REVIVE-IT REGISTRY

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

Manual of Procedures (MOP)

Final Version 4.3 (02Mar2018)

Revision History

Version	Date	Change
4.3	3/02/2018	Modified to capture administrative changes and operational clarifications
4.2	2/15/2016	Modified to add additional operational clarifications and deviation standards
4.1	11/19/2015	Modified to align with Protocol Version 7.0
4.0	8/10/2015	Modified to align with Protocol Version 6.0
3.0	1/14/2015	Modified to align with Protocol Version 5.1
2.0	8/8/2014	Modified to align with Protocol Version 4.0
1.0	8/14/2013	Final Version
0.1	8/1/2011	Final Draft

Contents

List of Abbreviations

Abbreviation	Definition
6MWT	Six Minute Walk Test
ACE	Angiotensin-Converting Enzyme
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
BiVAD	Biventricular Assist Device
BSA	Body Surface Area (m^2)
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CPX	Cardiopulmonary exercise testing
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
DCC	Data Coordinating Center
DNR/DNI	Do Not Resuscitate / Do Not Intubate
OSMB	Observational Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D	EuroQoL Questionnaire (Health Status tool)
FEV1	Forced Expiratory Volume
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HRQOL	Health-related Quality of Life

Abbreviation	Definition
IABP	Intra-Aortic Balloon Pump
IRB	Institutional Review Board
ICD	Implantable Cardiac Defibrillator
INTERMACS®	InterAgency Registry for Mechanical Assisted Circulatory Support
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MCSD	Mechanical Circulatory Support Device
MedaMACS	Medical Arm of Mechanically Assisted Circulatory Support
MRS	Modified Rankin Scale
NYHA	New York Heart Association (heart failure classification)
Peak VO_2	Peak exercise oxygen consumption
QOL	Quality of Life
RER	Respiratory Exchange Ratio
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SHFM	Seattle Heart Failure Model
SOC	Standard of Care
VAD	Ventricular Assist Device(s)

SECTION 1: OVERVIEW

1.1 Purpose

This manual provides guidance to REVIVAL study sites to facilitate safe, consistent and efficient research activities study wide. Contents of this document will provide study structure information and will detail important elements of REVIVAL related procedures and policies. This is a living document and routine updates are anticipated to ensure that this be an effective tool for our research sites.

SECTION 2: STUDY ORGANIZATION

2.1 REVIVAL Study Team

The REVIVAL study team is led by two Co-Principal Investigators (Co-PIs), four study Co-Investigators (Co-Is) and a study chair and consists of the Data Coordinating Center (DCC), Clinical Sites, three Core Laboratories, the National Heart, Lung and Blood Institute (NHLBI), an Observational Safety Monitoring Board (OSMB), and study collaborators.

2.1.1 Study Co-PIs:

- Keith Aaronson, MD, MS
- Garrick Stewart, MD

The REVIVAL study co-PIs will provide scientific and administrative oversight of the study in consultation with the REVIVAL Study Chair, Executive and Steering Committees, OSMB, Co-Investigators, Clinical Site Investigators, and REVIVAL DCC.

2.1.2 Study Chair:

- Douglas Mann, MD

The Study Chair for the REVIVAL study will provide strategic direction to ensure integrity of the scientific aims of the study. The Study Chair will preside over the REVIVAL Executive and Steering Committees. The Study Chair will also be responsible for advising on study administrative matters and be the final arbiter of matters related to the REVIVAL study for issues where consensus in the study cannot be reached by study investigators.

2.1.3 Study Co-Is:

- Francis Pagani MD, PhD
- Cathie Spino, Sc.D
- Lynne Stevenson, MD
- Robert Kormos, MD

Study Co-Investigators will provide consultation and scientific and administrative input to the REVIVAL study

2.1.4 Data Coordinating Center (DCC)

The REVIVAL DCC will be located at the University of Michigan.

2.1.4.1 Responsibilities of DCC

The DCC will provide extensive resources for clinical operations, a secure clinical data entry and management system, project management, and coordination of the study. Overall clinical study administration, including protection of human subjects, subject enrollment, data collection and analysis will be centrally coordinated. The Data Manager and Clinical Project Manager(s) will maintain regular contact with the sites and data from sites will be reviewed in real time to ensure appropriate study conduct, human subjects protections and data collection.

The Data Coordinating Center has the following responsibilities:

- Oversight of study
- Organizing Subcommittee, Steering Committee and Observational Safety and Monitoring Board meetings
- Facilitating communication among the study organization
- Collecting and maintaining the study data
- Caregiver subject follow-up
- Analyzing data and preparing data for publications
- Overseeing clinical site study conduct
- Clinical site training
- Overseeing clinical site adherence to the protocol
- Overseeing subject recruitment
- Providing regulatory support and guidance
- Collecting adverse events (AEs) and study outcome data

2.1.5 Clinical Sites

Up to twenty-five sites will be participating in REVIVAL. The following are the clinical sites currently participating.

1. Abington Jefferson Health (AJH)
2. Brigham & Women's Hospital (BWH)
3. Cedars-Sinai Medical Center (CSH)
4. Cleveland Clinic Foundation (CCF)
5. Henry Ford Health System (HFH)
6. Inova Heart and Vascular Institute (IHV)
7. INTEGRIS Health Advanced Cardiac Care (INT)
8. Johns Hopkins Hospital (JHH)
9. The Methodist Hospital (MTH)
10. Montefiore Medical Center (MMC)
11. Mount Sinai Hospital (MSH)
12. University of Alabama (UAB)
13. University of Colorado, Denver (UCD)
14. University of Maryland, Baltimore (UMB)
15. University of Michigan (UOM)
16. University of Pennsylvania (PEN)
17. University of Pittsburgh (PIT)
18. University of Utah (UUT)
19. UT Southwestern (UTS)
20. Virginia Commonwealth University (VCU)
21. Washington University St. Louis (WSH)

Each of the clinical sites selected for REVIVAL represent experienced centers in the treatment of advanced heart failure.

2.1.5.1 Responsibilities of Clinical Sites

The REVIVAL study will include a principal clinical site investigator at each of the enrolling centers. The principal site investigator will be an advanced heart failure cardiologist and will be responsible for oversight of study enrollment and ensuring complete follow-up of subjects entered into the study.

Site Specific responsibilities include:

- Comply with the protocol, MOP, Institutional Review Board (IRB) and Federal and state regulations
- Attendance of site training meetings as required throughout the project
- Maintain the required regulatory documentation
    - Ensure all CVs, medical licenses, NHLBI non-disclosure agreements, NIH Information Security and Privacy Awareness Training documentation for

all personnel listed and human subject training documentation for site PI are complete and current

- Recruit, screen, enroll and follow study participants
- Collect data and follow study participants through study completion
- Timely entry of data into the Electronic Data Capture (EDC) System
- Complete Hazardous Goods Training for those team members that will be shipping samples to the Core Laboratories
- Provide blood samples and data to the Core Laboratories as described in this MOP
- Resolve data queries promptly
- Retain records per study and site guidelines
- Communicate questions, concerns and/or observations to the DCC
- Notify the DCC when site study team member changes occur

2.1.6 Core Laboratory Sites

The unifying emphasis of the Core Laboratory support of REVIVAL will be to provide expertise and guidance to the study and to provide standardized high quality clinical data. The three Core Laboratories are as follows:

2.1.6.1 Cardiopulmonary Exercise (CPX) Core Laboratory

The Cardiopulmonary Exercise (CPX) Core Laboratory at the Icahn School of Medicine at Mount Sinai Hospital, New York will serve as the exercise core laboratory (herein referred to as the CPX Core Lab) for REVIVAL. Donna Mancini, MD, will serve as the Director. The core lab will ensure uniformity in application of the exercise protocol and independent confirmation of study data.

The responsibilities of the CPX Core Lab are as follows:

- Review exercise tests and site equipment information and give the site feedback, if necessary, on areas to improve
- Provide independent confirmation of study data
- Perform CPX validation for each site; provide a certificate of validation and notify DCC of a site's validation status
- Answer questions for sites via email and telephone
- Enhance standardization of test performance across the sites and provide uniform test interpretation, thereby improving the quality of exercise data
- Contribute to the development of the protocol, interpretation of the results and reporting of results for the scientific literature
- Participate in cardiopulmonary exercise core lab-related abstract development and submission to scientific meetings as well as manuscript

development and submission to peer-reviewed journals in collaboration with the DCC and site investigators
- Participate in regularly scheduled teleconferences
- Submit progress reports to the REVIVAL Principal Investigators (PIs) as requested

2.1.6.2 Echocardiography Core Laboratory

The Echocardiography Core Laboratory within the Cardiovascular Institute of the University of Pittsburgh will serve as the echocardiography core laboratory (herein referred to as Echo Core Lab) for REVIVAL. John Gorcsan, MD, will serve as the Director.

The responsibilities of the Echo Core Lab are as follows:

- Provide a unified application of the echocardiography protocol
- Perform echocardiogram validation for each site; provide a certificate of validation and notify DCC of a site's validation status
- Organize and train study team and site personnel on all aspects of echocardiographic data collection
- Organize and process the digital echocardiographic images and enter data into the database
- Provide independent confirmation of study data
- Enhance standardization of test performance across the sites and provide uniform test interpretation, thereby improving the quality of echo data
- Contribute to the development of the protocol, interpretation of the results and reporting of results for the scientific literature
- Participate in echocardiography core lab-related abstract development and submission to scientific meetings as well as manuscript development and submission to peer-reviewed journals, in collaboration with the DCC and site investigators
- Participate in regularly scheduled teleconferences
- Submit progress reports to the REVIVAL PIs as requested

2.1.6.3 Biomarker Core Laboratory

The Cardiovascular Institute at the University of Pittsburgh will serve as the biomarker core laboratory (herein referred to as the Biomarker Core Lab) for REVIVAL. Dennis McNamara, MD, will serve as the Director.

The responsibilities of the Biomarker Core Lab are as follows:

- Coordinate DNA, RNA and serum banking from all participants
- Perform genomic analysis for participants who consent for this activity
- Perform sample analysis
- Participate in biomarker core lab-related abstract development and submission to scientific meetings as well as manuscript development and submission to peer-reviewed journals, in collaboration with the DCC and site investigators
- Participate in regularly scheduled teleconferences
- Submit progress reports to the REVIVAL PIs as requested
- Provide confirmation of sample receipt to the DCC

2.2 National Heart, Lung and Blood Institute (NHLBI)

2.2.1 Overview

The NHLBI is engaged as the sponsor of this study.

2.2.2 Responsibilities

- Meet frequently with the Executive Committee to address any issues as they arise
- Monitor study progress, including surveillance and assessment of performance and recommend changes in requirements
- Perform technical evaluations/inspections
- Approve the REVIVAL study protocol and protocol-related documents

2.2.3 Observational Safety Monitoring Board (OSMB)

To provide an independent expert perspective, an NHLBI-appointed (independent) OSMB will meet, at a minimum, annually. The principal role of the NHLBI-appointed OSMB is to regularly monitor the data from the registry, review and assess the performance of its operations, evaluate participant burden, assure participant confidentiality, and make recommendations, as appropriate, to the NHLBI and REVIVAL investigators with respect to:

- the performance of individual centers (including possible recommendation on actions to be taken regarding any centers that perform unsatisfactorily);
- issues related to maintenance of participant informed consent, safety, and confidentiality, including notification of and referral for abnormal findings;
- adequacy of registry processes in terms of:
    - the number of participants enrolled into REVIVAL and the number of MCSDs that were implanted
    - quality control

    - data completeness
    - data analysis, and
    - publications
- issues pertaining to participant burden;
- impact of proposed ancillary studies and sub-studies on participant burden and overall achievement on the main registry goals;
- possible modifications in the registry protocol; and
- overall scientific direction of the registry

The OSMB is composed of a Chair and members with expertise in biostatistics, bioethics, heart failure, and cardiovascular imaging. Ad hoc members may be added to the OSMB to have greater representation of expertise in a relevant biomedical field. All standing members of an OSMB may vote. Ad hoc members have the same voting rights as standing members when reviewing the protocol and amended protocols.

The DCC will prepare and distribute data reports at least 10 working days prior to an OSMB meeting/conference call. The basic format for the presentation of ongoing data is established at the initial OSMB meeting.

During the meeting, the OSMB discusses the registry's overall performance, data quality, and subject burden. The DCC, in consultation with the Executive Committee, is responsible for preparing the meeting materials. Meeting materials are distributed by the DCC to the Board members approximately 10 days prior to the meeting. The NHLBI Executive Secretary facilitates the meetings in conjunction with the Chair and prepares minutes for approval by the Chair and NHLBI.

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

2.2.4 Study Consultants

James Kirklin, MD (INTERMACS PI) and Representatives from the INTERMACS DCC will consult with the REVIVAL study team with respect to data analyses activities, as needed.

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SECTION 3: COMMITTEES

3.1 Executive Committee

3.1.1 Overview

The Executive Committee meets frequently to discuss the progress of REVIVAL including activities conducted in the Planning Phase, the Active Clinical Study and Closeout.

3.1.2 Membership

The REVIVAL Executive Committee will be led by the REVIVAL Co-Principal Investigators. Voting members of the Executive Committee will include the REVIVAL Study Chair, REVIVAL Co-Principal Investigators, REVIVAL Co-Investigators, NHLBI representatives and REVIVAL DCC representatives.

3.1.3 Responsibilities

The Executive Committee will be responsible for overseeing the activities conducted in all phases of the REVIVAL Study.

3.2 Steering Committee

3.2.1 Overview

The Steering Committee will be led by the REVIVAL Study Chair, Douglas Mann, MD from Washington University at St. Louis.

Voting members of the Steering Committee: REVIVAL Study Chair, REVIVAL Co-Principal Investigators, REVIVAL Co-Investigators, REVIVAL Site Investigators and NHLBI representatives.

Non-voting members of the Steering Committee: Site Coordinators, Core Lab representatives, and DCC representatives.

3.2.1.1 Duties of the Chair

- Assist the DCC Co-PIs in the development and maintenance of an organizational structure that meets the needs of the study and the NHLBI
- Remain informed of all the operational aspects of the study and, working within the organizational structure, formulate policy and take necessary action to ensure the smooth operation of the study
- Intervene and interact with clinical sites to maximize enrollment of study participants

- Advise the DCC Co-PIs on data monitoring and other issues of importance to the overall conduct of the study
- Advise the DCC on appointments of study participants and non-participants to appropriate positions and committees
- Represent the Steering Committee to the OSMB

3.2.2 Responsibilities

The responsibility of the Steering Committee will be to ensure the scientific success of the REVIVAL study.

3.2.3 Steering Committee Meetings

The REVIVAL Steering Committee will meet as needed by teleconference. Minutes from Steering Committee meetings will be posted to Confluence.

SECTION 4: SUBCOMMITTEES

4.1 Overview

The REVIVAL subcommittees are: The Coordinator Council and the Data Access, Analysis and Publications committee. The chair of each subcommittee is appointed by the Study PIs in consultation with the Steering Committee. The functions of these subcommittees are outlined briefly below.

4.2 Subcommittees

4.2.1 Coordinator Council

4.2.1.1 Overview

The Coordinator Council Subcommittee will provide ongoing educational activities and operational support directed specifically to the clinical coordinators and support staff at clinical sites.

4.2.1.2 Membership

The Coordinator Council Subcommittee will consist of representatives from the DCC, NHLBI, and the Clinical Coordinators from each of the clinical sites.

4.2.1.3 Responsibilities

- Ensure uniform activities and interpretation of responsibilities of coordinators at each of the clinical sites
- Enhance accuracy of data entry
- Promote optimal engagement of Clinical Coordinators in the REVIVAL study

4.2.1.4 Coordinator Council Meetings

The REVIVAL Coordinator Council will meet monthly by teleconference. Minutes from Coordinator Council meetings will be posted to Confluence.

4.2.2 Data Access, Analysis and Publications (DAAP) Committee

4.2.2.1 Overview

The DAAP Committee will be responsible for evaluating the scientific merit of proposals, prioritization of proposals and assignment of authorship opportunities.

4.2.2.2 Membership

The DAAP Subcommittee will consist of the REVIVAL Study Chair; REVIVAL Co-Principal Investigators; REVIVAL Co-Investigators; NHLBI Contracting Officer's Representative; NHLBI Statistician; INTERMACS PI; REVIVAL Core Lab Directors; and site PIs from the four highest performing sites.

Responsibilities

- Develop a publications policy for the REVIVAL Study that facilitates fair and equitable distribution of writing projects
- Assist in formation of writing groups and identifying writing group chairs
- Assist in identifying writing responsibilities and timelines for publication of study reports

4.2.2.3 DAAP Meetings

The REVIVAL DAAP meetings will be scheduled as needed, with frequent meetings anticipated at the time of database lock.

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SECTION 5: COMMUNICATION

5.1 Overview

The DCC will be responsible for clinical site coordination, data collection, management, analyses, and preparation of regulatory packages in support of the study as well as fulfilling all regulatory requirements relating to successful completion of the study. Communications between the entities of the DCC, Core Laboratory Sites, Clinical Sites, Steering and Executive Committees and Subcommittees, as well as NHLBI are outlined below.

5.2 General Approaches

In addition to standard lines of communication between the DCC and all entities making up the REVIVAL study, several other forms of communication will be created to enhance overall trial organization and flow:

- Internal website (Confluence) used as a shared space to post study documents (i.e. protocol, informed consent template, meeting minutes, case report forms, etc.)
- REVIVAL Newsletter that will provide information to Clinical Site Investigators and Core Sites
- Study will be maintained on the ClinicalTrials.gov website

5.3 Confluence

The University of Michigan Medical School internal website Confluence will be used to store and share REVIVAL Study information.

The Commons Area space on Confluence is accessible by clinical sites and is reserved for documents common to both the Data Coordinating Center and the Study Teams. Examples of common documents include the study protocol, informed consent templates, presentations, and blank case report forms (CRFs).

If you are looking for a specific document that is not currently in the Commons Area, you may not have the proper permissions to view it. Please contact the DCC to request access to specific documents or to change your access rights.

Site regulatory documents are also posted to Confluence on site-specific pages. It is the responsibility of the site in conjunction with the DCC to ensure that these documents remain current and updated as appropriate.

Log in to Confluence using the username and the password provided by the DCC.

5.4 ClinicalTrials.gov Posting

The ClinicalTrials.gov Identifier for the REVIVAL study is NCT01369407. Please contact the DCC with any identified errors or updates. The posting can be accessed by following the link below:

http://www.clinicaltrials.gov/ct2/show/NCT01369407?term=REVIVE-IT&rank=1

5.5 Communication between DCC and Clinical Sites

Communication between the DCC and clinical sites occurs frequently utilizing various communication methods.

The DCC will send frequent communications to each clinical site. Email summaries will be **supplemented with *ad hoc direct* email communications and telephone contact as needed** to maintain coherent trial organization and flow.

5.6 Communication between DCC and Core Laboratories

Communication between the DCC and Core Laboratories occurs as needed. The core laboratories are invited to attend the Steering Committee teleconferences. Ad hoc communication to discuss specific subject questions and issues are anticipated.

5.7 Communication between DCC and Steering and Executive Committees

DCC representatives will be present at all Executive and Steering Committee meetings and will post meeting documents and a listing of meeting attendees to Confluence. The DCC will also provide a ***weekly summary of enrollment progress and a monthly project summary*** to all members of the Executive Committee.

SECTION 6: STUDY SITE REGULATORY REQUIREMENTS

6.1 Study Site Initiation Requirements

The following documents and information must be submitted to the DCC prior to subject accrual approval and must be maintained throughout the duration of the REVIVAL study:

- Signed Delegation of Authority Log (See Template in Appendix 2)

- Curriculum Vitae (signed and dated within past 2 years), current medical or nursing license, and NHLBI Employee Non-Disclosure Form for all study team members listed on the Delegation of Authority Log
- Human Subjects Training (HST) certificate (taken within past 2 years or with institutional specific expiry date not exceeded) for Principal Investigator
- IRB Approval Letters
- IRB Approved Consents/HIPAA Authorizations
- IRB approved subject recruitment materials (if applicable)
- Fully executed subcontract
- NIH Information Security and Privacy Awareness training for all team members with access to the clinical electronic Case Report Form (eCRF) database
- OpenClinica Access form and Attestation statement for all team members with access to the clinical eCRF database
- Hazardous Goods Training (taken within past 2 years) for team members responsible for handling and shipping blood and tissue specimens
- CLIA/CAP Certifications
- Current lab reference ranges for all labs collected in REVIVAL.

Each clinical site will be required to submit qualifying test ECHO DICOM images and cardiopulmonary exercise test files for review and approval by the Echocardiography and Cardiopulmonary Exercise Core Lab, respectively. Core lab site approvals should be maintained in Confluence and in the site investigative file.

After all initial essential documents have been verified and all necessary site training has occurred, the clinical site will be approved to enroll subjects into REVIVAL. The DCC will provide formal authorization to accrue subjects. No subject accrual is permitted prior to this notification.

SECTION 7: ETHICS/PROTECTION OF HUMAN SUBJECTS

7.1 Review of Submissions to Institutional Review Board (IRB)

Each participating institution must provide to the DCC for review and approval all informed consent documents and any subject recruitment material prior to submission to their IRB.

No site-specific modifications to the study protocol or amendments are permitted.

The initial IRB approval letter as well as documentation for future study continuances should be forwarded to the DCC and also saved in the site investigative file.

7.2 Informed Consent Process

The consenting process for REVIVAL must be in accordance with local site SOPs/guidelines/requirements and consistent with GCP/ICH principles. The person(s) conducting the consent must be listed on the Delegation of Authority Log and assigned this role and responsibility.

7.3 Subject Compensation

For clinical sites where the IRB permits subject stipends, subjects may receive approximately $25 (in the form of cash or gift card) for each completed study visit:

Baseline A, Baseline B, Six (6) Month Follow Up, Twelve (12) Month Follow Up, Eighteen (18) Month Follow Up and Twenty Four (24) Month Follow Up (maximum $150/subject).

The subject stipends are paid to clinical sites and are part of the subject fees as outlined in the clinical subcontract/budget document.

SECTION 8: STAFF TRAINING

8.1 Overview

Each site investigator and primary site coordinator will be responsible for attending a REVIVAL training meeting. This may be a virtual Investigator meeting or a site-specific training session. Other study team members are strongly encouraged to attend. It is the responsibility of the site Investigator to ensure the study team assigned has adequate protocol training for REVIVAL. The DCC is available to support site training needs beyond the standard training upon request.

In addition to protocol-specific training, the following training must also be completed:

8.2 Human Subjects Training

The Site Principal Investigator must complete Human Subjects Training either via the Collaborative Institutional Training Initiative (at www.citiprogram.org) or an equivalent program. The certificate of completion must be submitted to the DCC.

8.3 NIH Information Security Awareness and Information Management Training

All site staff listed on the Delegation of Authority Log who will have access to the OpenClinica

eCRF database must complete the NIH Information Security Awareness for New Hires and Information Management for New Hires training. The training modules can be accessed via the following link: http://irtsectraining.nih.gov/

To access Information Security Awareness for New Hires training:

1. Click on “Public Access to NIH Courses Enter Here” (bottom left hand corner)
2. Click on “Enter Training”
3. Click on “Information Security Awareness for New Hires”

To access Information Management for New Hires training:

1. Click on “Public Access to NIH Courses Enter Here” (bottom left hand corner)
2. Click on “Enter Training”
3. Click on “Information Management for New Hires”

The certificates (2 total per study team member, one for each course) of training completion must be submitted to the DCC. Valid annual refresher certificates (1 total per study team member for the refresher course) are required for existing team members who have completed the initial training. The NIH Information Security, Counterintelligence, Privacy Awareness, Records Management Refresher can be reached using the following link: http://irtsectraining.nih.gov/publicUser.aspx

8.4 Hazardous Goods Training

Any staff listed on the Delegation of Authority Log whose responsibilities include handling and/or shipping blood samples to the REVIVAL Biomarker Core Laboratory must complete Hazardous Goods Training prior to initiation of those responsibilities.

If your site does not have a Hazardous Goods Training program available, a training option is offered through the Mayo Clinic. This training can be found at the following link:

http://www.mayomedicallaboratories.com/education/online/dangerousgoods/

A copy of the training certificate must be submitted to the DCC.

8.5 OpenClinica eCRF Database

The DCC Data Manager will provide in-depth, study-specific training (via webinar) of the system’s capabilities and requirements prior to first subject enrollment for each site.

In addition, study coordinators performing data entry will need to complete the required OpenClinica forms before access to OpenClinica will be provided.

SECTION 9: SUBJECT RECRUITMENT

9.1 Study Recruitment

The main mechanism for subject recruitment into the REVIVAL registry is to contact site patients after preliminary chart review.

Subject recruitment will be monitored via weekly accrual reports prepared by the DCC.

SECTION 10: SUBJECT SCREENING, ELIGIBILITY, ENROLLMENT & BASELINE VISITS

10.1 Screening Procedures Overview

The following sections provide general guidance for the preliminary identification of patients to be screened for the REVIVAL Study and the completion of the screening log.

The REVIVAL Screening Log (Appendix 3) should be maintained in Excel format and contain a ***cumulative list of patients that meet preliminary study criteria and were contacted*** regarding participation in the REVIVAL study. The screening log should be completed and sent to the DCC ***every other Friday*** via MiShare before 12:00 pm ET (See Section 22.1 and Appendix 4a for MiShare instructions).

Sites with lower than anticipated screening and enrollment will be requested to send their screening log to the DCC on a more frequent basis to allow the DCC to assist the site with identifying obstacles to enrollment.

10.2 Screening Procedures

Potential REVIVAL Study subjects should be identified by means of the medical record/electronic database with screening criteria subsequently confirmed following a patient clinic visit or patient contact.

If a site patient is identified and contacted regarding REVIVAL but 1) Opts not to consent or 2) Provides additional information to the site that disqualifies participation, the patient should be entered onto the screening log.

The screening log should be monitored routinely at the site to determine if any patients listed should be re-approached for REVIVAL.

Patients currently enrolled in the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) Registry may also be approached for REVIVAL.

If a patient has been enrolled in MedaMACS at least 12 months, meets current REVIVAL criteria and is willing to consider participation in both registries, they may be approached for REVIVAL.

10.3 Screening Log Completion

The following should be completed for all patients *(Columns A – G)*:

- Screening Number – assigned by site using site's convention
- Date Approached – date subject was initially approached about participation in REVIVAL
- Subject Initials – unless local IRB prohibits providing to the DCC
- Age
- Gender
- Ethnicity
- ICF signed
    - If "Yes", enter the OpenClinica Subject ID # (e.g., UOM-001) (*Column H*)
    - If "No", choose from the list of reasons in "If ICF#1 not signed, reason": (*Column I*)
        - **If subject was Ineligible** – additionally select the single most relevant criterion not met in "Reason Patient Ineligible" (*Column J*)
            - NOTE: if the patient was excluded by more than one criterion, choose the one criterion that would most likely prevent future rescreening (e.g., #1: condition that would be expected to limit two-year survival)

If your institution prohibits reporting out any of the above data during the screening phase please contact the DCC for guidance on appropriate "dummy data" to include on your logs.

10.4 Inclusion/Exclusion Criteria Details

A complete list of the study inclusion/exclusion criteria is available in Protocol Section 5.1 and 5.2. This section contains expanded explanations for the criteria to facilitate a common interpretation of the criteria across all study sites.

Regarding REVIVAL LVEF criterion (Inclusion #4): The protocol states subjects should have a last left ventricular ejection fraction ≤ 35% by any imaging modality. The LVEF measurement should be within the past two years. In addition, the measurement should be minimally 3 months post-implantation of a CRT or CRT-D device.

Regarding REVIVAL medication criterion (Inclusion #7): The protocol states subjects should be "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". It is understood and acceptable for REVIVAL that intolerance to one of these medications may result in an additional medication not being taken. This is allowable as there is substantial evidence to support that some medications required for REVIVAL (example hydralazine or nitrate) do not improve survival or any other outcome when taken alone; the guidelines state that they should be used in combination. When a subject is intolerant of a medication used in combination with other therapies, there is not a requirement for the subject to be on either drug.

Many HF subjects are beginning to use ENTRESTO. ENTRESTO is permitted for REVIVAL. If a patient was taken off an ACE inhibitor and switched to ENTRESTO, there is not a need to restart the clock on the three months of maximum therapy. If the patient is new to ENTRESTO and was not on an ACE/ARB previously, the patient should stabilize on the new medication regimen for three months per protocol.

The protocol states "hydralazine/long-acting nitrate [required of African-American subjects only] for ≥ 3 months absent contraindications or intolerances". To clarify the intent of this criteria, this requires that African-American subjects would be on both hydralazine and a long-acting nitrate or have documented contraindications or intolerances for each medication type.

Regarding REVIVAL sarcoidosis criterion (Exclusion #7): The protocol states subjects with cardiac sarcoidosis are excluded. To clarify the intent of this criteria, this refers to active sarcoidosis only.

10.5 Enrollment Procedures Overview

If a heart failure patient meets all inclusion criteria for REVIVAL (after chart review and dialog with patient regarding the REVIVAL study) and is interested in participation, the Baseline A visit should be scheduled and the patient should be consented as the first assessment associated with the Baseline A visit. Enrolled subjects should be entered into OpenClinica after the Baseline A visit occurs. Trial Inclusion and Exclusion Criteria must be evaluated at the Baseline A visit. See Protocol Sections 5.1 and 5.2 for the full list of Inclusion and Exclusion Criteria.

Note: If a patient is scheduled for an elective/planned invasive procedure, it is suggested that enrollment is delayed until after the procedure has occurred and the patient has recovered from the procedure.

10.6 Baseline Visits Overview

The protocol states that standard of care testing will be included in the heart failure subject evaluation for study visits, and all standard of care procedures have been labeled as such.

Please be advised that any assessments performed as standard of care at each subject visit are expected, but not *required* if these assessments are not consistent with your institutions' standard of care practices for heart failure patients. In other words, if any assessments marked as standard of care are not performed as part of the routine clinical care of a study subject, the data will not be collected, and a protocol deviation will not be recorded in accordance with the Sponsor's intent.

10.6.1 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 (6MWT)
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.

In most cases, it is anticipated that all Baseline A assessments will take place during one clinic visit. To offer flexibility, the protocol permits a two-week time span to complete all Baseline A procedures.

The Baseline B visit should be scheduled to occur 2 months (± 30 days) after consent. The Baseline B visit is not dependent on the end date of the last assessment completed at Baseline A. If subjects need to come back to finish the Baseline A visit and it is outside the two-week window (but before the Baseline B visit), this is NOT a protocol deviation. Please make all reasonable attempts to complete Baseline A assessments within the time frame of two weeks.

10.6.2 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. 6MWT
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.

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. Specific transfer information can be found in Sections 16 and 17.

It is important that the 6MWT and CPX test be performed on the same day whenever possible. The 6MWT should always be performed *prior* to the Cardiopulmonary Exercise (CPX) Test and the CPX test should be performed **at least 2 hours** after the 6MWT.

Please note that the Subject follow up CRF at this visit inquires about recent EF data. It is understood that as the ECHO is a research only procedure at most REVIVAL sites that a local read will not be done to establish EF, therefore data from the research ECHO would not be included here. The intent of this CRF question is to capture clinical EF readings that may have occurred since the subject's last visit.

In most cases, it is anticipated that all Baseline B assessments will take place during one clinic visit. To offer flexibility, the protocol permits Baseline B assessments to take place anytime throughout the visit window. In cases where a subject is hospitalized during their Baseline B visit window, all information that can be safely collected during the hospitalization (including ECHO and 6MWT if this is clinically acceptable for the subject) should be collected. The CPX (and any other assessments that could not be performed during the hospitalization) should be scheduled to occur within 2 weeks of discharge to allow for recovery time from bed rest. If any assessment cannot be completed within the visit window due to a hospitalization, please contact the DCC for case specific guidance. For the baseline visits, there are not strictly defined per protocol visit limits as there are for the follow up visits so visits outside of the recommended visit window are not protocol deviations. All reasonable attempts should be made to complete Baseline A and B assessments within the recommended time frames.

SECTION 11: STUDY SUBJECT FOLLOW-UP, ADHERENCE AND RETENTION

11.1 Overview

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 6 months, 12 months, 18 months and 24 months.

Every attempt should be made to perform evaluations at the designated time points. For all follow up visits except the 24-month visit, the window has been expanded to +/- 45 days in

accordance with protocol amendment 7.0. For the 24-month visit, the window remains at +/- 30 days due to contractual timelines, which cannot be changed.

Any visits missed or not completed within the protocol-specified window should be recorded in the Protocol Deviations eCRF.

11.2 Schedule of Follow-up

11.2.1 Follow up visit assessments

The follow up visits for REVIVAL subjects are identical for the 6-month follow up, 18-month follow up and 24-month follow up. Standard of Care [SOC] testing will be included in the heart failure subject evaluation for these visits. All SOC testing is labeled below. At all of these visits, the following assessments will be performed:

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. 6MWT
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.

The 12-month follow up visit has additional assessments to the ones listed above and include:

1. ECG
2. Blood draw for:
    a. Uric Acid
    b. Total cholesterol
    c. INR

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.

11.3 Patient Diary

Subjects will be given a pocket day planner provided to the sites by the DCC. Subjects will be asked to record information about all hospitalizations, emergency department visits, admissions to long term care facilities, admissions to nursing homes, admissions to rehabilitation facilities and to capture procedures not scheduled in the study protocol. If the subject did not have any health care interactions, the subject should record a "0" on the page so as to discern lack of service from missing data.

Study personnel should review the visit diary at each study visit. Data collected from the planners should be entered on the appropriate eCRFs. Chart review and dialog with the subject should occur as needed to confirm any additional details about recorded events. If a subject needs a new diary due to using up all pages in the existing diary or due to loss, a new diary should be dispensed. Completed diaries should be collected from subjects and saved as a part of the source documentation for that subject.

If the subject failed to complete the diary, the site should interview the subject and record the subject's answers pertaining to specific outcomes listed for the study on the paper CRF. The paper CRF should be retained as source documentation in the subject's file, and the data should be entered into the OpenClinica database.

11.4 Criteria for Discontinuation or Withdrawal of a Subject

A subject may discontinue his or her participation without giving a reason at any time during the study. Subjects may also be withdrawn at the request of the investigator.

For all subjects who are withdrawn by their choice or the investigator's choice, efforts should be made to request permission to follow up the patient for outcomes at Month 24. This outcome follow up would occur in the form of chart review (for patients still under care of the site after the point of withdrawal) and correspondence with the subject to report accurate outcomes as they are known at the Month 24 time point. If a subject agrees to allow for follow up after withdrawal, the Subject Visit Termination form should be completed and the Final Status – Withdrawn Subject form **SHOULD NOT** be completed until the final contact or chart review occurs for that subject. Specific instructions are provided on the form. If a subject does not agree to allow for follow up, the Final Status eCRF should be completed.

- Additional options for withdrawal are possible for REVIVAL. The primary reason for discontinuation or withdrawal of the subject from the study should be noted on the "Final Status" eCRF using the following categories: Subject withdrew consent, no Month 24

follow-up. The subject (or subject's legally authorized representative) wishes to withdraw from the study.

- Investigator withdrawal, no Month 24 follow-up. The investigator believes it is in the best interest of the subject to terminate participation in the study.
- Adverse Event. The Adverse Event eCRF should also be completed.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. All attempts to contact the subject will be documented. After standard follow up efforts have been employed, the site should send two certified letters to the subject with no response before formally classifying the subject as lost to follow up.
- Subject received a heart transplant. The Hospitalization eCRF should also be completed.
- Subject received a durable implantable VAD. The Hospitalization eCRF should also be completed.
- Death. The Death eCRF should also be completed.
- Study termination. The sponsor, institutional review board (IRB), ethics committee (EC), or regulatory agency terminates the study.
- Other.

NOTE: *All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.* Document in the research record each instance of a subject's withdrawal.

Outcomes reporting at the time of termination:

All known events/outcomes collected in REVIVAL up to the point of subject participation termination should be reported on the appropriate eCRFs. In cases where subject participation is terminated at a time point that is not a REVIVAL study visit, the Subject Follow-Up eCRF should be completed and the "early termination" option should be selected. Known hospitalizations that have occurred since the last REVIVAL study visit should be reported on the "Hospitalization" eCRF. If applicable, the "Death" eCRF should also be completed.

11.5 Study Suspension/Study Termination

Decisions regarding study suspension or termination will be provided to the participating sites in a formal communication with details provided regarding management of currently enrolled subjects. If the subjects are terminated as a result of study suspension/termination, the DCC will provide a letter for sites to submit to their IRBs that will summarize the details of the discontinuation in language that is understandable to the subject. It would be expected that this letter would be supplemented with direct conversations between the subject and Investigator (or designee) and that key details of these discussions would be captured in the research chart notes.

REVIVAL

SECTION 12: PROTOCOL PROCEDURE GUIDELINES AND DETAILS

12.1 Overview

The intent of this section is to provide guidance for the sites regarding procedures.

12.2 Medical History

While much medical history reporting is straightforward, clarifications may be needed for types of “Surgery for atrial or ventricular arrhythmias” should be reported. Please note that items such as Surgical MAZE Procedures for AFib, Surgical cryoablation for VT and Surgically placed permanent epicardial wires or pacer/ICD generators should be included. ICD, CRT and CRT-D implants should not be reported in this area. Catheter-based procedures should be listed in this area and described using “other” and then “specify”, detailing the specific procedure as appropriate.

12.3 Seattle Heart Failure Model (SHFM) Scores

The SHFM score will be calculated by the DCC using data entered by the site for the Baseline A, Baseline B and 12-month follow up visit. No site action is required to calculate this value, and it will not appear on an eCRF. It will be available at the DCC and will be an included element in statistical analyses.

If a site is calculating 1 year predicted survival to determine eligibility criteria, the public SHFM website (http://depts.washington.edu/shfm/) should be used to determine this. A copy or screen shot of the calculation should be included in the source documentation for that subject. Please note that derived values in the calculations that the system generates after key actual information is imputed into the model are acceptable for REVIVAL.

NOTE – For any study subjects that are on Bumetanide, the public SHFM website only allows for the Bumetanide dose up to 4mg. For any subjects that are on a greater dose than 4mg, please multiply the Bumetanide dose by 20 to obtain an equivalent Torsemide dose, and utilize this dose to calculate the SHFM score.

12.4 Heart Failure Survival Scores (HFSS)

The HFSS will be calculated by the DCC using data entered by the site for the Baseline B visit. No site action is required to calculate this value and it will not appear on an eCRF that is viewable by the site. It will be viewable at the DCC and will be an included element of the clinical database.

If a site is calculating the HFSS to determine eligibility for REVIVAL, they may utilize the HFSS Excel calculator provided on Confluence. A copy of this calculation should be included in the source documentation for that subject.

12.5 INTERMACS® Patient Profile

The INTERMACS Patient Profile classifications (refer to Protocol Appendix B) should be obtained by a qualified individual for all subjects at each REVIVAL visit. For subjects receiving an LVAD implant during the study, the INTERMACS Patient Profile will be obtained at the time of implant, or within two weeks of implant, in lieu of obtaining this variable at the next scheduled study visit. The classification can be readily determined by reviewing the subject's medical record.

Whenever possible, the same assessor should perform the INTERMACS® Patient Profile for all of the subject's visits to maximize consistency of assessment.

The REVIVAL study data (absent of any genetic data) will be linked to the INTERMACS and MedaMACS datasets to perform comparative analyses of outcomes of patients treated with medical verses VAD therapy.

12.6 New York Heart Association (NYHA) Classification

The NYHA classification (refer to Protocol Appendix C) should be obtained by a qualified individual for all subjects at each REVIVAL visit.

Whenever possible, the same assessor should perform the NYHA classification for all of the subject's visits to maximize consistency of assessment.

If a chart has varied NYHA classification data throughout, the Principal Investigator should review the chart. If they determine the patient's symptoms for at least 45 of the last 60 days are consistent with NYHA class II-IV, then a statement to this effect should be added to the chart and the patient may be approached for REVIVAL if they meet all other study inclusion criteria. This applies for any NYHA classification determination that is made by the Principal Investigator that is different than what was noted in the chart previously. The statement in the chart should not only include the classification, but also the rationale for the classification and for the time period of the classification.

12.7 Cardiopulmonary Exercise Test (CPX), Gait Speed Test and 6MWT Timing

At the Baseline B visit, three assessments that require physical movement are required. The 6MWT should always be performed *prior* to the CPX Test on the same day and the CPX test

should be performed **at least 2 hours after** the 6MWT. In addition, the Gait Speed Test should be done a minimum of 1 minute before the 6MWT. Therefore, the sequence of events at Baseline B would be:

Gait Speed Test (rest minimum of 1 minute) → 6MWT (rest minimum of 2 hours, completing other visit assessments such as QOLs during this timeframe) → CPX.

The Gait Speed Test and 6MWT are done for every study visit for REVIVAL. The requirement to have the Gait Speed Test at least 1 minute prior to the 6MWT applies to all REVIVAL visits.

12.8 Six Minute Walk Test Procedure and Protocol

The 6MWT will be obtained at all REVIVAL study visits.

The 6MWT should always be performed *at least 2 hours prior* to the CPX Test (if applicable for study visit) and, at a minimum, 1 minute after the Gait Speed Test.

It is recommended that the 6MWT should be performed along a long straight quiet 30-meter corridor. As results differ by length of the course, it is essential that the same course be used for all tests. The subject's usual medications should be continued. Subjects should not have exercised vigorously for at least 2 hours prior to the walk test. Exercise can be done after a light meal. Repeat walk tests should be done around the same time of day to minimize intraday variability.

The subject should sit in a chair near the start line for at least 1 minute before the test starts. Resting heart rate and blood pressure should be checked. Subjects with any potential contraindications for the 6MWT should be cleared by the site principal investigator as necessary.

The subject should then stand at the starting line. Their level of perceived dyspnea and fatigue should be recorded using the modified Borg scale (Table 3, Section 16.5). Heart rate and blood pressure should be recorded at the start and end of the exercise test.

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

Use the following script to instruct the subject:

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

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

During the test I will tell you how much time has elapsed. I will let you know when there is only 15 seconds remaining. At the end of 6 minutes, I will tell you to stop. Please stay where you are and I will come to you. I will measure your heart rate and blood pressure and ask you to rate your fatigue and shortness of breath using the scale I've shown you.

Let me know when you are ready to start."

The technician performing the test should not walk with the subject but should stand near the starting line. He/she should use an even tone of voice and standard phrases of encouragement. He /she should not tell or signal to the subject to speed up or hurry. The technician should report the time remaining to the subject. Use phrases like –'Keep up the good work. You have x minutes remaining.' 'Good job, you're halfway through'. 'You are doing well, x minutes remaining'.

At the conclusion of the test, complete the 6 Minute Walk Test eCRF in OpenClinica.

12.9 Gait Speed Test Procedure

The Gait Speed Test will be obtained at all REVIVAL study visits. Subjects with any potential contraindications for the Gait Speed Test should be cleared by the site principal investigator as necessary.

Record the time (in seconds) required for the subject to walk 15 feet.

The "starting" line and the 15 foot line should be clearly marked. Record the time to the first footfall at 0 feet and ends with the first footfall at 15 feet in the nearest. 0.1 sec with a stopwatch. Do this once, before the 6 minute walk. Allow the subject to rest at least 1 minute prior to the 6MWT.

At the conclusion of the test, complete the Gait Speed Test eCRF in OpenClinica.

12.10 Handgrip Strength Test

Handgrip strength will be assessed at all REVIVAL study visits. Study sites will be provided with a Jamar hand dynamometer for this assessment. This instrument should be used for all REVIVAL study assessments. For each assessment, three handgrip strength trials will be performed using the subject's dominant hand. The method used for this assessment is based on direction from Mathiowetz, V, Weber, K., Volland, G., & Kashman, N. from their 1984 publication in the Journal of Hand Surgery titled "Reliability and Validity of Hand Strength Evaluations".

To use the Dynamometer:

1) Set the adjustable handle to the second handle setting from the inside. Before moving the handle from the original position to the required position, note that the handle clip is located at the lower post (furthest from the gauge). If the handle is not replaced in the correct position, the readings will not be accurate.
2) Rotate the red peak-hold needle counter clockwise to line up with the black needle (which will be in the zero box).
3) Subjects should use their dominant hand to perform the assessment. Have the subject sit with their shoulder adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position, and wrist between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation. Ensure the dynamometer is in the second handle position from the inside. Lightly hold the readout dial to prevent inadvertent dropping. Let the subject comfortably arrange the instrument in his/her hand.
4) When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. No other body movement is allowed. The subject should be strongly encouraged to give a maximum effort. After the individual is positioned properly, say, “Squeeze as hard as you can…harder!...harder!...relax.”. The peak-hold needle will automatically record the highest force exerted.
5) Record the trial reading on the paper CRF (which will serve as your source for this assessment) and reset the peak-hold needle to line up with the black needle (which will be in the zero box).
6) Repeat the above trial two additional times, permitting the subject approximately 30 seconds to rest in between trials. In between trial readings, make sure the red needle is reset to be present in the middle of the black needle. This will give a uniform reading for all three trial readings per subject.

Note: If the black gauge needle is anywhere in the “zero” box, consider the machine calibrated. If the gauge needle on the dynamometer is not resting at zero when you receive the instrument, please reference the instrument manual for directions on how to reset the instrument. Please contact the DCC if the issue is not easily resolved.

12.11 Caregiver Participation

One objective of REVIVAL is 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.

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. This consent should be in place during the visit window for the heart failure subject's Baseline B visit.

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

If the primary caregiver changes, the caregiver registry follow up will be discontinued.

It is recommended that the Caregiver element of REVIVAL be introduced to the subject at the Baseline A visit. If their primary caregiver has accompanied them to this visit, discussion with the caregiver and review of the consent is encouraged. Consent must be in place at or before the Baseline B visit; therefore, advanced planning is required to ensure that the caregiver can be present at that visit or so it can be arranged to consent the caregiver prior to the visit occurring so that questionnaires can be mailed to the caregiver.

12.12 Electrocardiogram (ECG)

For study purposes, ECG data provided at Baseline A, Baseline B and the Month 12 time points should be a 12-Lead ECG assessment. Please note that historic ECGs (within the past 30 days) may be used. ECGs should be evaluated by the Investigators. Note: If the subject is being paced, a response of "NA" is acceptable for applicable ECG parameters. This is the only time that the "NA" field should be utilized.

12.13 Directed Physical Exam Guidance

On the Physical Exam/Vitals CRF, data from Jugular Venous Pressure results is requested as a number in cm. Whenever possible, please report the actual number. If this level of detail is not available in the chart but there is data to support a value within the acceptable range (e.g., reports states "normal" or "less than 6 cm"), please report a value of 5cm on the CRF.

SECTION 13: OVERVIEW OF DATA COLLECTION INSTRUMENTS

13.1 Overview

Subject and caregiver self-report instruments completed during a REVIVAL visit will be completed on paper and entered into the web-based portal (OpenClinica) by the Study Coordinator, or designee. In addition to the subject instruments, the study team will enter subject clinical study data into the same web-based portal.

The web-based system will permit the study team to enter information from any networked computer, using a secure, password protected sign-on.

Paper versions of all eCRFs and the subject and caregiver self-report instruments are located in the Virtual Casebooks on Confluence.

13.2 Quality of Life (QOL) Data Collection

The REVIVAL study has all study materials available in English. If your site would like to include subjects in REVIVAL who do not have English competency, sites are permitted to have certified translations of the informed consent form done (at the site's expense). QOL questionnaires will be provided in English only and therefore should not be completed by any subject who does not have English competency.

Data collection for QOL questionnaires will begin at Baseline A and continue through every REVIVAL study visit.

Heart failure subjects will be asked to complete the following QOL questionnaires:

- Heart failure-related QOL (KCCQ)
- EuroQoL (EQ-5D)
- State-Trait Anxiety Inventory (STAI)
- Depression (Personal Health Questionnaire [PHQ-8])
- Patient Preferences for end of life care and thresholds for VAD implantation (MEDAMACS VAD Survey)

Order of instrument administration:

EQ-5D, KCCQ, PHQ-8, STAI

Administration procedures specific to instruments:

PHQ-8

Score the instrument immediately after completion by summing all of the circled numbers. The range of scores is 0-24. *Scores >10 indicate the need for clinical assessment and management. Notify the subject of his or her score, and refer the subject to mental health clinicians (e.g., social work, psychology, and/or psychiatry) for follow-up.*

If the instrument is completed while the study subject is hospitalized at the time of the study follow up visit, clinical management of scores >10 will be managed at the discretion of the medical team attending to the subject.

STAI

If more than one response is provided by the subject and this is not identified while the subject remains in clinic, the most severe of the responses should be reported in the eCRF. Questionnaires should be reviewed while the patient is in clinic to avoid this issue whenever possible.

13.3 Caregiver QOL Data Collection

Caregiver follow up is not dependent on continued heart failure subject enrollment. If the heart failure subject receives a VAD or transplant their follow up in REVIVAL will end due to meeting a hard endpoint; however, caregiver follow up will continue for the full 24-month period for consented caregivers.

Caregivers will be asked to complete questionnaires at Baseline B, 6-month follow up, 12-month follow up, 18-month follow up, and 24-month follow up. The questionnaires they will complete are:

- Caregiver Health History (initial and follow up version are available)
- Oberst Caregiving Burden Scale (OCBS)
- Caregiver EQ-5D

Caregiver Questionnaire Process:

- If caregiver accompanies subject to visit, they should be provided with copies of the questionnaires for them to complete while they are waiting for the subject to finish their visit.
- Questionnaires should only be provided to the caregiver if they have time to complete them while in clinic; they should not take them home to complete them.
- If they do not complete the QOL questionnaires in clinic, the CRF should be completed to indicate this, and the DCC will mail the questionnaires to the caregiver with a postage paid return envelope

Order of instrument administration

EQ-5D, OCBS, Caregiver Health History

13.4 Questionnaire distribution

In most cases, questionnaires will be given to heart failure subjects and caregivers at the hospital (if the subject is hospitalized) or at a clinic visit (for completion on site). Questionnaires may also be mailed to caregivers at home or at a location near the hospital (e.g., a hotel) with addressed, stamped, return envelopes. Subjects/Caregivers may also choose to be interviewed.

Heart failure subjects and caregivers will be instructed to read the directions carefully for each questionnaire, speak with the team about any questions, answer the questions to the best of their ability, and complete the questionnaires as soon as possible.

Tips to encourage questionnaire completion: educate subjects and caregivers about the importance of completing QOL questionnaires. For example, you could say “we want to know

more about the quality of life of patients and their caregivers as they participate in this study and the only way to know is to ask patients like you."

If heart failure subjects or caregivers do not complete questionnaires, research coordinators will report this information on the appropriate eCRF.

Method of questionnaire completion (i.e., self-report or interview) and location will be documented on each questionnaire.

13.5 Quality Control

Research coordinators will examine all self-report questionnaires for response errors (e.g., missing data, unclear responses, two responses circled instead of one response) and will review data on the paper forms with the subject or caregiver as soon as possible. Ideally, this review should be immediately after forms have been completed and while the heart failure subject or caregiver is present (e.g., in the hospital or at a clinic visit). If the reviewer determines items have been left blank, the research coordinator may ask the subject or caregiver if they intended to leave the information blank. If they did not, they may complete the form as appropriate.

Heart failure subject and caregiver self-report forms completion will also be monitored in the study database by the DCC.

SECTION 14: OPENCLINICA

14.1 Overview

All subject data collected during the conduct of the REVIVAL study will be collected in the OpenClinica Enterprise Edition. The OpenClinica Enterprise Edition (supported by OpenClinica, LLC of Waltham, Massachusetts) is installed as a validated, 21 CFR Part 11 application at University of Michigan Institute for Clinical and Health Research (MICHR). It supports regulatory guidelines such as 21 CFR Part 11, HIPAA compliance and is built on a modern architecture using leading standards.

OpenClinica is a web-based clinical data management system (CDMS), which includes EDC, data management and data monitoring capabilities.

The OpenClinica Enterprise Edition provides audit trails on user access to and modification of data. Data discrepancies for data entered in eCRFs will be issued and tracked, with updates made to the database as applicable by the site. Upon completion of the study and after resolution of any outstanding data issues, the database will be locked.

Additional details are located in the eCRF Completion Guidelines (See Appendix 5).

14.2 System Requirements

OpenClinica is accessed via the internet and currently supports the latest versions of ***Internet Explorer, Firefox, and Chrome (on Windows OS or Mac OS***) with **JavaScript enabled and all popup blockers disabled.**

Refer to the eCRF Completion Guidelines (Appendix 5) for instructions on how to disable the popup blocker feature.

14.3 Data Access for Study Staff

The Site PI will be responsible for determining which individuals will need access at their respective sites. Typically, study coordinators assume data entry roles at the clinical site. Site PI's will not need access to the electronic database to review and sign off on eCRFs since their review and approval will be obtained via paper form. The DCC will work with site investigators to ensure all required signatures are obtained.

Study Staff must be trained on the protocol and the OpenClinica system and information, including name, title/position/role, phone number and email address, must be provided to the DCC prior to granting access to OpenClinica.

To obtain access to the OpenClinica system, please contact the DCC.

The DCC will forward new Study Staff the training material for review. The new Study Staff member will need to review the training material and send the 'OpenClinica Role-based Training and Usage Agreement' form and the 'External Account Access Request Form: OpenClinica Enterprise Edition' contained in the materials back to the DCC. In addition, training documents for NIH Information Security Awareness for New Hires and Information Management for New Hires training will be collected from all individuals with access to the OpenClinica database.

The Study Staff will receive system instructions, log-in information containing temporary passwords and instructions on how to change passwords for OpenClinica.

If you have any problems with OpenClinica, contact the DCC for assistance.

14.4 REVIVAL Study Databases

Access the OpenClinica Enterprise Edition by clicking on the following link:

https://openclinica.med.umich.edu/OpenClinica/pages/login/login

Contact the DCC Clinical Data Manager for general questions related to technical support for the OpenClinica project or questions related to the completion of the eCRFs.

For critical issues contact MICHR Support at MICHR-Support@umich.edu

MICHR Support is available 8:00 a.m. - 5:00 p.m. Eastern Standard Time - Monday through Friday

Be sure to include "REVIVAL" in the email subject line.

14.5 General Instructions for Completing Study EDC Forms

Study Subject IDs are assigned sequentially by the site coordinator at the time the heart failure subject signs informed consent.

Study Subject IDs will have the site ID and then a sequential number assigned (UOM-001, PIT-001, etc.).

All OpenClinica users only have access to specific studies, data and functionality that is appropriate for their role (e.g., only view data for their own site and ability to enter or update data for their own site).

For users who are responsible for data entry, note that edit checks are programmed to verify accuracy and data completeness. Users will also be responsible for responding to discrepant data notes that are generated during or after data entry.

Electronic CRFs should be completed within two weeks of the subject's completed visit.

14.6 Form Specific eCRF Instructions

See Appendix 5 – eCRF Completion Guidelines for instructions on completing the CRFs in the OpenClinica system.

14.7 Paper CRFs

All paper CRFs are located on Confluence.

SECTION 15: TRANSFER OF DATA USING MiSHARE

15.1 Overview

Because REVIVAL study data will contain sensitive information (e.g., procedure dates, etc.) all data transfers (e.g., cardiopulmonary exercise test results, echocardiograms, etc.) will occur via a secure system. REVIVAL will utilize MiShare to accomplish this task.

MiShare is a secure collaborative file exchange system provided by the University of Michigan Medical Center Information Technology (MCIT). The MiShare infrastructure provides a method to securely exchange files, including files that contain electronic Protected Health Information (ePHI) or other sensitive information.

See Appendix 4a and 4b for instructions for sending and accessing files (referred to as packages) via MiShare.

IMPORTANT NOTES regarding MiShare:

- Distribution lists are not functional in MiShare. Please refrain from using them as it will not work.
- If you are sending files to the DCC, in the *Recipient Email(s)* field, type the portion of the recipient's email address BEFORE the "@" symbol only, **not the full email address**.

  Example: "llacroix, shereceb"

REVIVAL

SECTION 16: CARDIOPULMONARY EXERCISE (CPX) TEST CORE LABORATORY DATA HANDLING AND TRANSFER

16.1 Overview

For REVIVAL, all enrolled heart failure subjects will have a CPX assessment at the Baseline B visit. CPX data will be transferred to a central core lab for all REVIVAL subjects.

16.2 Objectives

The CPX Core Laboratory will be based at Mount Sinai Hospital, New York**.** The primary objective of core laboratory data analysis is to ensure the following:

- Unified application of exercise protocol
- Independent confirmation of study data
- Uniform test interpretation, thereby improving the analysis of exercise data

16.3 Collection Time Points

The CPX will be obtained at the Baseline B visit. The REVIVAL DCC, CPX Core Director, Donna Mancini, MD is available to answer questions.

If you have questions send email to REVCPXCore@umich.edu or call:

Donna Mancini, MD
Phone: 212-241-4619

NOTE: Do not send patient information via email, please use MiShare.

16.4 Quality Control and Site Validations

The lead CPX technician for each site will be required to sign the Delegation of Authority log as a study team member upon completion of required training. The lead CPX technician will be responsible for training any other CPX technicians within the department and for the delegation of collection of study data as required. It is expected that each site will have multiple technicians trained on REVIVAL CPX collection so that appropriate back up is in place in cases where the lead CPX technician is not available to perform the procedure.

Prior to submitting subject CPX data, each center will perform a validation test. No center can submit CPX subject data for analysis until **one case of test data is accepted at the core lab** that includes:

- Adequate flow calibration
- Adequate transfer and reading of a complete data set

Tabular data averaged every 30 seconds is captured in the clinical database and will not be forwarded to the core lab as part of the validation test.

If a site obtains new CPX equipment throughout the course of REVIVAL that is a different make or model than the equipment used for your site test transfer, please contact the DCC to arrange for a new site validation test. REVIVAL sites participating prior to initiation of protocol version 6.0 with validation in place that have not had changes in CPX equipment do not need to perform a second validation.

16.5 CPX Procedures and Protocol

General Guidelines: Administration of Exercise Tolerance Test by Treadmill

Exercise testing should be conducted only by properly trained personnel. Equipment, medications and personnel trained to provide cardiopulmonary resuscitation must be available.

Symptom limited maximal exercise testing will be performed. Exercise may be terminated by the supervising physician for reasons such as: sustained ventricular or supra-ventricular arrhythmias, increasing chest pain, or significant fall in systolic blood pressure.

Equipment and Calibration

Treadmill

The treadmill should have front and/or side rails for subjects to steady themselves. Subjects should not tightly grasp the rails since this decreases VO_2 and increases exercise time and muscle artifact. It is helpful if subjects close their fists and place one finger on the rails to maintain balance after they are accustomed to walking on the treadmill.

If the subject has not performed a prior cardiopulmonary stress test, he/she should be appropriately introduced to the equipment and procedure specifics prior to beginning their test.

Metabolic Cart

A metabolic cart will be used for the study. Prior to each exercise test, the metabolic cart should be calibrated and the results sent with the exercise test data. The exercise protocol and data submission will be standardized. Each center's metabolic cart should be programmed to provide tabular text reports and graphs required by the core lab for data analysis.

Cardiopulmonary Exercise Testing Protocol

The CPX will be obtained at the Baseline B Visit. Data from the CPX will not be used for fulfillment of inclusion/exclusion criteria.

Predicted VO_2 will be calculated from the Wasserman-Hansen formula. Normal weight is calculated from height.

For men, normal predicted weight is derived from the equation:
Normal weight = 0.79*height-60.7

For women normal weight is calculated as
Normal weight =0.65*height-42.8

For normal weight sedentary men, the formula to calculate predicted VO_2 for treadmill exercise is as follows: (Weight in kg; age in yrs.)
VO_2 (mL/min)= 1.11 ((weight)*(50.72-0.372*age))

For normal weight sedentary women:
VO_2 (mL/min)=1.11((weight+43)*(22.78-0.17*age))

See Table 1 for calculation of VO_2 in patients above or below normal weight

Table 1. Definition of Percent Predicted VO_2 Equations[1]

Wasserman	**Sedentary Male** **Step 1: Calculate** Cycle Fact or=50.72 – 0.372 (age) Predicted weight: = 0.79(height)-60.7 **Step 2: Classify weight** Measured weight </=/> predicted weight **Step 3: Selection equation** Measured weight <Predicted weight Peak VO_2 (ml/min) = [(Predicted Weight + Actual weight)/2]* cycle factor Measured weight = Predicted weight Peak VO_2 (ml/min) = Measured weight * cycle factor Measured weight >Predicted weight Peak VO_2 (ml/min) = (predicted weight* cycle factor) + 6* (Measured weight –predicted weight) **Step 4: Mode of exercise consideration** If treadmill used for test Multiply predicted VO_2 from step 3* 1.11	**Sedentary Female** **Step 1: Calculate** Cycle Factor = 22.78 – 0.17 (age) Predicted weight: = 0.65(height)-42.8 **Step 2: Classify weight** Measured weight </=/> predicted weight **Step 3: Selection equation** Measured weight <Predicted weight Peak VO_2 (ml/min) = [(Predicted Weight + Actual weight+ 86)/2]* cycle factor Measured weight = Predicted weight Peak VO_2 (ml/min) = Measured weight + 43*cycle factor Measured weight >Predicted weight Peak VO_2 (ml/min) = (predicted weight + 43*cycle factor+ 6* (Measured weight – predicted weight) **Step 4: Mode of exercise consideration** If treadmill used for test Multiply predicted VO_2 from step 3* 1.11
Jones	**Males** Peak VO_2 (L/min) =5.41 (height)-0.025 (age) -5.66	**Females** Peak VO_2 (L/min) =3.01 (height)- 0.017 (age) -2.56

[1]Hansen JE, Sue DY, Wasserman K. Predicted Values for clinical exercise testing. Am Rev Resp Dis 1984; 129:S49-S55

Subject Preparation

- Subjects should be instructed not to eat for 3 hours before the test and to dress appropriately for exercise, especially with regard to footwear.
- Contraindications to testing should be ruled out by reference to medical history and physical examination.

Exercise Protocol

All cardiopulmonary exercise tests performed for REVIVAL will use the 3-minute incremental modified Naughton Protocol (Table 2). Exercise will be performed in the fasting state with the subject maintained on his/her medications.

The subject will be connected to the metabolic cart. Baseline metabolic data will be collected for 3 minutes. Respiratory exchange ratio (RER) should be between 0.78 and 0.90. If higher values are recorded, the baseline collection period will be extended. Re-calibration may be needed if the high RER is not due to hyperventilation. The beginning and end of exercise will be clearly marked. **Heart rate, Rating of Perceived Exertion (RPE) and blood pressure will be recorded at rest and during the last minute of each exercise stage**. The modified Borg Scale (Table 3) will be used with patients to obtain a RPE for dyspnea and fatigue. All measurements (HR, BP, RPE) **MUST** be obtained at peak exercise. These measurements will be sent to the Core Lab with the standard site report and the raw data from the metabolic cart.

At the end of exercise, the treadmill settings will be immediately decreased to 0 grade at 1.5 mph. The subject will continue to walk for one minute at this setting prior to stopping exercise. Each subject will be asked the reason for limiting exercise and this will be recorded.

Symptom limited maximal exercise testing is permitted. RER at peak exercise must be greater or equal to 1.1.

Table 2. Exercise Protocol: Modified Naughton Protocol [2]

Stage	Time (min)	Speed (mph)	Grade (%)
1	3	2	0
2	3	2	3.5
3	3	2	7
4	3	2	10.5
5	3	2	14
6	3	2	17.5
7	3	3	12.5
8	3	3	15
9	3	3	17.5
10	3	3	20

[2] Naughton J, Seveluis G, Balke B. Physiological responses of normal and pathologic subjects to a modified work capacity test. J Sports Med 1963; 3:201-207.

Table 3. Borg Scale [3]

Rating	Perception of Effort
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Very, very hard
20	

[3]Borg G. Perceived exertion as an indicator of somatic stress. Scandinavian J of Rehabilitation Med 1970;2(2):92-98.

Data Analysis - Measurements and Calculations

Data file exchange between the site, DCC and Core Lab will be accomplished using MiShare.

NOTE: CPX data should not contain patient's name or initials.

A copy of the file from the CPX machine will be sent to the DCC and one copy will be maintained in each patient file at the site. Each site is required to enter data onto the Cardiopulmonary Exercise Test Tracking eCRF in OpenClinica and submit their standard exercise report, 30 second averaged data tabulated in a time down table, and the graphs listed below via MiShare. If there is any additional information from the CPX exam not included in the standard file that the Investigator feels would be relevant to the Core Lab's assessment, please send it in a separate document and specify the reason for sending.

The following information is required on the 30 second averaged data table: VO_2 (mL/min), VO_2 (mL/kg/min), VCO_2 (mL/min), RER, VE/VO_2, VE/VCO_2, VE, HR, Respiratory rate, $PetO_2$, Pet CO_2

Peak VO_2 will be the highest continuous 30 second average of VO_2.

Oxygen Uptake Efficiency Slope (OUES) will be derived from the slope of VO_2 and VE 30 second averaged data expressed in L/min with VE on the x axis logarithmically transformed and VO_2 recorded on the y axis

$\underline{VE/CO_2 \text{ slope}}$ will be calculated from 30-second average data of VE and VCO_2 plotted to the ventilator threshold

Graphs should include at least 3 minutes of resting data and 3 minutes of recovery data. The following graphs should be submitted to the Core Lab:

- Graph 1: VO_2, VCO_2 vs. time
- Graph 2: VE/VO_2, VE/VCO_2 vs. time
- Graph 3: $PetCO_2$, $PetO_2$ vs. time
- Graph 4: VCO_2 vs. VO_2
- Graph 5: RER vs. time
- Graph 6: VE vs. time
- Graph 7: The composite Anaerobic Threshold Plot will include: VCO_2 , $PetO_2$, VE/VO_2, RER versus VO_2
- Graph 8: Oxygen Uptake Efficiency Slope
- Graph 9: VE/VCO2 slope

The key criteria used to select the anaerobic threshold will be the following:

1. The nadir for the ventilatory equivalent for VO_2 without change in the ventilatory equivalent for VCO_2.
2. The nadir for the ventilatory equivalent for $PetO_2$ without change in the ventilatory equivalent for $PetCO_2$.
3. The computerized V slope method. Intersection of the lines drawn between one minute after the end of warm-up and respiratory compensation (RC) point of the plot of VCO_2 versus VO_2.

16.6 Core Laboratory Coordination

The DCC will be responsible for ensuring that individual sites submit exercise data in a timely manner. Site personnel are required to record each submission of CPX data on the Cardiopulmonary Exercise Test Tracking eCRF in OpenClinica.

16.7 Core Laboratory CPX Data Submission Process

Electronic File Submission:

1. Download file(s) from CPX machine/computer

Med Graphics machine (must be COW file):

1. Site will create a folder on CPX computer desktop labeled REVIVE-IT
2. Close BreezeSuite software and open DBTools
3. Go to Tools → export → patients
4. Click visit date to organize visit date by chronological order

5. Highlight subject(s) to export
6. Under directory, select the REVIVE-IT folder on desktop
7. Click “Export” to export highlighted subjects to REVIVE-IT folder

SensorMedics machine:

1. Go to “File Manager” and list patient files
2. Select “F1” to list patients
3. Unlock data to permit download
4. Highlight the subject(s) you want to archive (i.e. download) and select “F7”
5. If using SensorMedics software Version 7.x or higher it will ask “Do you wish to create a secure….” Select “Esc” for NO. The software may also ask if you want to delete after archiving. Select “ESC” to keep the files on the SensorMedics machine (otherwise they will be removed and will not be able to be retrieved at a later date)

2. Complete CPX Tracking eCRF in OpenClinica

3. Submit the CPX file (either MedGraphics or Sensormedics) containing Tabular data of 30-second breath averages, and Graphs in color, signed and dated to the DCC via MiShare

   Note: File naming convention: CPX_SubjectID _VISITDATE*[DDMMMYYYY]*
   (i.e. CPX_UOM001_ 05JUN2015)

If the clinical site is unable to submit the files electronically:
(Should only be done for sites that do not have a MedGraphics or SensorMedics machine)

1. The site should send the following files via MiShare:
   - Tabular data of 30-second breath averages, signed and dated
   - Graphs in color, signed and dated

2. Notify the study team (REVCPXCore@umich.edu) once the documents have been sent via MiShare.

Submission of Data to Core Laboratory from the DCC

The DCC will produce a Cardiopulmonary Exercise Test Core Lab report, which includes data from the Cardiopulmonary Exercise Test Tracking eCRF and will send the CPX report and the CPX file to the Core Lab via MiShare. **Note:** Site data entry of the CPX CRFs must be completed in order for the DCC to run the report and send the file to the core lab.

The DCC will enter analysis data on behalf of the Cardiopulmonary Exercise Test Core Lab directly into the study CPX database. Core lab analysis will not be provided to research sites.

Feedback from the core lab including tips for improving future assessments will be sent to sites from the DCC as necessary.

SECTION 17: ECHOCARDIOGRAPHY CORE LABORATORY DATA HANDLING AND TRANSFER

17.1 Overview

For REVIVAL, all enrolled heart failure subjects will have an ECHO assessment at the Baseline B visit. ECHO data will be transferred to a central core lab for all REVIVAL subjects.

Quantitative echocardiography will be an essential component of documenting cardiac structure and function.

17.2 Objectives

An Echocardiography Core Laboratory will be based at the University of Pittsburgh, Pennsylvania**.** The primary objective of core laboratory data analysis is to ensure the following:

- Unified application of echocardiography protocol and study specific criteria
- Independent confirmation of study data
- Uniform test interpretation, thereby improving the analysis of echocardiography data

17.3 Collection Time Points

All subjects will have standard full echoes performed at the Baseline B visit.

Following completion of the transthoracic echocardiograms, studies will be forwarded to the Echocardiography Core Laboratory at the University of Pittsburgh.

17.4 General Comments on Echo Data Acquisition

- **DIGITAL data acquisition is the standard.** Record all studies in digital **DICOM format**. This is very important! Keep a copy of the CD or other digital medium and send the original to the core lab. Simultaneous recording on videotape will only serve as a back-up, as per the individual site's clinical routine. Do not send videotape to the Echo Core Lab.
- An **excellent quality** ECG signal should be obtained with a high amplitude R wave and recorded for gating of the digital acquisition system.
- **Harmonic imaging** is the default for all data acquisition. It is preferable to *slightly* overgain rather than to under gain, but the goal is for optimal endocardial definition.

- **Set 3-Beat Capture for each view, X 2**, for a total of 6 beats per view.
- **Spectral Doppler, Capture 2 Screens (2-3 beats per screen).**
- Record more beats if premature ventricular or atrial beats or atrial fibrillation is present.
- **WHEN IN DOUBT, RECORD MORE IMAGES**
- Adjust the depth for the apical images to include the entire left atrium and maintain the same depth setting for all apical images and Doppler signals that are required by the protocol. It is not necessary to narrow the sector angle for two-dimensional imaging
- Record Doppler spectral velocity signals at sweep speeds of 50-100 mm/sec. Use of excessive wall filter should be avoided.
- Maximize the size of the pulsed and continuous Doppler spectral velocity tracings by adjusting the scale and using the baseline. Optimize the gain to provide clearly defined spectral envelopes.
- Optimize Color Flow Doppler frame rate by narrowing the sector angle.
- Locate the continuous wave signal of tricuspid regurgitation from the parasternal and apical windows. The highest velocity waveforms will be analyzed.

17.5 General comments on Echocardiography Imaging Systems

In general, all digital echocardiography systems with DICOM recording capabilities may be used. The following are preferred equipment: GE Vivid 7 or E9, Philips IE 33, or Siemens (Acuson) Sequoia or newer, or Toshiba Artida.

17.6 Quality Control and Site Validations

The lead ECHO technician for each site will be required to sign the Delegation of Authority log as a study team member upon completion of required training. The lead ECHO technician will be responsible for training any other ECHO technicians within the department and for the delegation of collection of study data as required. It is expected that each site will have multiple technicians trained on REVIVAL ECHO collection so that appropriate back up is in place in cases where the lead ECHO technician is not available to perform the procedure.

Prior to submitting subject ECHO DICOM images, each center will need to submit qualifying test scans for review and approval by the Core Lab. No center can submit study subject ECHO DICOM images for analysis, until **one case of test data is accepted at the core lab that includes:**

- Image in correct format
- Adherence to the ECHO protocol
- Adequate transfer and reading of the data

The site should submit a qualifying test scan following the Echocardiographic Protocol outlined below in Appendix 15 prior to participation in the study and submission of actual subject scans.

The DICOM Image should be sent to the DCC via MiShare. REVIVAL sites participating prior to initiation of protocol version 6.0 with validation in place that have not had changes in ECHO equipment do not need to perform a second validation.

The DCC will notify the site of the results of the validation test. (See Appendix 10 Echo Core Lab Site Validation Notification)

17.7 Patient Identifier Entry – all studies

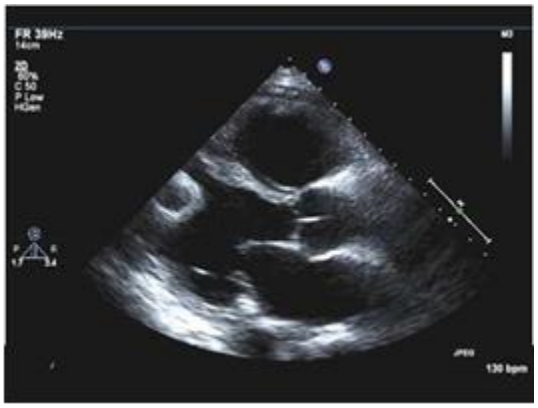
1. ***Under Last Name:*** Enter Subject Initials
2. ***Under First Name:*** Enter BLB (for Baseline B)
3. **Under ID**: Enter Subject ID (for example UOM-001, PIT-001 etc.)

17.8 Echocardiographic Protocol

A one-page summary of the following echocardiographic protocol is located in Appendix 15..

Full Echo (Baseline)

A. Parasternal Long Axis View



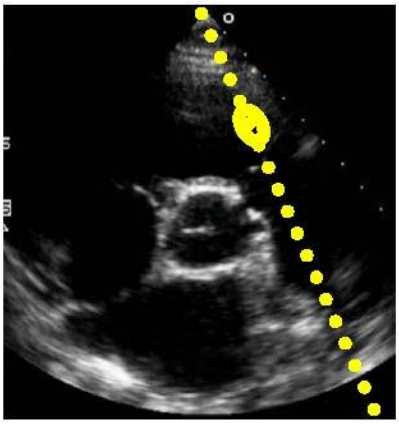
- 2-D recording at depth shown.
- **3-Beat Capture X 2**
- Measurements of LV end-diastolic diameter, end-systolic diameter.
- Color flow Doppler of the left atrium for mitral regurgitation and LVOT for aortic regurgitation.
- **3-Beat Capture X 2** for MR and AR

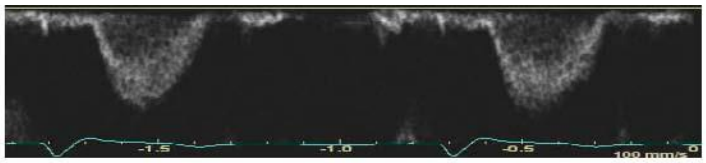
B. Right Ventricular Inflow Tract:

A careful color Doppler assessment of tricuspid regurgitation (TR) is performed.

- **3-Beat Capture X 2 for TR**
- Continuous wave Doppler of TR recorded for peak velocity **(Capture 2 screens).**
- Set spectral velocity sweep speeds at 50-100 mm/sec.

C. Parasternal





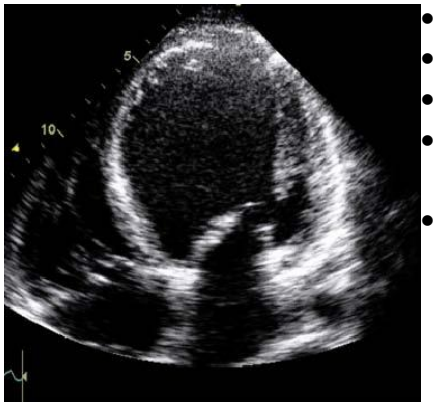
- Orient at base so RVOT is seen.
- Place Pulsed Doppler in RVOT
- Set spectral velocity sweep speeds at 50-100 mm./sec
- **Capture 2 Screens (2-3 beats per screen)**

D. Parasternal Short Axis View Mid-LV:

- Mid-LV short axis at papillary muscles level
- Orient LV as ***circular*** as possible,
- Adjust frame rate between 60-80 frames/sec
- **HAVE PATIENT HOLD THEIR BREATH for each capture**
- **3-Beat Capture X 2**

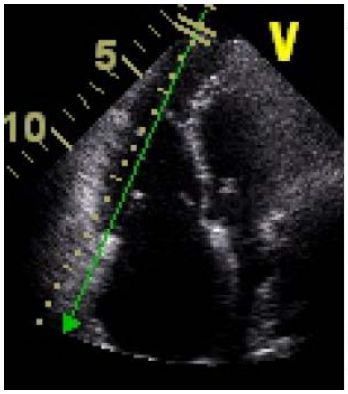
E. Apical 4 Chamber View:

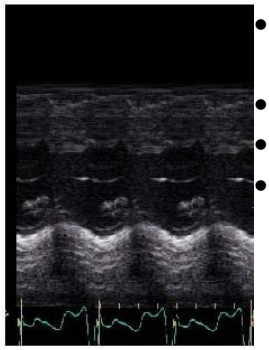
- Orient image to maximal LV apex to LA length.
- **Include all of LV apex** (Transducer may need to be moved laterally and inferiorly to do this).



- Center LV in sector.
- Include entire RV in Image.
- **Capture 3 Beats X 2**
- Color Flow Doppler of mitral and tricuspid regurgitant jets are obtained.
- **Capture 3 Beats X 2 (Color Flow)**

F. M-mode of Tricuspid Annulus (from Apical 4-chamber View)

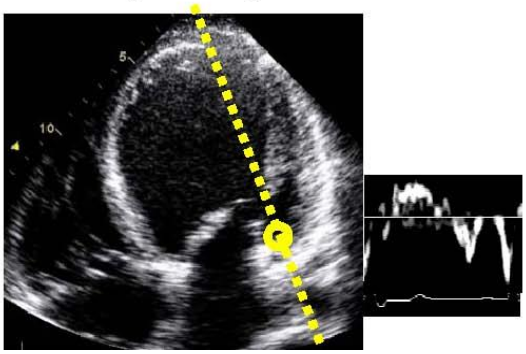




- M-mode at cursor through lateral tricuspid annulus
- Set sweep speeds at 50-100 mm/sec
- **Capture 2 screens**
- **Continuous Wave** Doppler of peak tricuspid regurgitant velocity. **Capture 2 screens**

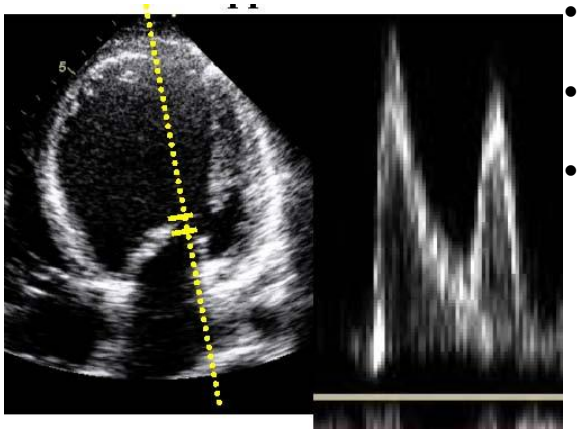
G. Pulsed-TDI *Mitral Annulus* (from Apical 4-chamber View)

Pulsed-TDI Preset: Please consult your local ***applications specialist*** for the optimal pulsed-TDI on your echo system for pulsed TDI of the mitral annulus, if not done already.



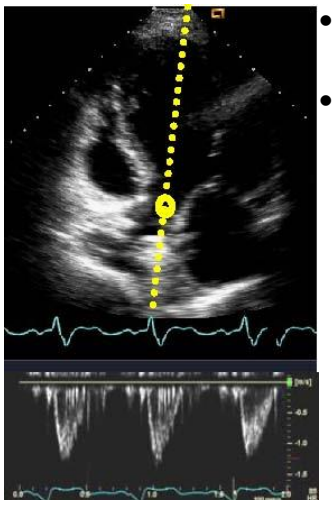
- Activate Tissue Doppler presets.
- Open Pulsed sample volume to 0.5-1.0 cm.
- Lateral Mitral Annulus : **Capture 2 Screens**

H. Pulsed-Doppler Mitral Inflow and LV Outflow (from Apical 4-chamber View)



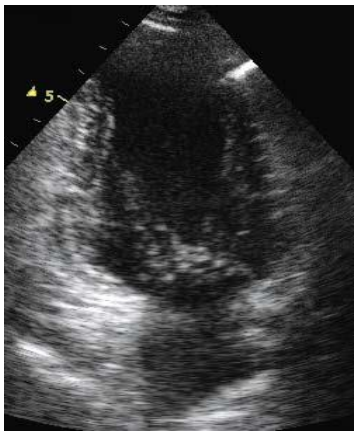
- **Pulsed Doppler of Mitral Inflow** at tips of leaflets (shown left).
- Set spectral velocity sweep speeds at 50-100 mm/sec
- **Capture 2 screens**

I. Pulsed Doppler of LVOT: (5 chamber view)



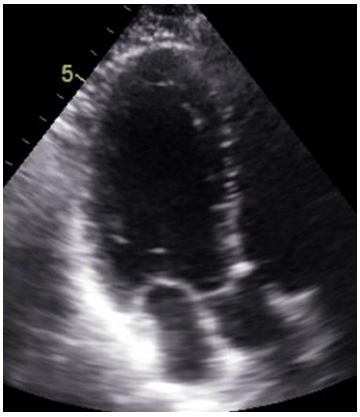
- Set spectral velocity sweep speeds at 50-100 mm/sec
- Place sample volume approximately 1 cm from aortic valve in center of LV Outflow track
- **Capture 2 Screens (2-3 beats per screen)**

J. Apical 2 Chamber View:



- Orient image to maximal LV apex to LA length.
- Include all of LV apex (Transducer may need to be moved laterally and inferiorly to do this).
- Center LV in sector **vertically** as possible.
- **Capture 3 Beats X 2**
- Color Flow Doppler of mitral regurgitant jets
- **Capture 3 Beats X 2 (Color Flow of MR)**

K. Apical long axis View:



- Orient image to maximal LV apex to LA length.
- Center LV in sector **vertically** as possible.
- **Capture 3 Beats X 2**

17.9 Digital DICOM File transfer procedures

Digital DICOM Requirements:

- All Echo-Doppler recordings must be in digital DICOM format. Do not send videotape.
- It is preferred to make a copy of the respective echo studies from the sites **digital archiving system or server.**
- **Please take care not to have the DICOM images "View Only" protected**.
- Each site must double check to make sure that the copied study ***is readable*** before it is sent to the echo care lab.
- As a "last resort" make copy of echo study in DICOM format on Echo System.
- Please make 2 copies of each entire study. One to send to the Core Lab, one to keep on-site as a back-up.

The clinical site should complete the Transthoracic Echocardiogram Tracking eCRF in OpenClinica.

Data file exchange between the site, DCC and Core Lab will be accomplished using MiShare.

The DCC will produce an Echocardiography Core Lab report and send the report and the DICOM images to the Core Lab via MiShare. NOTE: Site data entry of the ECHO CRFs must be completed in order for the DCC to run the report and send the file to the core lab.

The Echocardiography Core Lab will review the data. Results of the review will be entered by the Core Lab into the Transthoracic Echocardiogram eCRF in OpenClinica. This data is not held in the database accessed by the sites and will not be provided to the sites.

The Echocardiography Core Lab will enter analysis data directly into the study ECHO database. Core lab analysis will not be provided to research sites. Feedback from the core lab including tips for improving future assessments will be sent to sites from the DCC as necessary.

The REVIVAL DCC, Echocardiography Core Director, John Gorcsan, MD, and sonographer, Kathy Edelman-Anderson, RDCS are available to answer questions.

If you have questions send email to REVEchocardiography@umich.edu or call:

John Gorcsan, MD
Phone (412) 647-6570

Kathy Edelman-Anderson, RDCS
Phone (412) 802-6753

SECTION 18: BIOMARKER CORE LABORATORY DATA HANDLING AND TRANSFER

18.1 Overview

The Biomarker Core Laboratory will bank serum, leukocyte RNA from peripheral blood, and a genomic DNA blood sample for subjects who consent to participate in REVIVAL.

From the developed RNA/serum bank, the goal will be to develop novel peripheral biomarkers that will help to predict outcomes in subjects referred for DT. In addition, given the nature of the REVIVAL population, the DNA genomic bank presents a unique opportunity for analysis of the impact of genomic variation on heart failure outcomes.

The final selection of known 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 (procollagen types I and III, n-terminal telopeptide, procollagen type I c-terminal telopeptide, osteopontin), galectin-3, 8-isoprostane, IL-6, soluble receptor of type I alpha-TNF, ST-2, high-sensitivity CRP and troponin.

18.2 Objectives

A Biomarker Core Laboratory will be based at the University of Pittsburgh**.** The primary objective of the core lab is to:

- Determine if the peripheral transcriptomes and proteomics can identify subjects at higher risk for poor outcomes;
- Determine if genetic variation in advanced Heart Failure can predict outcomes or response to therapy

- Serve as the serum, DNA and RNA bank during REVIVAL to facilitate future investigation of novel biomarkers.

18.3 Hazardous Goods Training

Only Study Staff designated on the Delegation of Authority Log who have completed Hazardous Goods Training and have the training certificate on file with the DCC shall be permitted to mail samples for the REVIVAL Study.

If your site does not have a Hazardous Goods Training program available, Mayo Clinic training at the following link may be used as a substitute:

http://www.mayomedicallaboratories.com/education/online/dangerousgoods/

A copy of the training certificate must be submitted to the DCC.

NOTE: Please carefully review the patient's history to determine if samples should be labeled as "Infectious Substance Affecting Humans" and shipped per IATA Guidelines for Category A substances.

18.4 Collection Time Points

Blood specimens for biomarkers, leukocyte-derived RNA, and genomic DNA will be collected at the Baseline B visit.

18.5 Blood Collection and Shipping Kits

After all site initiation requirements are met, the DCC will provide approval for the Biomarker Core Lab to send the clinical site coordinator an initial supply of kits. All materials and mailing costs will be supported by the Core Lab and biomarker studies will be at no additional cost to the sites.

To obtain additional kits, complete Appendix 11, including the quantity of items and the date the supplies are needed, and send it to Karen Hanley-Yanez, at REVBiomarker@umich.edu or by fax 412-647-5724.

Please be aware that the biomarker kits have expiry dates. Sites must do routine inventory to ensure that an inventory of usable kits is maintained on site. The Biomarker Core Lab may grant kit extensions up to one week from the date of the expiry on the lab kit (depending on the type of kit). Please contact the DCC if an urgent kit extension approval is needed.

18.6 Initiation of the Biomarker Study

The Biomarker Core Lab will assist in establishment of protocols and techniques for participation in the REVIVAL Biorepository for peripheral RNA, serum, and genomic DNA.

18.7 Summary of Blood Collection

All patients will have blood sent to the Biomarker Core Lab for serum and RNA analysis. Eight (8) cc in a 10 cc red top tube will be collected for serum analysis and 5 cc will be collected in PaxGene tubes (two 2.5 cc tubes with clear fluid in them) for RNA analysis at the Baseline B visit.

An additional 8 cc in a purple top tube for genomic DNA analysis will be collected for patients who consent to do so at the Baseline B visit.

All samples can be kept at room temperature and should be shipped the same day via Fed Ex overnight using provided kits to the University of Pittsburgh for processing and storage.

(**Note:** Friday shipments of blood samples should be avoided but if unavoidable should be sent for Monday delivery as the Core Lab cannot routinely accept Saturday delivery).

If a subject withdraws consent and requests that their samples be removed from the Biomarker Core Lab inventory and destroyed, please contact the DCC to make arrangements. Please note that samples will not be destroyed automatically when a subject withdraws participation.

18.8 Specimen Preparation, Handling and Shipping of Blood Samples

A checklist to assist sites with the steps needed to prepare, handle and ship the REVIVAL blood samples is available in Appendix 12.

18.8.1 Specimen Collection, Preparation, Handling for Blood Collection for Serum and Total blood RNA

A total of 8 cc of blood will be collected in 10 cc red top tubes at the Baseline B visit for the serum sample. These tubes are to be provided by the Core Lab, but any common red top tubes such as those used for electrolytes, can be used (either two 5 cc tubes or one 10 cc). Please make sure that tubes are full, which generally means about 8 cc of blood in a 10 cc tube or approximately 4 cc each in the two 5 cc tubes.

A total of 5 cc of blood for RNA will be collected in Paxgene tubes (two 2.5 cc tubes with clear fluid in them) at the Baseline B visit.

1. Each tube should be labeled with the patient/subject ID code (letter and number code) and date drawn. No other identifying patient information should be placed on this specimen.

2. Serum tubes do not have to be mixed and can be shipped as drawn without further handling. For the RNA tube, **please invert the tube 10 times after**

obtaining the blood to ensure mixing of the blood with the solution of the PaxGene tube that preserves the RNA.

3. No further processing of blood is needed. Blood should be stored at room temperature until shipped. **Do NOT freeze or refrigerate the blood unless you have been specifically directed to do so.**

18.8.2 Specimen Collection, Preparation, Handling Genomic DNA

1. If the subject consents for it, an additional 8 cc of blood will be collected in a 10 cc purple top tube at the Baseline B visit.

2. Each tube should be labeled with the patient/subject ID code (letter and number code) and date drawn. No other identifying patient information should be placed on this specimen.

3. Genomic DNA tubes do not have to be mixed and can be shipped as drawn without further handling.

4. No further processing of blood is needed. Blood should be stored at room temperature until shipped**. Do NOT freeze the blood!**

18.8.3 Serum/Blood RNA and DNA Packaging

1. Blood for serum, blood for RNA and blood for DNA can be shipped together at room temperature in the same package.

2. Please ensure that each individual tube is labeled with the patient/subject ID code (letter and number code) and date drawn.

3. Place tubes in the small plastic bag provided, along with a single piece of gauze. Seal bag (ideally without much air trapped).

4. Place the bagged tubes in the styrofoam package provided. Make sure tubes fit in slots. The edges of the plastic bag will overhang the package, but do not fold inside the styrofoam, instead allow the excess to fold over the outside of the styrofoam.

5. Place the styrofoam package in the outer sleeve (small white box). Please secure both ends of the small box with a piece of routine scotch tape or packing tape.

6. Surround the small box with paper towels or newspaper and place the whole package in the brown corrugated fiberboard box. DO NOT overstuff the brown box. Place just enough surrounding material to prevent undue movement of the smaller box placed inside. Place the **UN 3373 Diagnostic Specimen** label on the outside of the fiberboard box.

Shipment of Biologic specimens not considered "dangerous goods" unless the patient is known to have an infection

DO NOT ship samples on ice or with ice packs!

7. Please utilize one of the pre-addressed FedEx labels for shipping to the core lab. **The shipments are to be sent FedEx express standard overnight with payment billed to Third party (DCC). No weekend deliveries.** If the pre-addressed FedEx labels are unavailable, the sample should be sent to the following address:

   Dennis McNamara, M.D.
   University of Pittsburgh Medical Center
   200 Lothrop Street
   630 Scaife Hall
   Pittsburgh, PA 15213
   Phone: (412) 383-8645
   FedEx Account Number: 376776239

8. Complete the Sample Collection for Serum Analysis eCRF (RVREG-024-Serum Collection), the Sample Collection for RNA Analysis eCRF (RVREG-025-RNA Collection), and if the subject consents, the Sample Collection for Genomic DNA Analysis eCRF (RVREG-026-Genomic Collection) in OpenClinica, print per directions in the eCRF Completion Guidelines and follow the shipping directions below.

18.8.4 Instructions for the Day of Shipping – Serum/Blood RNA/Genomic DNA

It is important that all samples be shipped the day they are drawn. On the day of shipping, the serum, RNA and DNA (if applicable) forms must be completed in OpenClinica. These forms will include the name of the shipper and the date of shipment, your site name and your site number, along with the date the sample was drawn. These eCRFs should be placed in the package with the specimens **AND** a notification MUST be sent to:

REVBiomarker@umich.edu

DO NOT ship samples on ice or with ice packs!

This will notify the DCC and the Core Lab to look for the shipment. Once the shipment is received, the Core Lab will fill out the bottom portion of the form and send to the REVIVAL DCC via MiShare confirming that the Core Lab has received the shipment. The REVIVAL DCC will enter the information into the OpenClinica study database.

SECTION 19: ADVERSE EVENT AND OUTCOME REPORTING

19.1 Overview

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 in subject 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. If a reportable outcome event takes place after the subject has consented, but prior to completion of Baseline A procedures, the outcomes should be collected and reported at the Baseline B visit time point.

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. **Planned procedures will not count as a heart failure related outcome.**

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.

19.2 Definitions

Adverse Event (AE): An adverse event is any undesirable clinical occurrence in a subject whether or not it is related to the study intervention. 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.

Serious Adverse Event (SAE): SAEs are defined by FDA regulation as any experience that

- results in a death 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.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Please note that the REVIVAL definition of hospitalization is any cumulative stay in a hospital or emergency department ≥ 24 hours (including time for observation), or any formal admission.

Unanticipated Problem (UP): A 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 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 AEs are not UPs, and many UPs are not AEs. However, some AEs are also UPs. For example, a SAE that is unexpected and at least possibly related to study participation is also by definition a UP. As stated above, a UP may not necessarily be an AE, 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 a UP that is not an AE.

19.3 Adverse Event Reporting Requirements

AEs will be collected from the time the subject signs the informed consent form until his/her participation in the study is considered complete.

Caregiver AEs will be collected from the time the caregiver signs the Caregiver consent form until his/her participation in the study is considered complete.

All Clinical Study Sites shall collect the following data as defined per protocol:

- AEs
- SAEs
- UPs

AEs occurring during or as a result of a research procedure that are noted by the PI will be recorded on the appropriate adverse event eCRF.

Within 24 hours of a study team becoming aware of any SAEs or UPs, the clinical site must submit the appropriate paper CRF and Cover Sheet (Appendix 13) to the REVIVAL DCC via MiShare.

> **NOTE:** AEs not meeting the definition of an SAE or UPs are not subject to the expedited reporting to the DCC using paper case report forms via MiShare as stated above. The AE information should be entered into the OpenClinica system within 2 weeks of knowledge of the event.

In addition to the MiShare transmission, the site must send an email notification to REVIVEIT-SAE@umich.edu indicating a report was submitted to the DCC. The email subject line should contain “safety report/<date of report>/<Initial or Follow-up>

> **NOTE:** subject information should NOT be included in this email.

The DCC will review the safety report. If additional information is required, the DCC will contact the clinical site.

The clinical site should enter the safety report information into the OpenClinica eCRF database within no more than 2 weeks of knowledge of the event.

The clinical site must provide any follow-up reports as soon as they are available, within 24 hours of receipt of new information.

The DCC will provide notification and the corresponding evaluation report to the NHLBI and participating clinical site investigators of any SAEs that are unexpected and related within 7 working days of safety report finalization by the DCC. In addition, the DCC will provide follow-up reports as soon as possible, but no later than 7 working days of finalization of reports containing new information.

AEs should be reported to site IRBs as required by local site policy and will be reported to the OSMB annually throughout the duration of the REVIVAL study.

19.4 Outcomes reporting

REVIVAL collects information about events throughout participation using the hospitalization CRF as a collection tool. REVIVAL outcomes include:

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

Data on these events will be collected for outcomes data collection purposes only and will not meet expedited reporting criteria as an adverse event if it was not directly related to a study procedure. It is recommended that site coordinators complete paper CRFs recording outcomes as they occur for patients and enter all gathered data as needed at the time of the REVIVAL visit.

Regarding the outcome of “MCSD” – this refers to the implantation of a durable, mechanical circulatory support device, whether investigational or approved for commercial use, that the subject leaves the hospital with. Examples include LVAD, BiVAD, RVAD, and Total Artificial Heart.

Regarding the outcome of “resuscitation status”, this information will be collected and anticipated to be available for all heart failure subjects for all routine REVIVAL visits. The “Unknown” option on the eCRF should only be completed in cases of Early Termination where the site is unable to obtain the DNR/DNI status from the subject, for example, in cases of death, subject unable to communicate, or lost to follow up.

Regarding the outcome of “entry into hospice”, for REVIVAL entry into hospice refers to both inpatient hospice or home hospice care.

SECTION 20: PROTOCOL DEVIATION REPORTING

20.1 Overview

Except in emergency situations, an intentional protocol deviation requires prior written approval from the REVIVAL DCC and appropriate IRB clearance at your clinical site. If, in the opinion of the National Co-Principal Investigators, these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior written IRB approvals are required.

20.2 Procedure

Protocol deviations should be reported to the DCC in a timely fashion and to the local IRB as per institutional guidelines. To report a protocol deviation, complete the appropriate eCRF. The OpenClinica database will notify the DCC of the completed eCRF.

20.3 Specific Guidance

The following deviation standards have been established for the REVIVAL study to ensure consistent management of deviation reporting:

Chemistry labs: Ensure a comprehensive metabolic panel is ordered. Occasionally, a few of the lab parameters are missing (ALT, AST, albumin, etc.). If values are missing, a protocol deviation will be required. Missing total cholesterol, uric acid, or INR is also a protocol deviation as these are research labs required per protocol at Baseline A, Baseline B, and the Month 12 follow up visit.

Hematology labs: Ensure CBC with platelets and differential count is ordered. WBC, hemoglobin, hematocrit, platelets, and lymphocytes are expected. If any are missing, this is a protocol deviation. If sample was collected and analysis attempted (e.g. platelets that are “clumped”), this is NOT a deviation.

6MWT: All values for HR, BPs, and BORG are expected. It is understood that in some cases the BP may not be possible to record. This should be noted in a discrepancy note to avoid a

request for a deviation. A protocol deviation will need to be completed if any other portions of the assessment are missing.

CPX Tracking: The stages provided on the eCRF should include rest through the recovery stage. HR should always be provided; if missing, this would be a protocol deviation.

Visit window clarification: The protocol states that "Baseline A procedures *should* be completed within two weeks of consent". If subjects need to come back to finish the Baseline A visit and it is outside the two-week window (but before the Baseline B visit), this is NOT a protocol deviation. Please make all reasonable attempts to complete Baseline A assessments within the time frame of two weeks.

SECTION 21: DATA MANAGEMENT AND MONITORING

21.1 Overview

Data will be managed by the DCC at the University of Michigan. Participating sites will enter data into the OpenClinica database.

21.2 Data Management Review

The DCC Clinical Data Manager will review and clean eCRF data on an ongoing basis.

21.3 Site Monitoring

The DCC is responsible for remote monitoring of enrolled subjects and caregivers. Monitoring will consist of, but may not be limited to, source document verification. Data elements needing remote verification will be requested from the site and sent to the DCC via MiShare. The purpose of study monitoring is to ensure informed consent is in place prior to any research procedures being performed and to support the integrity of study data collected in REVIVAL.

Feedback regarding any remote monitoring findings and any other identified trends will be sent to the site throughout REVIVAL. If any major concerns are identified, the REVIVAL Executive Committee and NHLBI will be notified.

SECTION 22: QUALITY ASSURANCE AND DATA SAFETY MONITORING

22.1 Quality Assurance

The DCC will ensure quality data by using standard and streamlined processes for data

collection and processing, data entry and data monitoring. The Clinical Data Manager will monitor CRF completion rates, missing data and data discrepancy rates to identify site performance and protocol adherence issues which will ultimately result in improved data quality.

In addition, the REVIVAL Observational Safety Monitoring Board will advise on such matters as futility of study enrollment as well as issues related to data completeness, data integrity and data analyses as well as the success of the study in terms of meeting stated scientific aims which will ultimately result in improved data quality.

SECTION 23: INTERMACS REGISTRY

As REVIVAL has a hard endpoint for LVAD implant, heart failure subjects who receive an LVAD will not continue to be followed through REVIVAL. Heart failure subjects in REVIVAL receiving an **LVAD should be entered by the clinical site into INTERMACS® at the time of implantation per INTERMACS® guidelines**.

SECTION 24: STUDY COMPLETION AND CLOSE-OUT PROCEDURES

24.1 Overview

Study close-out activities will be performed to confirm that the site investigator's study obligations have been met and that post-study obligations are understood. Close-out activities include, but are not limited to:

- Ensure all required regulatory documents are on file and current
- Ensure that all AEs have been reported and appropriately documented
- Ensure that documentation of notification to IRB of all safety updates is on file
- Ensure that all CRFs have been completed with adequate resolution of all data queries
- Ensure the IRB has been notified of study discontinuation and ensure this notification is placed in the Investigator Regulatory File
- Review the record retention policy and publication policy with the Investigator

24.2 Procedures

Close out activities will be managed virtually. The DCC will provide a close out checklist to the site detailing activities that need to be accomplished to close out the REVIVAL study at the site.

Once all preliminary close out activities are accomplished, a close out call with site representation from the Principal Investigator and the primary study coordinator will be scheduled.

The final status of study enrollment will be noted; including number of enrolled subjects, number of withdrawn/discontinued subjects and number of completed subjects and caregivers will be summarized on the close out visit memo prepared by the DCC.

A Study Close-out memo to the site will be created and forwarded to the clinical site for inclusion in the regulatory binder and the DCC Trial Master File.

SECTION 25: APPENDICES

Appendix 1: Study Flow Diagram
Appendix 2: Delegation of Authority Log
Appendix 3: Screening Log
Appendix 4a: Data Exchange using MiShare: Sending a Package
Appendix 4b: Data Exchange using MiShare: Accessing a Package
Appendix 5: eCRF Completion Guidelines
Appendix 6: Baseline A and B Worksheets
Appendix 7: Follow Up Visit Worksheets
Appendix 8: Early Visit Termination Worksheets
Appendix 9: CPX Core Lab Site Validation Notification
Appendix 10: ECHO Core Lab Site Validation Notification
Appendix 11: Biomarker Supply Re-order Form
Appendix 12: Biomarker Core Checklist
Appendix 13: Safety Reporting Cover sheet
Appendix 14: REVIVAL QOL Questionnaires
Appendix 15: Echocardiography Protocol