assessments, heart failure subjects will progress to the follow up phase of REVIVAL, with in-clinic follow up visits planned at six (6) months, twelve (12) months, eighteen (18) months and twenty four (24) months.

6.2.3 Six (6) Month Follow up (+/- 45 days)

Standard of Care [SOC] testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. For the six (6) month follow up visit, subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
3. Handgrip strength (by dynamometer)
4. Gait Speed Test
5. 6 minute walk test
6. Quality of life and health utility questionnaires
7. Caregiver questionnaire collection (if applicable)
8. Obtain information needed to complete follow up eCRF
9. Outcome assessments for:
    - Hospitalizations
    - Stroke
    - MCSD
    - Transplant
    - Death (Cardiovascular related vs. Non-cardiovascular related)

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

6.2.4 Twelve (12) Month Follow up (+/- 45 days)

Standard of Care [SOC] testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. For the twelve (12) month follow up visit, heart failure subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. ECG [SOC]
3. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
    c. Uric Acid
    d. Total cholesterol
    e. INR
4. Handgrip strength (by dynamometer)
5. Gait Speed Test
6. 6 minute walk test
7. Quality of life and health utility questionnaires
8. Patient preference questionnaire
9. Caregiver questionnaire collection (if applicable)
10. Obtain information needed to complete follow up eCRF
11. Outcome assessments for:
    - Hospitalizations (Cardiovascular related vs. Non-cardiovascular related; Heart Failure related vs. Non-Heart Failure related) Stroke
    - VAD
    - Transplant
    - Death (Cardiovascular related vs. Non-cardiovascular related)

If the heart failure subject has an historic ECG on file that was completed within 30 days of the assessment date, this may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic ECG is highly likely to represent the subject's current health status.

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

6.2.5 Eighteen (18) Month Follow up (+/- 45 days)

Standard of Care [SOC] testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. For the eighteen (18) month follow up visit, heart failure subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
3. Handgrip strength (by dynamometer)
4. Gait Speed Test
5. 6 minute walk test
6. Quality of life and health utility questionnaires
7. Caregiver questionnaire collection (if applicable)
8. Obtain information needed to complete follow up eCRF
9. Outcome assessments for:
    - Hospitalizations
    - Stroke
    - MCSD
    - Transplant
    - Death (Cardiovascular related vs. Non-cardiovascular related)

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

6.2.6 Twenty-four (24) Month Follow up (+/- 30 days)

Standard of Care [SOC] testing will be included in the heart failure subject evaluation for this visit. All SOC procedures are labeled as such below. For the twenty four (24) month follow up visit, heart failure subjects will undergo the following testing and evaluation:

1. Directed history and physical (including NYHA and INTERMACS Patient Profile)
2. Blood draw for:
    a. CBC with platelets and differential count [SOC]
    b. Comprehensive metabolic panel [SOC]
3. Handgrip strength (by dynamometer)
4. Gait Speed Test
5. 6 minute walk test
6. Quality of life and health utility questionnaires
7. Patient preference questionnaire
8. Caregiver questionnaire collection (if applicable)

9. Obtain information needed to complete follow up eCRF
10. Outcome assessments for:
    - Hospitalizations
    - Stroke
    - MCSD
    - Transplant
    - Death (Cardiovascular related vs. Non-cardiovascular related)

If the heart failure subject has historic laboratory results on file that were drawn within 14 days of the assessment date, these results may be used for fulfillment of this visit requirement if, in the opinion of the investigator, the historic laboratory result(s) are highly likely to represent the subject's current health status.

7.0 Adverse Event and Unanticipated Problems

7.1 Adverse Event and Unanticipated Problems Reporting Requirements

Only adverse events resulting from research related procedures will be collected for safety purposes from heart failure subjects and caregivers. Additional adverse event data will be collected for outcome data collection purposes, but this data will not meet expedited reporting criteria in any circumstance (Refer to Appendix D).

Investigators **must** notify the REVIVAL DCC within 24 hours of discovering any SAEs or UPs, and to their IRB as dictated by the local IRB policy. All SAEs and UPs must be documented on the appropriate eCRF and submitted to the REVIVAL DCC.

The REVIVAL DCC will provide notification of reported SAEs, AEs and UPs to the required oversight bodies as detailed in the REVIVAL MOP.

7.2 Adverse Event Category Definitions

Adverse Event

An adverse event is formally defined as any undesirable occurrence in a study subject, whether or not it is related to the study. Any condition that was recorded as pre-existing is *not* an AE unless there is a change in the nature, severity or degree of the condition.

For REVIVAL, only adverse events resulting from research related procedures will be collected for safety purposes from Heart Failure subjects and Caregivers. Additional adverse event data will be collected for outcome data collection purposes, but this data will not meet expedited reporting criteria in any circumstance.

Serious Adverse Event

Serious adverse events (SAEs) are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. The REVIVAL definition of hospitalization is any cumulative stay within a hospital or emergency department ≥ 24 hours (including time for observation) or any formal admission. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unanticipated Problems (UPs)

An Unanticipated Problem (UP) generally includes any incident, experience, or outcome that meets **all** of the following criteria: (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the heart failure subject population being studied; *and* (2) Related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); *and* (3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Based on the definitions above many adverse events are not unanticipated problems, and many unanticipated problems are not adverse events. However, some adverse events are also unanticipated problems. For example, a SAE that is unexpected and at least possibly related to study participation is also by definition an unanticipated problem. As stated above, an unanticipated problem may not necessarily be an adverse event, which is the case when the problem does not cause actual physical harm to participants. For example, if a laptop computer with sensitive, identifiable study data is stolen, this theft places the participants at greater *risk* of psychological or social harm; this is an unanticipated problem that is not an adverse event.

7.3 Causality

The investigator will assess the relationship of an adverse event to the research procedure. Causality will be defined as follows:

Probable
Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the research procedure. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the research procedure/intervention, and
- The event is a known reaction to the research procedure/intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible
Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the research procedure, but for which there is evidence to suggest a causal relationship. The following characteristics will apply:

- The event occurs after research procedure, and
- The event is not a known reaction to research procedure, but cannot be explained by a commonly occurring alternative etiology.

Unlikely
Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to the research procedure and for which a connection is doubtful but cannot be ruled out. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the research procedure, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the research procedure.

8.0 Statistical Considerations

8.1 General Statistical Considerations

All registry participants who are consented will be included in analyses. Descriptive tabular and graphical summaries of data will be used to characterize time-to-event outcomes such as survival and time to VAD implantation and profiles of continuous outcomes such as QOL scores and 6-minute walk test distance over time. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum will be presented. Continuous data subject to censoring (i.e., time-to-event data) will be summarized by the 25th percentile, median and 75th percentile, when estimable from the Kaplan-Meier estimates.

Statistical models will be employed to estimate important features of outcomes, as well as to understand the impact of important covariates (such as biomarkers) on these outcomes. The models considered for use in these analyses allow for a missing at random (MAR) mechanism. MAR means that the missing values mechanism can be explained by observed data (e.g., past values of covariates and outcomes) and does not depend on the unobserved values of outcome measures. However, some participants may dropout from the study due to unobserved factors related to the outcome itself; for example, sicker participants may be more likely to dropout than healthier patients and so we lack survival information on those sicker patients. If we suspect such bias is present, the methods which assume MAR are not applicable. Instead we would need to use methods that model the missing data mechanism itself to achieve valid inferences. We will incorporate plausible missing values mechanism into the model as discussed in Little[28] and investigate how such mechanism may affect the estimates of prognostic factors. To this end, sensitivity analyses will be conducted involving selection and/or pattern-mixture models with an appropriate sub-model used to describe dropout.[29]

Model assumptions will be thoroughly checked using informal (e.g., inspection of residuals) and formal methods (e.g., score test for extra parameters or methods based on likelihood displacement). If individual outliers are detected, their influence will be evaluated using influence diagnostics methods based on comparing estimates from models fitted to data with and without outlying values. Whenever we are not successful in fitting the parametric models (linear or non-linear), then non-parametric analyses and/or transformation of the variables involved in the analysis will be considered.

Two-sided testing will be conducted using a nominal significance level of 0.05 for all tests. No adjustments for multiplicity will be applied. Further details of the analyses will be documented in the Statistical Analysis Plan.

8.2 Sample Size Considerations

The sample size for this prospective cohort (registry) study is based primarily on logistical considerations. It is anticipated that 400 eligible subjects will be enrolled in the study in the 12-month recruitment period. We predict that 30% of the 400 enrolled participants will achieve clinical outcomes such as death or VAD, or will drop-out during the 2-year study follow-up. Thus, we project that 280 participants will provide year 2 data and we provide the degree of precision with which we can estimate the important clinical outcomes using the conservative estimate of 280 registry participants. A sample of 280 participants will provide precision (half-width of a 95% confidence interval, based on normal approximation; East v6.3; Cytel Inc., 2014) ranging from 2.6% to 5.9% for true incidence rates ranging from 5% to 50% (where precision is minimal), respectively. Figure 3 below shows the correspondence of precision and true proportion of participants experiencing clinical outcomes in the 2-year study period for a sample size of 280 participants. The precision of estimation is improved with the use of time-to-event methods instead of the simpler binomial approach used in the calculations above.

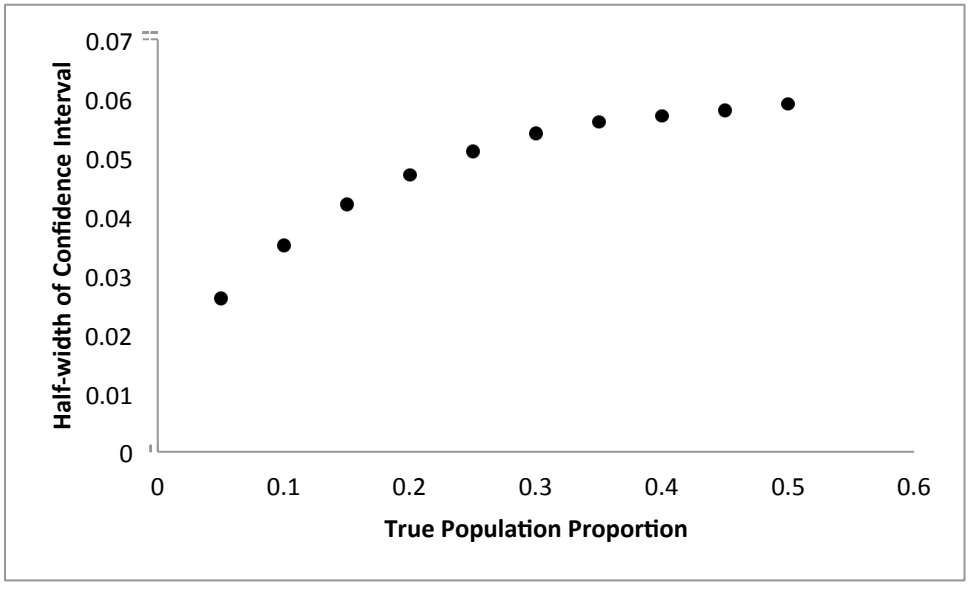


Figure 3: Correspondence of precision and true proportion of participants experiencing clinical outcomes in the 2-year study period for sample size of 280 participants.

8.3 Analysis Approach

8.3.1 Demographic and Baseline Characteristics

We will present descriptive statistics for demographic and baseline patient characteristics as described above [objective 1]. We will compare these characteristics for those who dropout and those who do not dropout using two-sample t-tests or Wilcoxon rank sum tests for continuous variables and Chi-square or Fisher's exact tests for discrete variables.

8.3.2 Characterization of Clinical Outcomes and Other Outcomes

We will present descriptive statistics for clinical outcomes [objective 1] and other outcomes measured over time (e.g., patient preferences [objective 2], caregiver burden [objective 3]). In addition, exploratory analyses will be performed to better understand the characteristics of different definitions of health utility measures (e.g., EQ-5D VAS or EQ-5D index scores) incorporated into a composite endpoint that includes survival without heart transplant and MCSD.

8.3.3 Modeling of Clinical Outcomes

We seek to estimate the morbidity and mortality rates in this population and to evaluate the effectiveness of baseline factors in determining their prognosis. To accomplish this goal [objective 1], we will use logistic regression for dichotomous outcomes (e.g., proportion of subjects with an interest in VAD therapy), Poisson regression for count outcomes (e.g., number of hospitalizations per participant), Cox proportional hazard models for time-to-event outcomes (e.g., survival, time to VAD implantation) and linear mixed-effects models for continuous outcomes (e.g., quality of life, functional capacity)[30-32]. For time-to-event outcomes, survival time will be defined as the time from consent to the event or, for participants who did not experience an event, to the last study visit. Given the potentially small number of events, differences between groups will be tested by means of the log rank test. For longitudinal continuous outcomes, we will model correlated errors with a first order autoregressive (AR1) process since it is reasonable to assume adjacent values are more correlated than observations father apart in time. Alternative variance-covariance structures will be investigated, if needed.

Univariable models will be developed first, using baseline characteristics as the predictors. Multivariable models will be built incorporating known prognostic factors (i.e., those identified in the literature) and those suggested from the univariable analyses (i.e., those with $p<0.10$). Given the sample size and the potential for small numbers of events (in time-to-event outcomes), we will apply the principle of parsimony to the number of potential prognostic factors included in the ultimate model. In addition to using such standard methods to develop multivariable risk prediction models, we will derive simplified scoring systems to aid in clinical decision-making. Alternative classification schemes (e.g., CART) will be employed as sensitivity analyses. To assess the performance of the risk prediction models, we will evaluate their calibration (or reliability) discrimination and accuracy[33].

Comparison among existing classification systems and the use of second early assessments (baseline B measures instead of baseline A measures) with the improved risk prediction model(s) developed above will be based on the concordance index, parsimony of the model, and the other performance metrics described above[34].

8.4 Modeling of Other Outcomes

The general approach described in Section 8.3 will be used to evaluate the impact of modeled prognosis, self-assessed prognosis, preferences for end-of-life care on the likelihood that a patients considers a VAD implant [objective 2]; the impact of heart failure severity, quality of life, functional limitations and caregiver health status on caregiver burden [objective 3]; the impact of caregiver burden on patient preferences for care and thresholds for considering device implant [objective 3]; and, the impact of pre- and post-VAD therapy or heart transplant on trajectory of caregiver burden [objective 3].

8.5 Health Associated Costs

For Objective 4, health associated costs will be estimated for heart failure subjects in the registry from hospitalizations (days hospitalized, days in the ICU), major cardiac procedures and published data on average costs associated with each. For those subjects enrolled in Medicare fee for service, we will utilize the Medicare Claims (HIC) number to obtain CMS claims data from Medicare Parts A, B and, if purchased by the subject, Part D. The CMS claims data will be obtained for a period beginning one year prior to study enrollment through the end of study follow-up.

8.6 Comparative Analyses of Outcomes

REVIVE-IT registry data will be provided to the INTERMACS study group to be used in comparative analyses of outcomes between patients receiving medical therapy and those receive a VAD [Objective 5]. These analyses will not be performed as part of the REVIVE-IT registry study; rather, they will be performed by the INTERMACS study group. Appropriate consent will be obtained from REVIVE-IT registry participants so that they understand their registry data will be shared with INTERMACS, which is outside of the REVIVE-IT registry study group. Genetic data will not be provided to the INTERMACS study group.

9.0 Data Access, Analysis and Publications

REVIVAL will utilize a Data Access, Analysis and Publications (DAAP) Committee. The DAAP Committee will be responsible for evaluating the scientific merit of proposals, prioritization of proposals and assignment of authorship opportunities. Authorship opportunities will reflect the level of each individual's contribution to the success of the study (i.e., recruitment of subjects, identification of questions for investigation, study design, study leadership, etc.). Further information specific to the composition and activities of this Committee are detailed in the MOP.

10.0 Benefit and Risk Assessment

10.1 Potential Benefit

Data obtained for REVIVAL may provide information to the heart failure subject and his/her doctor regarding prognosis related to heart failure; which has the potential to change the treatments to best match the severity of heart failure.

Medical record information contained within the registry will be used to improve our knowledge and treatment of heart failure and this knowledge may benefit patients with heart failure in the future.

10.2 Potential Risk

All heart failure subjects participating in REVIVAL face risks including, but not limited to the following:

- Cardiopulmonary exercise tolerance test: heart attack, irregular heartbeats, or death in 1 out of 10,000 patients.
- 6MWT and Gait Speed Test: chest pain, shortness of breath, dizziness, fatigue, and falling.
- ECG: localized rash or irritation at the location of electrode placement (rare circumstances)
- Echocardiogram: mild discomfort of the probe touching skin
- Blood draws: fainting, pain, bruising and bleeding at the site of the needle stick and rarely, an infection.
- Biomarker sample collection: breach of confidentiality. Significant precautions will be taken to minimize this risk and prevent disclosure of subject identity to unauthorized individuals.

As with any research study, there may be additional risks that are unknown or unexpected.

In the event of unforeseen or increased risks to subjects, suspension or termination of the clinical study shall be considered (Refer to the MOP for subject management instructions in this event).

11.0 Investigator Responsibility

This clinical study will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, Code of Federal Regulations 45 CFR Parts 46 and 94 and any state laws or local policies, as applicable.

12.0 Institutional Review Board (IRB) Approval

Before implementing this study, the protocol, the proposed informed consent forms and other information to be provided to subjects, must be reviewed by a properly constituted Institutional Review Board and by the DCC.

This study will be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described below:

- ICH Harmonized Tripartite Guideline - Guideline for Good Clinical Practice E6(R1), Current Step 4 Version, 10 June 1996.
- US Code of Federal Regulations dealing with protection of human subjects, IRBs and investigator conflicts of interest/research objectivity in clinical studies (including, but not limited to Title 45 Parts 46 and 94).
- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human subjects).
- IRB local policies, as applicable
- NHLBI policies, as applicable

13.0 Caregiver

The study team member will explain to each heart failure subject's caregiver the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each caregiver will be informed that participation in the study is voluntary and that if he or she decides not to participate the heart failure subject will still be eligible to participate in the study. Also the caregiver will be informed that he or she may withdraw from the study at any time and that withdrawal of consent will not affect the heart failure subject's participation in the study. This informed consent will be given by means of a standard written statement, written in non-technical language. Alternative methods of providing informed consent information to the caregiver will be allowed per local IRB policies. The caregiver should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the caregiver cannot read or sign the documents, oral presentation may be made, if witnessed by a person not involved in the study, mentioning to the witness that the caregiver could not read or sign the documents. No caregiver can enter the study before the informed consent has been obtained. The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval in all languages that are approved by the DCC to be used for REVIVAL.

14.0 Subject Data Protection

Demographic information including data points that are considered Personal Identifiable Information (PII) will be collected and managed by the REVIVAL DCC. Access to the data is restricted to protect the privacy of the subject. Only authorized study team members will have access to this data. Data will be collected in accordance with IRB guidelines.

Data will be protected by several measures throughout the life of the study. Paper documents and records will be stored in a secured location with restricted access to authorized personnel

only. Electronic study documents and data will be kept in a password-protected environment, whereby access rights will be terminated at the request of the Site Principal Investigator when study members leave the project.

Protected Health Information (PHI)

PHI will be obtained from the following sources: medical records; any records relating to the condition, treatment received, and response; demographic information; personal identifiers.

The information to be obtained is the minimum necessary to achieve the objectives of the study.

Written HIPAA Authorization will be obtained from all participants with the informed consent process. Data will be linked to study specific identifiers. However, significant identifiers are stored in a separate electronic database table from other data. When the Site Investigator requests user accounts, he or she will specify whether account holders should access all data, or should be restricted from accessing tables with significant identifiers. So, access to identifiers will be limited when appropriate.

15.0 Protocol Deviations

Protocol Deviations must be reported in accordance to local site IRB guidelines. Any deviation acknowledged by the site IRB should be entered into the study database.

16.0 Monitoring and Quality Control

16.1 Site Training

Only trained personnel can perform study related procedures. The research sites will receive orientation and instruction regarding the informed consent procedures and documentation, conduct of the study and electronic data capture.

16.2 Monitoring of the Study

The Study Investigators and DCC study staff will regularly monitor the data from the registry, review and assess the performance of its operation, and make recommendations, as appropriate, to the REVIVAL Steering Committee, the REVIVAL Executive Committee and/or participating institutions as appropriate 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

16.3 Independent Data Review

To protect the interests of research subjects and ensure that they are not exposed to undue risk, this study will be monitored by an independent Observational Study Monitoring Board (OSMB), which shall have no formal involvement with the subjects or the investigation and function independently from the REVIVAL DCC. The members of the OSMB are appointed by the NHLBI and act as an independent advisory group to the NHLBI Director.

16.4 Reporting to Governing Agencies

The REVIVAL DCC will provide progress reports throughout REVIVAL to the NHLBI and OSMB. Formal responses to the progress reports will be provided to sites as necessary and should be reported to local IRBs in a timely fashion.

16.5 Investigational Site Enrollment Suspension

The REVIVAL DCC reserves the right to suspend enrollment at an investigational site for any of the following reasons:

- Failure to complete case report forms in a timely manner
- Failure to obtain Informed Consent
- Failure to report SAEs/UPs
- Failure to adhere to protocol
- Failure to screen and/or enroll an adequate number of subjects
- Failure to adhere to the MOP

17.0 Data Management

Data will be collected at the sites and managed by the REVIVAL DCC at the University of Michigan.

The study database will be programmed in a secure 21 CFR Part 11 Compliant, HIPAA compatible application called OpenClinica®. The system is a web-based remote electronic data capture (EDC) system where the data is entered by the Clinical Sites and the Core labs. The EDC is built on a flexible and extensible data model that can accommodate input of diverse clinical or laboratory data. The system possesses the ability to maintain an audit trail of the entire study, enabling traceability of entries and modifications to research-related data. Role-based access to the application, the databases and archives, and the underlying systems infrastructure comply with industry best practices and meet HIPAA security and privacy requirements, governed by HIPAA's "minimum necessary" principle.

Data will be collected on eCRFs through remote data access, which employs SSL encryption and role-based access mechanisms. All communication between the application server where data is stored, and any workstation used to enter or access data via the web is SSL encrypted. All users must have an individual ID and password to access electronic study data. User accounts and passwords will be issued and managed by the REVIVAL DCC, and will be terminated at the request of the site when study members leave the project.

Study data will be stored on dedicated servers administered by the REVIVAL study team (through a contract with the REVIVAL DCC and its agents) and housed behind a secure firewall, which are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Physical security is provided in a professionally managed and equipped data center with tightly controlled access. Security software (firewall, anti-virus, anti-intrusion) is installed and regularly updated on all servers, workstations, laptops, and other devices used in the project. Backups are performed per general operating procedures, and a disaster recovery plan is in place.

Upon completion of the study and after resolution of any outstanding data issues, the database will be locked. Study project data can then be securely transferred as outlined by the Data Transfer Agreement and MOP.

Refer to the MOP and the eCRF Completion Guidelines for additional information regarding the EDC System and Case Report Forms.

17.1 Case Report Forms

Good Clinical Practice Guidelines require that investigators maintain information in the subject's medical records, laboratory reports, clinic charts, etc. that corroborate data recorded on the eCRFs. In order to comply with these requirements, the following information should be maintained:

- Medical history/physical condition of the subject before enrollment sufficient to verify eligibility
- Protocol entry criteria.
- Laboratory reports.
- Information related to adverse events.
- QOL studies.

17.2 Laboratory Accreditation and Normal Values

Before initiation of the study, appropriate accreditation for all laboratories to be used in the study must be provided to the REVIVAL DCC by the Investigator at each site. Throughout the study, the Investigator must provide the REVIVAL DCC with documentation of all renewals of accreditation. The ranges of values considered normal for laboratory tests being performed for the study must be provided to the REVIVAL DCC in order to ensure poolability of the data.

17.3 Data Review

All eCRFs will be reviewed for completeness and clarity. Missing data will be investigated by the REVIVAL DCC and clarified by study personnel as necessary. Validation edit checks will be built into the database to aid in data cleaning. The REVIVAL DCC may request additional documentation such as physician procedure notes or written summaries relating to adverse

events or procedures. The REVIVAL DCC will be responsible for the quality control of the database and confirming the overall integrity of the data.

17.4 Data Ownership and Sharing Plan

The data collected in REVIVAL will be stored at the University of Michigan and will be the collective academic property of the REVIVAL Investigators and the National Heart Lung and Blood Institute (NHLBI). Project selection, prioritization of analyses and authorship opportunities will be determined by the Data Access, Analysis and Publication (DAAP) Committee. Authorship opportunities will reflect the level of each individual's contribution to the success of the study (i.e., recruitment of subjects, identification of questions for investigation, study design, study leadership, etc.).

Comparative analyses of outcomes of risk-adjusted cohorts of medically-treated and VAD-treated subjects are a mutual interest of the REVIVAL and INTERMACS investigators. To that end, a complete cleaned dataset containing all baseline and outcome data and supporting documents (i.e., "data dictionary") out to 1 year of follow-up will be provided to INTERMACS no more than two (2) months after last subject, last 1 year follow-up. A similar cleaned dataset containing all baseline and outcome data out to 2 years of follow-up will be provided to INTERMACS four (4) months following the last subject, last 2 year follow-up. Acceptable use of these data by INTERMACS will vary according to how much time has elapsed since critical events of the REVIVAL study. Once either two (2) years have passed since the publication of the principal manuscript from REVIVAL (i.e., the analysis of 2 year outcomes) or three (3) years have passed since the last subject, last 2 year follow-up – whichever comes first – these data may be used by INTERMACS for any purpose. Prior to this date, these data may be used by INTERMACS solely for joint investigations with REVIVAL investigators of comparative outcomes between medically-treated and VAD-treated subjects.

As per NIH policy and our contractual obligations, 2 years after the primary publication from REVIVAL (i.e., the analysis of 2 year outcomes), a public access dataset will be made available upon request.

A fully de-identified dataset is unlikely to be useful to investigators, as subject age and other medical information are likely to be crucial to any meaningful interpretation. For this reason, we will produce a limited dataset, with all identifiers removed and modified to provide age ranges and interval times from events for release and access. The limited access dataset will be uploaded to the NHLBI Data and Specimens Repository for dissemination. The availability of data sharing will be publicized by individual investigators as a footnote to publications and presentations.

In accordance with federal regulation and institutional policies, data and associated documentation will be available to users only under a data-sharing agreement that provides for: (1) a commitment to use the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed. A standard data use agreement developed by the University of Michigan will be used. In addition, all data sharing arrangements must comply with institutional policies, which are subject to change.

18.0 Maintenance of Study Documentation

The Investigator must maintain the following documents throughout the study:

- Essential Regulatory Documents
- Source Documents supporting information on eCRFs
- Any other study specific documents

19.0 Record Retention

The REVIVAL DCC and all participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed Informed Consent Forms, eCRFs, study documentation (listed above) and source documents for at least 2 years after study completion or termination. In accordance with the Investigator Agreement, the REVIVAL DCC should be contacted if the Principal Investigator plans to leave or otherwise absent themselves from the investigational site.

20.0 Study Oversight

The professional staff within the REVIVAL DCC will manage the overall conduct of the clinical registry and ensure that it is executed with high standards and in compliance with the project protocol, its timeline, and with all federal, state and local regulatory obligations.

The REVIVAL DCC will develop and implement the standardized MOP following DCC-standard operating procedures. Also, the REVIVAL DCC will work with sites to address site concerns regarding procedures and enrollment activities.

The REVIVAL DCC will coordinate communication across the entire research consortium.

APPENDICES

Appendix A: Time and Event Schedule

Event/Assessment	*Baseline A*	*Baseline B**	*+/- 45 days*			*+/- 30 days*
			6-Month Visit	*12-Month Visit*	*18-Month Visit*	*24-Month Visit*
6-Minute walk test	X	X	X	X	X	X
Blood draw – Labs	X**	X**	X	X**	X	X
Blood draw – Biomarker and Genetic testing		X				
Caregiver questionnaire		X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X
Demographics	X					
Directed history and physical exam (including NYHA and INTERMACS profiles)	X	X	X	X	X	X
Dispense Patient Diary	X					
ECG	X	X		X		
Gait speed test	X	X	X	X	X	X
Handgrip strength test	X	X	X	X	X	X
Heart Failure Survival Score (HFSS) ***		X				
Maximal treadmill CPX test		X				
QOL and health utility questionnaires	X	X	X	X	X	X
Seattle Heart Failure Model (SHFM) Score ***	X	X		X		
Transthoracic Echo		X				
Outcome assessments		X	X	X	X	X

*To take place 8 weeks (+/- 30 days) after consent
**In addition to standard of care labs (CBC and Comprehensive Metabolic Panel) study-specific (non-standard of care) labs are uric acid, total cholesterol and INR
*** Calculated and entered by DCC

Appendix B: INTERMACS® Patient Profiles

These statuses will provide a better description of the patients receiving implants. If there is significant clinical change between the initial decision to implant and the actual implant procedure, the status closest to the time of implant should be recorded. A-modifier - Recurrent ventricular tachyarrhythmias may dominate the clinical picture. An A-modifier should be added to the level for ventricular tachycardia or fibrillation with repeated shocks from ICD or external defibrillator, usually more than 2 weekly. The A-modifier may be added to any INTERMACS® level, (e.g. Level 4-A).

INTERMACS® 1: Critical cardiogenic shock describes a patient who is "crashing and burning", in which a patient has life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels. This patient can have modifier A or TCS (see 'Modifiers' below)

INTERMACS® 2: Progressive decline describes a patient who has been demonstrated "dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Patient profile 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance. This patient can have modifiers A or TCS.

INTERMACS® 3: Stable but inotrope dependent describes a patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between a patient who is truly stable at Patient Profile 3 and a patient who has unappreciated decline rendering them Patient Profile 2. This patient may be either at home or in the hospital. Patient Profile 3 can have modifier A, and if in the hospital with circulatory support can have modifier TCS. If patient is at home most of the time on outpatient inotropic infusion, this patient can have a modifier FF if he or she frequently returns to the hospital.

INTERMACS® 4: Resting symptoms describes a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with ADL. He or she may have orthopnea, shortness of breath during ADL such as dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites or severe lower extremity edema. This patient should be carefully considered for more intensive management and surveillance programs, by which some may be recognized to have poor compliance that would compromise outcomes with any therapy. This patient can have modifiers A and/or FF.

INTERMACS® 5: Exertion Intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. This patient has no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant. This patient can have modifiers A and/or FF.

INTERMACS® 6: Exertion Limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes of any meaningful physical exertion. This patient has occasional episodes of worsening symptoms and is likely to have had a hospitalization for heart failure within the past year. This patient can have modifiers A and/or FF.

INTERMACS® 7: Describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower. This patient may have a modifier A only.

INTERMACS® Modifier:

A - Arrhythmia. This modifier can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to the overall clinical course. This includes frequent shocks from ICD or requirement for external defibrillator, usually more than twice weekly.

TCS –Temporary Circulatory Support. This modifier can modify only patients who are confined to the hospital, Patient Profiles 1, 2, and 3 (a patient who is listed as Patient Profile 3 stable on inotropes who has been at home until elective admission for implantable VAD cannot have a TCS modifier.) Support includes IABP, ECMO, TandemHeart, Levitronix, BVS 5000 or AB5000, Impella.

FF – Frequent Flyer. This modifier is designed for Patient Profiles 4, 5, and 6. This modifier can modify Patient Profile 3 if usually at home (frequent admission would require escalation from Patient Profile 7 to Patient Profile 6 or worse). Frequent Flyer is designated for a patient requiring frequent emergency visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Frequent would generally be at least two emergency visits/admissions in the past 3 months or 3 times in the past 6 months. Note: if admissions are triggered by tachyarrhythmias or ICD shocks then the modifier to be applied to would be A, not FF.

Appendix C: New York Heart Association (NYHA) Functional Classification

The patient's functional status will be assessed by a qualified individual at the institution by utilizing the NHYA functional classification below:

ACC/AHA vs. NYHA Classification of Heart Failure

ACC/AHA Stage		NYHA Functional Class	
Stage	**Description**	**Class**	**Description**
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	No comparable functional class	
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.	I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.	II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
		III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
		IIIb	Very marked limitation in physical activity due to symptoms with minimal exertion.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.	IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA = American College of Cardiology/American Heart Association; HF = heart failure;
NYHA = New York Heart Association

Appendix D: Study Specific Reportable Events/Outcomes

The following study specific additional adverse event data will be collected for outcome data collection purposes, but this data will not meet expedited reporting criteria to the DCC (Refer to Section 7.1 of Protocol).

EVENTS/OUTCOMES
Hospitalizations Stroke Mechanical Circulatory Support Device (MCSD) Transplant Death Transplant Listing Status Resuscitation Status Entry into Hospice

CITATIONS:

[1]Park, S.J., et al., *Management of aortic insufficiency in patients with left ventricular assist devices: a simple coaptation stitch method (Park's stitch).* J Thorac Cardiovasc Surg, 2004. 127(1): p. 264-6.

[2]Rose, E.A., et al., *Long-term mechanical left ventricular assistance for end-stage heart failure.* N Engl J Med, 2001. 345(20): p. 1435-43.

[3]Slaughter, M., et al., *Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device.* N Engl J Med, 2009. 361(23): p. 2241-2251.

[4]Cowger, J., et al., *The HeartMate II risk score: predicting survival in candidates for left ventricular assist device support*. J Heart Lung Transplant, 2011. 30(4 Suppl I): p. S31 [abstract].

[5]Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, Timothy Baldwin J, Young JB. *Sixth INTERMACS annual report: a 10,000-patient database.* J Heart Lung Transplant. 2014;33(6):555-564.

[6]Stewart GC, Kittleson M, Cowger J, Patel C, Johnson F, Mountis M, Patel P, Rame JE, Testani J, Guglin M, Teuteberg J, Stevenson LW. *High event rates in medically managed advanced heart failure patients followed at VAD centers.* J Heart Lung Transplant. 2012;31(4):S11-S12.

[7]Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, Cook NR, Felker GM, Francis GS, Hauptman PJ, Havranek EP, Krumholz HM, Mancini D, Riegel B, Spertus JA. *Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation.* 2012;125(15):1928-1952.

[8]Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. *Long-term mechanical left ventricular assistance for end-stage heart failure. The New England journal of medicine.* 2001;345(20):1435-1443.

[9]Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, Oren RM, Krueger SK, Costanzo MR, Wann LS, Levitan RG, Mancini D. *Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure).* Circulation. 2004;110(8):975-981.

[10]Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. *Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation.* Circulation. 1997;95(12):2660-2667.

[11]Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. *The Seattle Heart Failure Model: prediction of survival in heart failure.* Circulation. 2006;113(11):1424-1433.

[12]Gorodeski EZ, Chu EC, Chow CH, Levy WC, Hsich E, Starling RC. *Application of the Seattle Heart Failure Model in ambulatory patients presented to an advanced heart failure therapeutics committee.* Circ Heart Fail. 2010;3(6):706-714.

[13]Sartipy U, Goda A, Yuzefpolskaya M, Mancini DM, Lund LH. *Utility of the Seattle Heart Failure Model in patients with cardiac resynchronization therapy and implantable cardioverter defibrillator referred for heart transplantation.* American heart journal. 2014;168(3):325-331.

[14]Setoguchi S, Stevenson LW, Schneeweiss S. *Repeated hospitalizations predict mortality in the community population with heart failure. American heart journal.* 2007;154(2):260-266.

[15]McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. *Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England journal of medicine.* 2014;371(11):993-1004.

[16]Mancini D, Lietz K. *Selection of cardiac transplantation candidates in 2010.* Circulation. 2010; 122:173-183.

[17]Wever-Pinzon O, Drakos SG, Kfoury AG, et al. *Morbidity and mortality in heart transplant candidates supported with mechanical circulatory support.* Circulation 2013; 127: 452-62.

[18] Levy WC, Mozaffarian D, Linker DT, et al. *The Seattle Heart Failure Model: prediction of survival in heart failure.* Circulation. 2006;113(11):1424-1433.

[19]Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. *Prediction of mortality in clinical practice for medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death.* J Am Coll Cardiol.

[20]Cahalin, L.P., et al., *The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure.* Chest, 1996. 110(2): p. 325-32.

[21]Ross, R.M., et al., *The six minute walk test accurately estimates mean peak oxygen uptake.* BMC Pulm Med, 2010. 10: p. 31.

[22]Roul, G., P. Germain, and P. Bareiss, *Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure?* Am Heart J, 1998. 136(3): p. 449-57.

[23]Mancini, D., T. LeJemtel, and K. Aaronson, *Peak VO(2): a simple yet enduring standard.* Circulation, 2000. 101(10): p. 1080-2.

[24]Bensimhon, D.R., et al., *Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing).* Am J Cardiol, 2008. 102(6): p. 712-7.

[25]Mancini, D.M., et al., *Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure.* Circulation, 1991. 83(3): p. 778-86.

[26]Parikh MN, Lund LH, Goda A, Mancini D. *Usefulness of peak exercise oxygen consumption and the heart failure survival score to predict survival in patients >65 years of age with heart failure.* Am J Cardiol, 2009.103(7):998-1002.

[27]Ruschitzka F, et al., *Cardiac-resynchronization therapy in heart failure with a narrow QRS complex.* N Engl J Med, 2013. 368(15):1395-405.

[28] Little, R. J. A. & Rubin, D. B. *Statistical Analysis with Missing Data.* Wiley & Sons, Inc., New York (2002).

[29] Molenberghs, G. & Kenward, M. G. *Missing Data in Clinical Studies.* Wiley & Sons, Inc., New York (2007).

[30] Laird NM, Ware JH. *Random-effects models for longitudinal data.* Biometrics 38, 963-974, 1982

[31]Verbeke, G. & Molenberghs, G. *Linear mixed models for longitudinal data. 1-568* Springer Verlag, New York, NY (2000).

[32]West, B. T., Welch, K. B., & Galecki, A. T. *Linear mixed models: a practical guide using statistical software.* Chapman & Hall/CRC Press,(2007).

[33]Ewout W. Steyerberg, Andrew J. Vickers, Nancy R. Cook, Thomas Gerds, Mithat Gonen, Nancy Obuchowski, Michael J. Pencina, and Michael W. Kattan. *Assessing the performance of prediction models: a framework for some traditional and novel measures.* Epidemiology. 2010 Jan; 21(1): 128–138.

[34] Frank E. Harrell Jr., Kerry L. Lee and Daniel B. Mark. *Tutorial in biostatistics. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors.* Statistics in Medicine, vol. 15,361-387 (1996)