Cardiothoracic Surgical Trials Network

Cardiovascular Cell Therapy Research Network

LVAD THERAPY: EXPLORING THE EFFECT OF INTRAMYOCARDIAL INJECTION OF MESENCHYMAL PRECURSOR CELLS ON MYOCARDIAL FUNCTION

MANUAL OF PROCEDURES

Sponsored By NHLBI, NINDS, CIHR

CT Surgery Network Research Group
In collaboration with
Cardiovascular Cell Therapy Research Network

Data Coordinating Center
InCHOIR
Mount Sinai School of Medicine
New York

CONFIDENTIAL

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I. MANUAL OF OPERATIONS REVISIONS

Revision	Section	Change	Reason	Page
2.0	Various	Various administrative and clerical changes	MOP consistency, correction or clarification	Through-out
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2.0	DCC Study Team Roster	Updated Quality Monitor and Core Laboratory contact information	Staff Update	6-7
2.0	Maintenance of Regulatory Documents	Added clarification on documents to be monitored by DCC	MOP Clarification	9
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II. DATA COORDINATING CENTER STUDY TEAM ROSTER

A complete trial directory for the Cardiothoracic Surgical Trials Network (CTSN) and the Cardiovascular Cell Therapy Research Network (CCTRN) and all documents approved for the trial may be found at the following website address: www.inchoir.org/lvad-website.

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III. CLINICAL CENTERS

The trial will be conducted in up to 25 clinical centers selected by the CTSN/CCTRN LVAD Cell Therapy Operations Committee, which is comprised of CTSN and CCTRN Investigators, CTSN and CCTRN DCC leadership, and NHLBI leadership. Clinical centers within the Networks who were interested in trial participation completed the LVAD Cell Therapy Site Informational Document, providing the Operations Committee with key information regarding the sites' qualifications, ability to recruit the study population, and the availability of adequate resources to conduct the trial.

In August 2011, the LVAD Cell Therapy Site Informational Document was released to all the CTSN and CCTRN sites. The Operations Committee discussed the Informational Documents submitted by CTSN and CCTRN sites on September 8, 2011 for trial participation consideration. The Operations Committee selected 13 clinical centers to participate in the first wave of study start-up. Due to Network resource logistics, clinical center participation is being rolled out in

two waves. The selected centers are all highly experienced LVAD and heart failure centers with a proven track record of conducting clinical trials in this area.

The clinical centers participating in the first wave of trial start-up are as follows:

1. Baylor Health Care System
2. Cleveland Clinic Foundation
3. Columbia University Medical Center
4. Duke University Medical Center
5. Minneapolis Heart Institute Foundation
6. Montefiore-Einstein Heart Center
7. Ohio State University Medical Center
8. Sharp Memorial Hospital
9. Texas Heart Institute
10. University of Florida
11. University of Maryland
12. University of Minnesota
13. University of Pennsylvania

IV. REGULATORY DOCUMENTATION

Sites are required to submit the following documents to the DCC's Regulatory Manager by email or fax prior to site initiation:

- Signature and Delegation of Duties Log
- Conflict of Interest Statements (CTSN and FDA 3455)
- Completed Form FDA 1572
- Protocol Document Approval Form
- IRB roster and Federal Wide Assurance (FWA) number
- Copy of IRB approval for protocol, informed consent, HIPAA, and Release of Medical information forms
- Investigator and Co-Investigator Curriculum Vitae (CVs)
- Study Personnel Licenses
- Clinical Center Laboratory Certification and normal ranges
- Specialized Training Certifications:
    - HIPAA, GCP and Human Subjects Protection Training for all staff
    - IATA/Dangerous Goods Training
    - Surgical Procedure Webinar Training Attestation
    - Coordinator Neurocognitive Training Certification
    - Echocardiography Webinar Training Attestation
    - Biospecimen Core Laboratories Training Attestation
    - Cell Technician Webinar Training Attestation
    - NIH Stroke Scale Training Certificate
    - Unblinded Study Drug Preparation Training Attestation
    - EDC Training
- Freezer Technical Information Survey Approval

Clinical Study Agreement with the CTSN DCC, InCHOIR, Department of Health Policy, Mount Sinai School of Medicine, must be fully executed prior to site initiation and enrollment.

A. *Maintenance of Regulatory Documents*

Each site will maintain a regulatory binder for the protocol that must be updated as new revisions of study documents are made and approvals are renewed.

The following documents are expected to be current and readily available for monitoring at site visits. A randomly chosen subset of these documents will be monitored at each site visit to ensure compliance with regulatory requirements.

- Copies of all revisions of the protocol
- Copies of all Protocol Document Approval Forms
- All versions of the Completed Form FDA 1572
- Conflict of Interest Statements (CTSN and FDA 3455)
- Copies of all revisions of the informed consent
- Informed Consent Log
- Copies of all revisions of the Revascor™ Investigator's Brochure
- All IRB correspondence
- IRB approvals for the protocol and informed consent
- CMS approval ,if required by regional CMS guidelines
- Clinical Study Agreements
- Signed and dated CVs for all study staff
- Monitor site visit log
- Site signature and delegation log
- Correspondence with DCC
- Clinical site echocardiography laboratory accreditation
- Specialized Training Certifications:
    - HIPAA, GCP and Human Subjects Protection Training for all staff
    - IATA/Dangerous Goods Training
    - Surgical Procedure Training Attestation
    - Coordinator Neurocognitive Training Certification
    - Echocardiography Webinar Training Attestation
    - Biospecimen Core Laboratories Training Attestation
    - Cell Technician Webinar Training Attestation
    - NIH Stroke Scale Training Certificate
    - Unblinded Study Drug Preparation Training Attestation
    - EDC Training
- Revascor™ Inventory Form
- Revascor™ Shipment Packing List
- Patient Contact Log
- Protocol Consent Version Tracking Log
- Serious Adverse Events/IND Safety Reports Log
- Protocol Deviation/Violation Log
- Biospecimen Shipment/Retention Log
- Manual of Procedures

- Source Document Worksheets/Case Report Forms (CRFs) (CRFs are available on the home page of the Electronic Data Capture (EDC) system)

B. *IRB Requirements*

Sites are required to follow their Institutional guidelines for obtaining initial approval by the IRB and for submitting continuing reviews to the IRB submission. The DCC will send clinical centers a reminder letter 90 days prior to IRB approval expiration date to help sites plan the annual renewal of the study accordingly. A copy of the IRB letter of re-approval must be forwarded to the DCC and filed in the site regulatory binder.

The informed consent must be reapproved in accordance with the clinical center's IRB polices or at least annually.

The DCC will provide the sites with DSMB protocol approval letters.

C. *Changes in Study Personnel*

The DCC should be informed of any personnel changes in Principal Investigator, co-investigator, and/or coordinators in writing within 15 business days of any change.

Complete documentation for the new study personnel should be sent to the Regulatory Manager at the DCC. This should include:

- Role in Study
- Complete contact information including telephone, fax, email address, and beeper number
- Curriculum vitae (signed and dated)
- GCP and HIPAA certification
- Clinical Study agreement, as applicable
- Specialized Training Certification, as applicable (e.g. Neurocognitive, NIHSS, EDC)
- Conflict of Interest Form (COI)—CTSN and FDA
- Protocol Training Attestation Form
- Signature on Delegation of Duties Log

V. STUDY COMPLIANCE

A. *Investigator Certification*

The protocol outlines specific requirements for investigator participation in the trial. Surgical and cardiology qualifications for all participating investigators will be collected as reported in the site in the Site Informational Document and regulatory binder.

- Surgical investigators must have performed at least 10 LVAD implantation procedures annually (averaged over a 2 year period) and a minimum of 25 LVAD implants to date.
- Heart failure/transplant cardiology investigators must have a minimum of 5 years of experience as an attending physician caring for critically ill cardiac patients and patients on LVAD support.

B. *Good Clinical Practices (GCP)/Human Subjects Protection Certificate*

All investigators, coordinators and other study staff who are involved in the care of study patients, and/or research data collection must submit certification that they have successfully completed their institutionally required GCP or Human Subjects Protection to the DCC prior to site initiation.

C. *HIPAA Certification*

All investigators, coordinators, and other study staff must provide documentation to the DCC prior to enrollment that they have successfully completed the institutional requirements to ensure patient rights, privacy and security under HIPAA.

D. *Conflict of Interest*

Two conflict of interest statements (FDA Form 3455 and a CTSN Conflict of Interest Statement) will be collected from all study investigators to ensure that no investigator may exert undue influence that may bias the trial. Any conflict of interest identified must be explained in writing and will be reviewed by the NIH and managed in compliance with 21 CFR 54 and 42 CFR 50(f). Conflict of interest statements will be updated as changes occur and no less than annually.

E. *Patient Confidentiality*

Confidentiality of all patient records will be maintained according to HIPAA guidelines. All unique patient and hospital identifiers will be removed prior to review of source documentation. Study Investigators, site Institutional Review Boards (IRBs), the DCC (InCHOIR), the Event Adjudication Committee (EAC), the NHLBI, Angioblast Systems, Inc. (now known as Mesoblast, Inc.), the Data Safety Monitoring Board (DSMB) and the FDA may review source documentation for enrolled patients as necessary to ensure patient safety.

F. *Protocol Deviations*

Efforts to maximize adherence to the study protocol will be made through careful and comprehensive training, early review of study data submitted via the EDC system, and routine communication with all site investigators. Despite the best efforts of the clinical investigators, protocol deviations and/or violations may occur. They may include but are not limited to randomizing an ineligible study participant, failing to obtain informed consent, failing to maintain IRB and related study documents, or administering the wrong treatment.

Relevant violations will be reported to the DCC, who will notify appropriate parties, including the study site Principal Investigator, NHLBI, NINDS, FDA and/or DSMB. The DCC will instruct each clinical center to maintain a log of protocol deviations and/or violations and report them routinely to the Regulatory Manager and/or Trial Monitor.

The following information will be documented on the Protocol Deviation/Violation Reporting Form and signed by the PI:

- Date of occurrence
- Date site aware of occurrence
- Subject ID
- Detailed description of violation/deviation/participant non-compliance
- Steps taken to resolve the particular occurrence

- Whether violation/deviation has occurred in any other subjects at site
- Whether site had preapproval from DCC for protocol deviation

All protocol deviations and violations will be listed in the protocol-specific Deviation/Violation log. This log will indicate the date of submission of the deviation or violation to the local IRB and the date of IRB acknowledgment. This log must be maintained at each site.

VI. INVESTIGATOR AND STUDY PERSONNEL TRAINING

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during the site initiation conference call, at an in-person meeting and/or on training conference calls, in advance of patient enrollment. Training will ensure that the investigators and all members of the team are thoroughly familiar with the intramyocardial injection procedure, the clinical trial protocol, and management of the patient.

A. *Protocol Training*

All study coordinators and VAD coordinators are required to attend a protocol training webinar, which includes a review of regulatory-required items, highlights of the protocol, randomization process, treatment intervention day overview, LVAD wean assessments and biospecimen collection. In addition to providing an overview of the overall study flow, another goal of the webinar is to review the proposed roles for the study coordinator and VAD coordinator. The training emphasizes the need for close collaboration amongst the study team members. Study coordinators and VAD coordinators are required to sign an attestation form documenting their participation. The attestation form is to be filed in the site regulatory binder and a copy forwarded to the DCC.

B. *Surgical Intramyocardial Injection Procedure Training*

All surgical investigators are required to participate in a Surgical Intramyocardial Injection Procedure Training session and submit an attestation of training completion to the DCC. The goal of the interactive webinar is to review the cell therapy injection technique for the trial and to ensure procedural consistency by the surgical investigators at the sites. Only surgeons who meet the protocol defined threshold for credentialing and have completed the training will be certified to perform the study intervention on study participants. The attestation form is to be filed in the site regulatory binder and a copy forwarded to the DCC.

Cardiology site investigators, study coordinators, VAD coordinator and other integral study staff members will receive an overview of the intramyocardial injection procedure during the site initiation conference call in advance of patient enrollment.

C. *Electronic Data Capture System (EDC) Training*

All site coordinators (study, VAD and regulatory) who are responsible for randomizing consented patients and entering data will be trained to input the data for the protocol into the web-based electronic data capture system. This training will consist of an in-person demonstration, web-based teleconference demonstrations and a web-based training site: https://www.inchoir.org/lvad-train/main.

Cell Technicians (primary and back-up) will be trained to input the data on the randomization form in the electronic data capture system. Training is done using an interactive web-based teleconference demonstration.

All training participants are required to sign an attestation form documenting their training participation. The attestation form is to be filed in the site regulatory binder and a copy forwarded to the DCC. Upon receipt of this form, the DCC Data Manager will provide the user with access to the EDC training site. Coordinators and cell technicians are required to show proficiency in the training site before production site access is provided. All regulatory documents must be on file for an individual user before any production site access is granted.

EDC user names and passwords must be kept confidential and not shared among other study personnel.

D. *Neurocognitive Training*

Study coordinators must be trained by the CTSN Neurocognitive Core Laboratory personnel in the administration of the neurocognitive testing. Upon completion of training, sites will receive certification and a recorder to conduct the testing from the core laboratory. Neurocognitive assessments must only be administered by personnel who have received proper training in the full battery and have been certified by the CTSN Neurocognitive Core Laboratory.

The certificate is to be filed in the site regulatory binder, and a copy should be forwarded to the DCC.

E. *NIH Stroke Scale (NIHSS) Training*

The study coordinators must receive on-line training in the NIHSS in order to administer this scale. A certificate can be printed and should be filed in the site regulatory binder at the completion of the training. A copy should be forwarded to the DCC. The certification program can be found at: http://www.nihstrokescale.org/.

F. *Echocardiogram Training*

The Echocardiography Core Lab will train the designated echocardiography attending and technician at each site in the protocol, the Core Lab Operating Procedures and transmission of data. Training will be conducted via a webinar and will include image acquisition for the full and limited image collection and transmission of data.

At least one echocardiography attending and one echo technician are required to attend a training session and sign an attestation form documenting participation. The attestation form is to be filed in the site regulatory binder and a copy forwarded to the DCC.

G. *Cell Technician Training*

Prior to enrollment, the study product manufacturer, Mesoblast, Inc., will train the designated site cell technicians on study product storage, preparation, dispensing and destruction via a webinar. All Cell Technicians are required to attend a training session and sign an attestation form documenting training participation. This document is to be filed in the site regulatory binder, cell technician operations binder and a copy forwarded to the DCC.

Each site is also mandated by the CTSN/CCTRN LVAD Cell Therapy Operations Committee to complete a mock run of study product and syringe preparation prior to first enrollment. It is recommended that the mock run follow site initiation to minimize the time between the mock run and first enrollment. Mesoblast, Inc. will provide each site with a training unit to conduct the mock run, and the DCC will work with the site to coordinate the delivery of the training unit. The training units arrive on dry ice and should be used within 24 hours of receipt. Mesoblast has strongly recommended that training units are not stored in a freezer to eliminate the risk that training units could be confused with Investigational product. Because dry ice shipments have to be shipped for use within 24 hours and are not shipped over a weekend period, mock runs cannot be completed on Mondays. Each site should practice in the EDC by creating a new patient and randomizing a patient during the mock run and/or before first enrollment. The Cell Technician, Study Coordinator and Principal Investigator are required to sign an attestation form documenting completion of the mock run. The attestation is to be filed in the site regulatory binder with a copy placed in the cell technician operations binder. A copy of the attestation is also to be forwarded to the DCC.

H. *Biospecimen Collection Training*

An overview of the biospecimen collection procedures, including a review of the Core Laboratories, is part of the protocol training webinar. Additional training of the biospecimen collection procedures will either be conducted by a representative from the Texas Heart Institute Core Laboratory either during an in-person conference or by the DCC core laboratory representative during the site initiation conference call. For more information, please see the Biospecimen Core Laboratory Manual.

I. *Site Initiation*

In order to be **eligible** for the site initiation conference call, the following requirements must be satisfied:

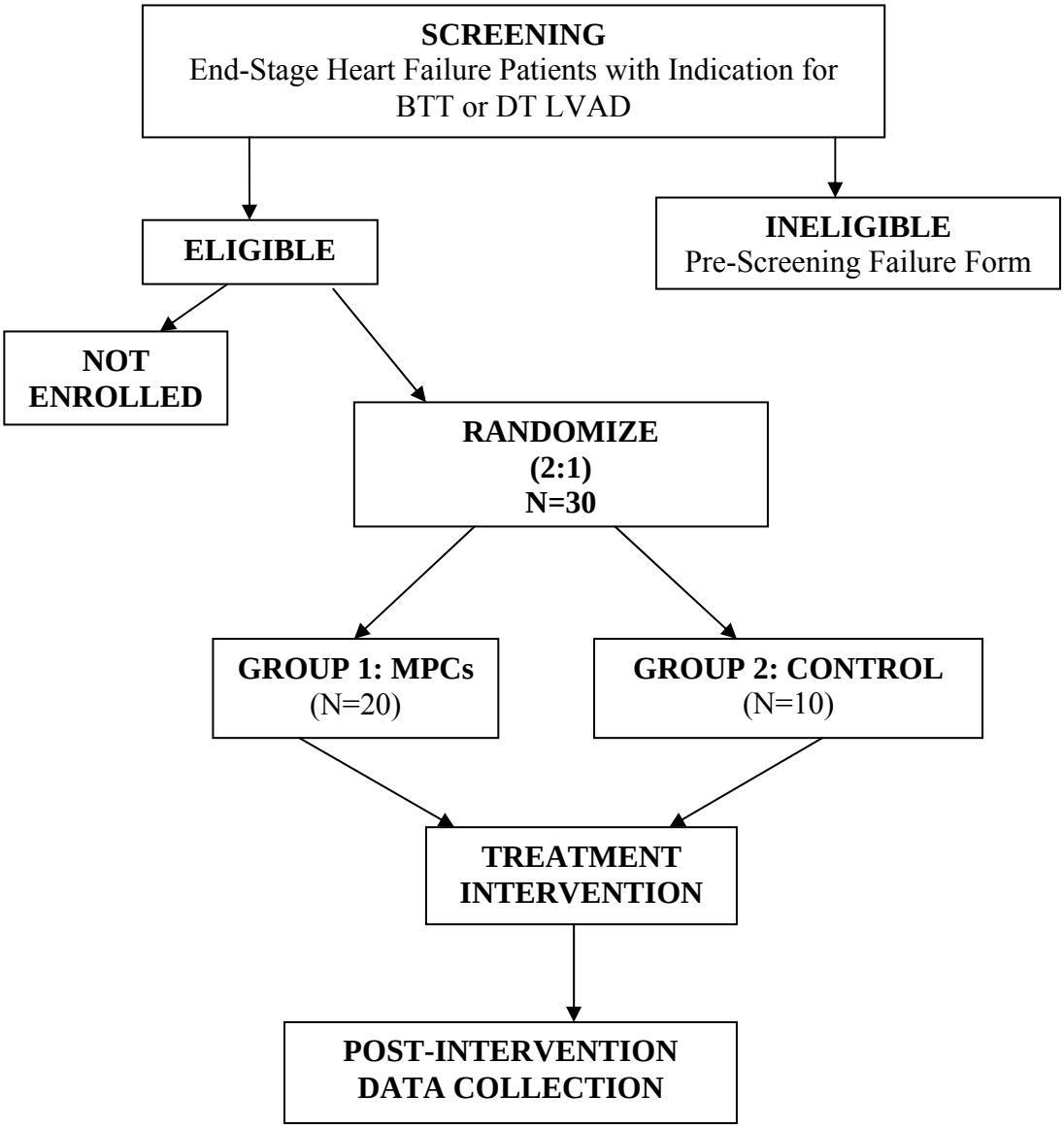
- IRB Approval for Protocol Rev. 1.4
- Fully Executed Contract
- Regulatory Check List Completed
- Training Check List Completed

Representatives of the DCC will conduct the site initiation prior to enrollment of the first patient for each site. The Principal Investigator, co-surgical investigator (if applicable), lead cardiologist, study coordinator, VAD coordinator, cell technicians (primary and back-up), echocardiology representative (attending or technician) and regulatory coordinator are all required to attend the site initiation conference call.

If it is not possible to have all required parties convene on one call (extreme circumstances), the DCC will consider multiple site initiation calls, although it is preferable for all site participants to be present for the same discussion. Sites will not be opened to enrollment until all required parties have been initiated.

All site initiation participants must review the training slides and sign an attestation that they completed training. This document is to be filed in the site regulatory binder and a copy should be forwarded to the DCC.

VII.STUDY FLOW



VIII. RECRUITMENT

A total of 30 patients with advanced congestive heart failure who are scheduled to be implanted with an FDA approved LVAD as Bridge-to-Transplant (BTT) or Destination Therapy (DT) will be enrolled into the trial. It is anticipated that 3 patients per month will be recruited at each clinical site and that enrollment will be complete within 10-12 months.

A. *Pre-Screening Failure Form*

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine their eligibility for inclusion in the trial. Pre-screening failure patients are patients who are not consented and not enrolled into the trial. These patients will be recorded in the Pre-Screening Failure form in the EDC. The data collected is HIPAA compliant and does not include patient identifiers. The screening quarter, screening year, age, gender and reason for ineligibility or non-enrollment are collected on the form. The log provides the DCC and NHLBI with an overview of the reasons why patients are ineligible for the trial enrollment.

IX. SCREENING AND ELIGIBILITY CRITERIA

Candidates who meet all inclusion criteria and no exclusion criterion will be eligible for the trial regardless of gender, race, or ethnicity.

A. *Inclusion Criteria*

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation;
2. Age 18 years or older;
3. If the subject or partner is of childbearing potential, he or she must be willing to use adequate contraception (hormonal or barrier method or abstinence) from the time of screening and for a period of at least 16 weeks after procedure;
4. Female subjects of childbearing potential must have a negative serum pregnancy test at screening;
5. Admitted to the clinical center at the time of randomization;
6. Clinical indication and accepted candidate for implantation of an FDA approved implantable, non-pulsatile LVAD as a bridge to transplantation or for destination therapy.

B. *Exclusion Criteria*

1. Planned percutaneous LVAD implantation;
2. Anticipated requirement for biventricular mechanical support;
3. Cardiothoracic surgery within 30 days prior to randomization;
4. Myocardial infarction within 30 days prior to randomization;
5. Prior cardiac transplantation, LV reduction surgery, or cardiomyoplasty;
6. Acute reversible cause of heart failure (e.g. myocarditis, profound hypothyroidism);
7. Stroke within 30 days prior to randomization;
8. Platelet count < 100,000/ul within 24 hours prior to randomization;
9. Active systemic infection within 48 hours prior to randomization;
10. Presence of >10% anti-HLA antibody titers[1] with known specificity to the MPC donor HLA antigens[2];
11. A known hypersensitivity to dimethyl sulfoxide (DMSO), murine, and/or bovine products;
12. History of cancer prior to screening (excluding basal cell carcinoma);

[1] Documented by clinical site laboratory
[2] Documented by Core Lab

13. Acute or chronic infectious disease, including but not limited to human immunodeficiency virus (HIV);
14. Received investigational intervention within 30 days prior to randomization;
15. Treatment and/or an incomplete follow-up treatment of any investigational cell based therapy within 6 months prior to randomization;
16. Active participation in other research therapy for cardiovascular repair/regeneration;
17. Prior recipient of stem precursor cell therapy for cardiac repair;
18. Pregnant or breastfeeding at time of randomization.

C. *Concomitant Investigational Modalities*

Medications and medical substances and devices not approved by the FDA for study subjects are prohibited during participation in the study.

X. INFORMED CONSENT, HIPAA, RELEASE OF MEDICAL INFORMATION

A. *Obtaining Informed Consent*

Obtaining informed consent and timing for the informed consent process must be consistent with the individual center's institutional IRB and privacy policies, and in accordance with CTSN guidelines. The consent form must have been approved by the DCC. The investigators or a designated individual will provide a thorough explanation of the objective, patient responsibilities, risks and benefits of the study, and will fully address concerns raised by the patient and/or family. The consent process (and its documentation) must begin prior to screening data collection and all protocol defined procedures. This is to ensure that all subjects will be given adequate time to review the informed consent document, and consider participation in the trial.

Patients should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time. All patients will be required to sign informed consent to participate in this study. As part of the informed consent process, all patients will be given the opportunity to opt in or out of the biological specimen collection process.

The person obtaining consent should be consistent with institutional policy. For instance, some centers require that only Investigators (PI, Sub-I or Co-I) obtain consent. Additionally, some centers may have the VAD coordinator obtain consent as they may have a closer relationship to the patient. The section on page 8 of the consent form template "Person Containing Consent" is intended to capture study team members who obtain consent and are not the PI or study coordinator.

The consent process must be documented in the medical chart and a signed copy of the consent must be given to the patient. In addition, the investigator must:

- Document any questions addressed with the patient and/or family during the informed consent process in the medical chart
- Confirm that all signatures on the informed consent are complete and dated

- File the original signed informed consent in the subject's study binder.

Although the consent form template states participants will not receive compensation, the budget is provided to the site as a "per patient" total amount, which will allow each site to determine how funds are allocated for this trial. The consent form template also states that participants and/or their "health insurance company[ies] remain responsible for…procedures, test visits, and hospitalizations." The majority of the study visits are standard of care. Each site should determine which assessments are non-standard of care locally. Again, the budget is provided to the site as a "per patient" total amount allowing the site to allocate funds based on institutional standards.

The consent form template also includes language regarding LVAD surgery and bypass risks. Some IRBs have asked that the consents include standard of care risks, and this information is provided to satisfy this request. IRBs may require that additional risks be added to their site-specific informed consent even after FDA's approval of the risk section. They may also rule that the risks are covered under the specific surgical consent form that the patient will sign to undergo the investigational intervention because the devices are approved. Sites are allowed to add additional risks if their IRB requires. The DCC recommends that coordinators do not volunteer adding risks simply because they think that their IRB may ask for these risks to be added. Sites must submit any consent modifications to the DCC for review prior to submitting to their IRBs.

B. *HIPAA and Release of Medical Information Forms*

Each site is required to follow their institutional policy for HIPAA Clinical Research Authorization and Release of Medical Information. Consent to authorize release of medical records to the trial investigators, monitors, sponsors (NHLBI, NINDS and Mesoblast, Inc.) and the DCC must be obtained for trial participation.

C. *Informed Consent Log*

Each study participant will be listed on an informed consent log that collects information on the date of informed consent and version of the consent form used. This log will also track reasons and dates of re-consent, if necessary.

XI. SCHEDULE OF ASSESSMENTS

Assessment	Pre-Implant	Randomiz-ation	LVAD Implant/ Inter-vention (INT)	12 hours post INT	1 Day post INT	7 Days post RAND	21 Days post RAND	30 Days post RAND	45 Days post RAND	60 Days post RAND	90 Days post RAND	Every 60 Days^	Month 6 post RAND	12 Months post RAND ‡	Event Driven	End Study
Window				**± 4 hours**	**+1**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**	**± 14**	**± 14**		
General																
Informed Consent	X															
Pre-Screening Failure Form	X															
Demographics	X															
Medical History	X															
Physical Examination	X				x	x	x		x	x	x	x		x		
Medications	X				x	x	x		x	x	x	x		x		
Immunotherapy Medication	X														x	
Laboratory Assessment	X			x		x	x		x	x	x	x		x		
Immunologic Assessment	x§							x			x		x	x		
Biospecimen: Chemo and Cytokine Analyses	X				x	x		x		x	x		x	x		
Biospecimen: Phenotypic and Functional Analyses	X				x			x			x					
Eligibility Evaluation	X															
Randomization & Treatment Assignment		x														
Hospitalization			x												x	
Surgical Procedure			x												x	
Cardiac																
Hemodynamics	X		x†					x$^{\Delta}$		x$^{o,\Delta}$	x^$^{\Delta}$	x^$^{\Delta}$				
Echocardiography	X							x		x	x	x		x		
Cardiac Histology#			x												x#	
Six Minute Walk								x		x	x	x		x		
Intervention Injection Verification			x													
Wean Assessment								x		x	x	x		x		
Neurological																
NIH Stroke Scale**	X														x	
Modified Rankin Scale**	X														x	
Neurocognitive Testing	X										x					
Event Driven Data																
Adverse Events															x	
Early Stopping Events			x	x	x	x	x	x	x	x	x	x		x	x	
Mortality															x	
Pump Retrieval and Explant (&/or Postmortem) Examination															x	
Missed Visit						x	x	x	x	x	x	x	x	x		
Study Completion/Early Termination																x
End of Study/Investigator Statement																x

† If <u>not</u> collected pre-implant then collect in the OR immediately prior to LVAD implantation

$^{\Delta}$ Hemodynamics by right heart catheterization to be performed during LVAD wean ***only at centers where this is standard practice for clinical LVAD wean monitoring***

[o] Dobutamine right heart catheterization is performed for all patients at 90 days. **The 60 day post-randomization time point is optional and may *only be conducted at centers where it is standard clinical post-LVAD practice.***
^ Every 60 days (±7) thereafter until cardiac transplantation or until 12 months post randomization, whichever comes first.
§ A screening anti-HLA antibody result must be obtained at the clinical site within 6 months of randomization. If this result is greater than 10 percent, a second sample must be obtained and sent directly to the Immunologic Core Lab for specificity analysis. In addition, a separate baseline sample must be taken to be sent to the Biospecimen Core Lab. Some local site laboratories now provide a calculated PRA rather than a measured PRA. For consistency across clinical centers, sites with laboratories conducting calculated PRAs will send their screening sample to the Immunological Core Lab for a measured analysis.
[#] At native heart explantation for cardiac transplantation or at autopsy (if applicable)
[**] Event driven within 72 hours of a neurological event, and at 30 (±10) and 60 (±10) days post neurological event
[‡] Final data collection

XII. PRE-IMPLANT DATA COLLECTION

A. *Informed Consent*

Prior to screening data collection and all protocol defined procedures
A signed informed consent form, which has been approved by the DCC and each individual site's IRB, is required. Please see Section X (Informed Consent, HIPAA, Release of Medical Information) for further information regarding the consenting process.

For the purpose of primary analysis, patients meeting the eligibility criteria are considered enrolled in the study at time of randomization.

B. *Demographics*

During screening, following informed consent
The following information will be recorded for each trial participant:

- **Confirmation that the patient has signed the Informed Consent form, HIPAA Clinical Research Authorization form and a Release of Medical Information form**
- **First, middle, and last initial**
- **Date of birth**
- Zip code
- Ethnic origin
- Racial category
- **Sex**
- Payor information
- Highest level of education

The above bullets noted in **BOLD** are required for randomization and highlighted in the EDC system for ease of use. Unless all the required items are completed electronically, the patient cannot be randomized. Please view Section XIII (Randomization) for complete randomization instructions.

C. *Medical History*

Within 7 days prior to randomization

The following information will be collected for each trial participant:

- Primary etiology of heart failure
- Cardiovascular disease history
- Cardiovascular procedure history
- Valve repair/replacement history
- Cerebrovascular disease history
- Peripheral vascular disease history
- Non-cardiovascular disease history
- Current medical condition
    - UNOS status
    - INTERMACS classification
    - NYHA classification
    - Respiratory status
    - Renal status

D. *Physical Examination*

Within 7 days prior to randomization

Physical examination will include the following:

- Vital signs, including temperature and respiratory rate
- Anthropometrics (height and weight)
- Neurologic exam
- Cardiovascular exam
- Pulmonary exam
- Abdominal exam
- Extremity exam
- Nutritional assessment
- Other clinically relevant findings

E. *Medications*

Within 7 days prior to randomization

All medications that the patient received within 7 days prior to randomization will be recorded.

- Cardiovascular therapy
- Inotropic or Vasoactive therapy
- Anticoagulation
- Antiplatelets
- Antibiotic therapy

F. *Immunotherapy Medication*

Within 30 days prior to randomization

All immunosuppressive medications/procedures that the patient received within 30 days prior to randomization will be recorded.

- Therapy
    - Intravenous Immunoglobulin
    - Plasmapheresis
    - Intravenous Cyclophosphamide

  - Intravenous Rituximab
  - Intravenous OKT3
  - Atgam
  - Thymoglobulin
  - Other (specify)
- Courses/Procedure
- Start date of therapy
- End date of therapy

G. *Laboratory Assessment*

Within 24 hours prior to randomization

The baseline laboratory assessment consists of the following tests:

- Blood Type and Cross
- Urine or serum beta HCG (IU/L) for women who have the potential to become pregnant
- Hematology
  - White blood cell count (10^3/mL) , Red blood cell (10^3/mL), Hemoglobin (g/dL), Hematocrit (%), Platelet count (10^3/mL), Neutrophils (%), Lymphocytes (%)
- Chemistry Panel
  - Sodium (mM/L), Potassium (mM/L), HCO_3 or CO_2 (mM/L), Blood Urea Nitrogen (mg/dL), Creatinine (mg/dL), Total Bilirubin (mg/dL),
- Liver Function Test
  - Alanine Aminotransferase (ALT; U/L), Aspartate Aminotransferase (AST; U/L), Alkaline Phosphatase (IU/L), Albumin (g/dL) and Lactate dehydrogenase (LDH; U/L)
- Coagulation Profile
  - Prothrombin time (PT/sec), Partial Thromboplastin Time (PTT/sec), International Normalized Ratio (INR)
- Plasma Free Hemoglobin (PFH)

Blood may be drawn from the central venous catheter.

H. *Biospecimen Analysis*

Within 24 hours prior to randomization

Instructions on collection, processing, storage and shipping the biospecimens to the core laboratory are located in the Biospecimen Core Laboratory Manual.

As a reminder, **plasma is to be isolated, aliquoted and frozen within 1 hour of blood draw at the clinical site.** Peripheral blood samples will be obtained at baseline for the following analyses:

- Phenotypic assessments
  - Stro1+, CD3, CD11b, CD14, CD19, VEGFR2, CD31, CD34, CD45, CXCR4+, and CD133
- Cytokine quantification:
  - IFN-γ, IFN-α, IP-10, Eotaxin, MIP–1α, MIP-1β, RANTES, TNF–α, MIG, IL–1RA, GM–CSF, IL–1β, IL–2, IL–4, IL–5, IL–6, IL–2R, MCP–1, IL–7, IL–8, IL–

10, IL–12 (p40⁄p70), IL–13, IL–15, IL–17, VEGF, ANG-1, ANG-2, SDF-1, PDGF, and SCF

- Colony forming ability of peripheral blood derived cells

I. *Immunologic Assessment*

Screening percent reactive antigens (PRA) will be obtained within 6 months prior to randomization (must be at least 2 weeks following receipt of PRBC or platelet administration, if applicable). Baseline Immunologic assessment samples will be obtained within 24 hours prior to randomization.

A screening anti-HLA antibody serum sample will be obtained and analyzed locally ***at the clinical site.*** Local immune reactivity results for % IgG Class I, and IgG Class II will be recorded in the EDC by the coordinator.

Some local site laboratories now provide a calculated PRA rather than a measured PRA. For consistency across clinical centers, sites with laboratories conducting calculated PRAs will send their screening sample to the Immunological Core Lab for a measured analysis.

The EDC will not allow randomization of a participant with an anti-HLA antibody titer > 10%. In this case a follow-up serum sample must shipped directly to and run at the Immunologic Core Laboratory at Baylor College of Medicine for cross-analysis of the recipient antibodies to the MPC donor HLA antigen profile. Please reference the Biospecimen Core Laboratory Manual (Appendix D) for information on the collection, processing and shipment of the second sample. When screening a patient for the trial, site personnel should anticipate the possible requirement of this second core laboratory immunological screening and allow adequate time (up to 7 days), this will otherwise delay randomization.

Coordinators will record in the EDC whether the samples were obtained, the date the samples were collected and the local anti-HLA results for % IgG Class I and % IgG Class II. Should a second sample be sent to the Immunologic Core Laboratory, sample collection date and confirmation sample was shipped will also be recorded. The Immunologic Core Laboratory will record specificity to the MPC donor anti-HLA antigens for the second sample.

In addition, a baseline anti-HLA antibody serum sample will be obtained for shipment to the Biospecimen Core Lab to be directed for analysis at the Immunologic Core Lab.

Anti-murine and anti-bovine antibodies

Testing for anti-murine and anti-bovine antibodies will be performed to detect any sensitization to xenogenic components in the manufacturing process of the MPC product, Revascor.

J. *Hemodynamics*

Within 7 days prior to treatment intervention

If clinically indicated, right heart catheterization should be performed within 7 days *prior to randomization*. In the absence of clinical indication, the hemodynamics must be obtained in the operating room *prior to treatment intervention* and LVAD implantation.

The following hemodynamics assessed by right heart catheterization will be are to be recorded:

- Central venous pressure (CVP)

- Pulmonary artery pressures
    - Systolic (PA_S)
    - Diastolic (PA_D)
    - Mean (PA_M)
- Pulmonary capillary wedge pressure (PCWP)
- Transpulmonary gradient
- Cardiac output (CO)
- Cardiac index (CI)
- Pulmonary artery oxygen saturation (PAO_2 sat)
- Pulmonary vascular resistance (PVR measured in Wood Units)

K. *Echocardiography*

Within 7 days prior to randomization

A complete echocardiogram as described in the protocol (Appendix IV: Echocardiography Procedures) will be performed prior to LVAD implantation to assess ventricular size, function and regional wall motion. The echo will be analyzed by the Echocardiography Core Laboratory.

Echocardiography image acquisition date, time and date shipped to the Echocardiography Core Laboratory will be recorded.

L. *NIH Stroke Scale*

Within 7 days prior to randomization

The NIH Stroke Scale will be performed prior to LVAD implant for baseline neurological assessment. Please follow the instructions for completing the NIH Stroke Scale in Appendix VIII of the protocol, which includes recording the date and time of the exam.

M. *Modified Rankin Scale*

Within 7 days prior to randomization

The Modified Rankin Scale will be performed prior to LVAD implant for baseline neurological assessment.

N. *Neurocognitive Testing*

Within 7 days prior to randomization

For patients who do not speak English or French as a first language, completion of the batteries is not required and should not be precluded from participating in the trial. Please follow the instructions in Appendix IX of the protocol for completing the assessments listed below.

Cognitive performance prior to LVAD implant will be assessed using the following battery of tests:

- Hopkins Verbal Learning Test
- Trailmaking Form A and B
- Digit Span
- Digit Symbol
- MCG Complex Figures
- Controlled Oral Word Association (COWA)

The testing will take a total of 45 minutes and will be administered by study personnel trained and certified by the Duke University Neurocognitive Core Laboratory. Results from these tests will be independently scored by investigators from the Neurocognitive Core Laboratory. All neurocognitive batteries will be tape recorded and the de-identified recordings sent to the core lab for quality assurance evaluation.

Coordinators are asked to record the whether the test was completed, the date of the testing and the date the tests were sent to the core laboratory.

The Trailmaking Part B assessment of the Neurcognitive battery is required by both this study protocol and the INTERMACS registry at the pre-implant and 90 day post-randomization time points. The battery should only be administered once at any given time point. The results from the Trailmaking Part B performed as part of the trial can be used to meet the requirements of the INTERMACS registry.

XIII. RANDOMIZATION

After the site investigator has confirmed that patient meets all eligibility criteria for trial participation, the coordinator may begin randomization process using the EDC. Randomized patients will be given an identification code by the EDC. A representative from the DCC will be available to discuss any questions regarding patient eligibility.

Participants are to be randomized within 24 hours prior to the LVAD implantation and treatment intervention.

Selected demographic, immunologic assessment and laboratory values are required to be entered into the EDC to prior to randomizing the participant. The EDC will not allow randomization unless the following fields are completed in the system:

- LVAD01 (Demographics)
  - Confirmation that patient signed Informed Consent, HIPAA Authorization and Medical Release Information Form
  - Subject initials
  - Date of birth
  - Sex
- LVAD02 (Immunological Assessment)
  - Confirmation of site anti-HLA sample collected
  - Anti-HLA sample date
  - IgG Class I and Class II site results of $\leq 10\%$ or core lab verified non-donor specific results of $> 10\%$
- LVAD03 (Laboratory Assessment)
  - Pregnancy test result of either negative or N/A
  - Pregnancy sample date
  - Platelet count result of > 100,000/ul

Upon completing the required EDC fields with source documented values, the Eligibility Evaluation form (LVAD04) containing a checklist of inclusion and exclusion criteria will be

generated in the EDC. The PI or cardiologist co-investigator is required to complete and sign a printed copy of the Eligibility Evaluation CRF to verify that the patient meets all eligibility requirements for this trial. The study coordinator will electronically sign the Eligibility Form following confirmation from the investigator.

The Randomize button will appear and the Randomization form (LVAD17) will be automatically generated. The study coordinator or PI must electronically sign the form certifying the randomization of the patient. *The signing of this form also confirms the start time of the 24 hour window in which treatment intervention and LVAD implant must be performed.* Sites do not have to wait the full 24 hours to proceed with the study intervention. The 24 hour window after randomization allows the study personnel adequate time to plan the logistics of the intervention.

For the purpose of primary analysis, patients meeting the eligibility criteria are considered enrolled in the study at time of randomization.

Once the Randomization form has been signed, the EDC system will generate the Treatment Assignment form (LVAD17a**). The Treatment Assignment form is only visible to the unblinded cell technician in order to maintain blinding of all other site personnel.** The randomization assignment is automatically generated based on a pre-determined randomization scheme. The cell technician must complete and electronically sign the form, certifying that the blinding of the treatment assignment will be maintained and that the assignment has been read and understood.

It is important for the study coordinator to immediately alert the cell technician that a participant has been randomized and provide information regarding the timing of the treatment intervention.

Sites must alert the DCC as soon as possible should any adverse or clinical event occur within the 24-hour window between randomization and intervention that might delay intervention or lead to patient exclusion.

XIV. TREATMENT ASSIGNMENTS AND MASKING

Patients will be enrolled in a single dose cohort and randomized in a 2:1 allocation to intramyocardial injection of study product or control at the time of LVAD implantation.

Group 1 (n=20): 25 million MPC (Revascor™)
Group 2 (n=10): 50% Alpha-MEM/42.5% ProFreeze NAO Freezing Medium/7.5% DMSO (Control)

Revascor™
Revascor™ is an investigational product and has not been approved by the FDA for any indication. Although Angioblast holds an IND for Revascor ™, the CTSN DCC, InCHOIR,

holds the IND for this study of Revascor™. The IND number is 13967, and Dr. Deborah Ascheim is the DCC representative for the IND.

Rationale for use of placebo
Intramyocardial needle sticks in and of themselves, have been demonstrated to induce angiogenesis within the myocardium. Since historical controls are fraught with selection bias, and active controls would be confounded by the intramyocardial needle stick issue, the decision was made to use randomized controls. The FDA was in favor of the randomized controlled design as well. The NIH Protocol Review Committee required that the control group receive the cell preservation solution injections as currently defined in the protocol.

A. *Masking*
This is a double-blind, sham procedure controlled trial*. In order to maintain blinding of investigators, the study intervention solutions will be thawed and prepared for intramyocardial injection by designated personnel (cell technician) at the site with very limited interaction with the study investigators, coordinators or the patient.* The syringes, once prepared will appear identical for both groups. Site personnel and patients, as well as the Data Coordinating Center (DCC) investigators (with the exception of one statistician), the Principal Investigator, and all core laboratory study personnel will be blinded to treatment assignment.

It is recommended that sites use **3M™ Steri-Strip™ Elastic Skin Closures E4546** for blinding the injection syringes. The 3M™ Steri-Strip™ Elastic Skin Closures E4546 are ¼ inch x 4 inch (6mm x 10mm) beige colored sterile flexible strips are supplied in packages of 10 strips. Due to the flexible material, the steri-strips easily stretch around the injection syringe and the beige steri-strip color provides the required protocol blinding. The 3M™ Steri-Strip™ Elastic Skin Closures E4546 are also easy to write on for marking the 1ml on the syringe.

B. *Preparation of Study Product and Injection Syringes*
Instructions for preparing the study product and the injections syringes can be found in Appendix I and Appendix II of the protocol, as well as in Appendix I of this document, the training video and Cell Technician Operation Binders supplied to the sites

As a reminder, allogeneic MPCs must be stored in the vapor phase of LN2 at -196ºC to -140ºC until ready for use. Each site will complete a Freezer Survey as part of study start-up that will be reviewed and approved by Mesoblast, Inc. Sites will not receive study product until acceptable study product storage conditions have been identified. Please refer to the Investigational Brochure for study product storage requirements. Temperature logs will be monitored to verify study product was stored under the appropriate conditions.

Once the site has completed all regulatory and start-up requirements and scheduled the Site Initiation with the CTSN DCC, Mesoblast, Inc. will coordinate the initial shipment of study product to the site with the CTSN DCC. Sites will receive study product after completion of their site initiation and mock run and once all regulatory and training obligations have been satisfied. Study product will be delivered in transport Dewars and each bag of study product will be stored in a product cassette measuring 3.75 inches x 6.25 inches x 0.25 inches. Initial shipment of study product will include up to 2 bags of Revascor™ (MPC) and up to 3 bags of Control (50% Alpha-MEM/42.5% ProFreeze NAO Freezing Medium/7.5% DMSO). Study

product will be shipped to the address supplied by the site for storage at either their Cell Therapy Lab or Research Pharmacy.

The unblinded representative (cell technician) is responsible for ordering replacement study product directly from Mesoblast, Inc. using the contact information and directions provided in the Cell Technician Operations Binder. It is important to have adequate back-up on site in the event that study product bags are compromised or not injected within 75 minutes of thaw time since they will have to be discarded. In order to ensure that there is no delay in randomizing the next patient, sites should place reorders no later than 24 hours after randomization. Please be aware that replacement product order cannot be fulfilled overnight. Dewars must be prepared 24 hours in advance to deliver product to your site. Please refer to the "Mesoblast Clinical Shipment Request Schedule" to find the appropriate lead times for product re-order.

The site Cell Technician is also responsible for completing the Investigational Product Tracking Log located in the Cell Technician Operations Binder. An unblinded DCC representative will assist with ordering, tracking and verification of the site correctly following the randomization scheme.

Sites are required to return the transport Dewar within 24 hours of receipt to Lonza. Please follow the instructions in the Cell Technician Operations Binder and Appendix I of the protocol for returning the Dewar to Lonza. As a reminder, all liquid nitrogen must be evaporated before sending the container back.

Mesoblast, Inc. is supplying the 18-gauge Monoject spinal needle required by the protocol for study product preparation. Delivery of the initial shipment of 18-gauge Monoject spinal needles will arrive with the study product and syringe preparation mock run training unit. Sites are responsible for ordering replacement 18-gauge Monoject spinal needles directly from Mesoblast, Inc. using the directions provided in the Cell Technician Operations Binder.

As described in Appendix I of the protocol and demonstrated on the training video, 7 ml of air will be injected into the study product bag to assist in displacing the contents of the bag. Should 7 ml of air not be enough to aid in the displacement of bag contents, cell technicians may inject more air to help inflate the bag and retrieve product. Prior to aspirating the product from the bag, sites may invert the bag and slowly inject 10cc of air above the solution line into the thawed product. In addition to inflating the bag, this will also help reduce air bubbles and possibly help in retrieving the product.

Per Appendix II of the protocol, four sterile 5ml syringes with a ¾ inch 23- gauge needle are required as part of the study drug injection procedure.

C. *Unblinding*

This study is a double-blind design. Neither the patient, physician nor sponsor will be aware of the treatment group to which the patient has been assigned. The well-being of the patients taking part in the study will always take priority over any other consideration when the decision as to whether or not to break the blind is to be taken.

The study code should only be broken for valid medical or safety reasons where it is necessary for the PI or treating healthcare professional to know which treatment the patient is receiving before the participant can be treated. To request that a treatment assignment be unblinded, please contact the DCC Principal Investigator and Regulatory Manager once the event has been related to treatment by the PI. The site will not break the blind for a patient without the DCC Principal Investigator approval. Participants may also be unblinded at the request of the Data Safety Monitoring Board.

Participants and sites will be unblinded to the randomization assignment following the completion of the 12-month visit for the last patent enrolled and after the data has been locked.

XV. TREATMENT INTERVENTION AND LVAD IMPLANT

LVAD implantation with the assigned treatment intervention must be administrated within 24 hours following randomization.

A. *Cardiac Histology*

Myocardial core samples will be obtained **prior** to the intramyocardial injections from two separate locations within the apical core. Samples will be processed and stored for histopathology, immunohistochemical analyses of neovascularization and cardiomyocyte proliferation and PCR-based detection of donor cell engraftment. Each sample will be approximately 2 cm x 1 cm x 0.5 cm in dimension. Please follow the instructions in the Biospecimen Core Laboratory Manual for tissue collection, processing, storage and shipping.

Coordinators are asked to record the following information:

- Number and location of tissue samples
- Date of shipment to core laboratory
- Time in 10% buffered formalin, where applicable

When labeling the tubes for tissue collection at implant, sites should record the region as "apical core"

B. *Intramyocardial Injections of Study Product*

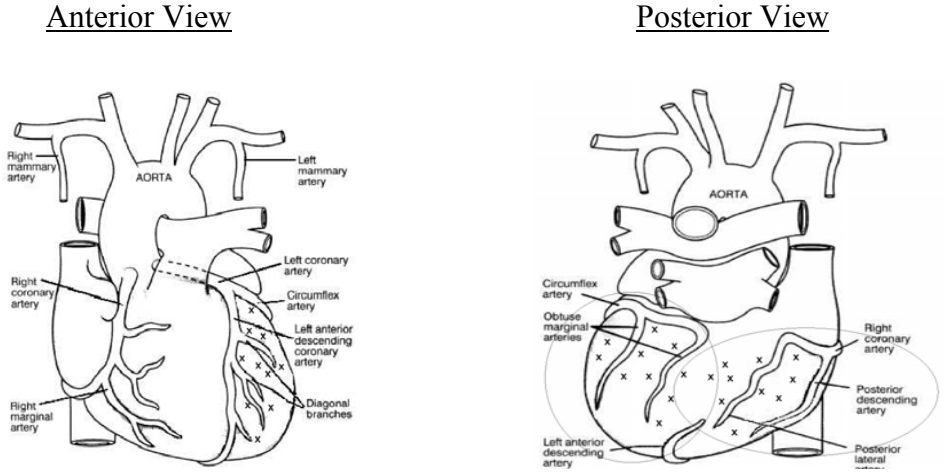
The coordinator and cell technician will work together to ensure that the four 5 ml syringes with ¾ inch, 23 gauge needles containing study product are prepared per protocol and maintained on the sterile field in the OR. Coordination of cell preparation and delivery to the OR is critical as **study product thawed longer than 75 minutes must be discarded and a new cryobag will need to be prepared.**

The intent of the procedure is to inject study product intramyocardially across as much of the left ventricular myocardium as possible. A total of 16-20 epicardial injections of 0.2 mL each (not to exceed a total of 4.0 mL) will be performed. The reason for the range is to account for differences in patient heart size and stability during surgery. The focus should be on the inferior, lateral and posterior walls with 6-7 injections done per wall. Five injections of 0.2 mL each totaling 1 mL of study product are expected per syringe. The injection process should take place within 15

minutes and must be completed within 75 minutes following thawing of the study product. Each syringe should be gently rocked by the study coordinator, cell technician or OR personnel during any downtime or delay to prevent clumping of study product.

Intramyocardial injections can be done on either a beating heart or while the patient is on bypass. Consider injecting cells during or around the time of LV apical cannula guide implantation as the heart is positioned for maximal access to the entire left ventricle. Injections should be made from an oblique angle into the mid-myocardium, with particular attention to avoid injection into the LV cavity. Injections should be made slowly with 0.2 ml injected over 5 seconds into each epicardial location. The needle should then be held in place for an additional 5 seconds before removing. A total of 4.0ml will be delivered into the myocardium. Recommended target injection sites are illustrated by the x-markers in the diagram (Figure 1). The intent is for the injections to be made diffusely across the entire free wall of the LV.

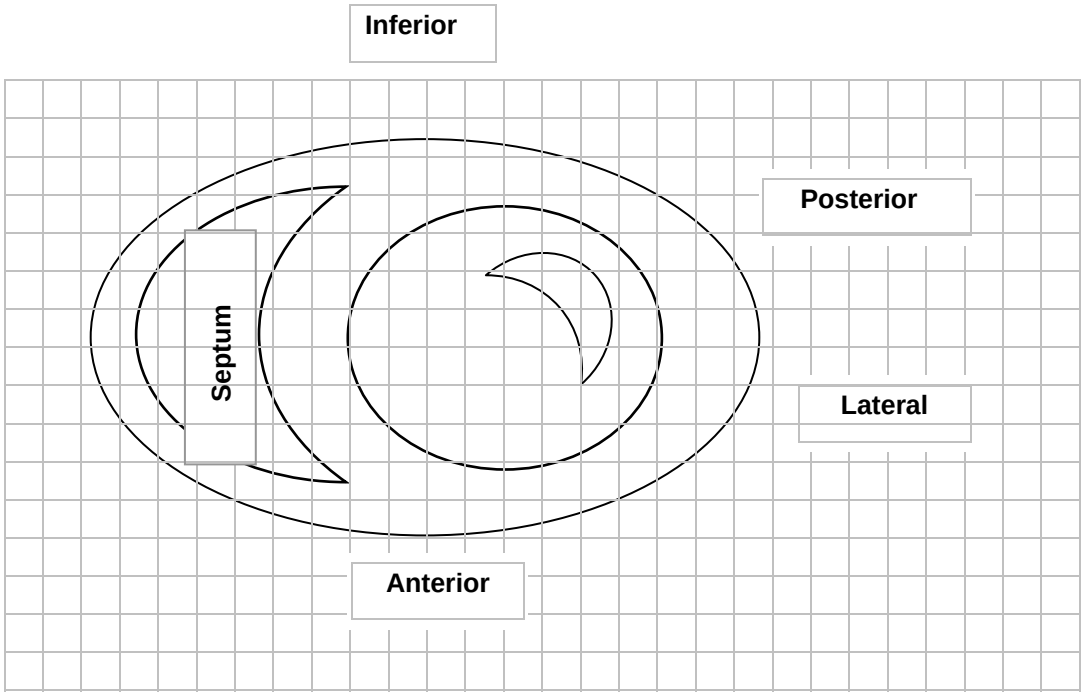
Figure 1



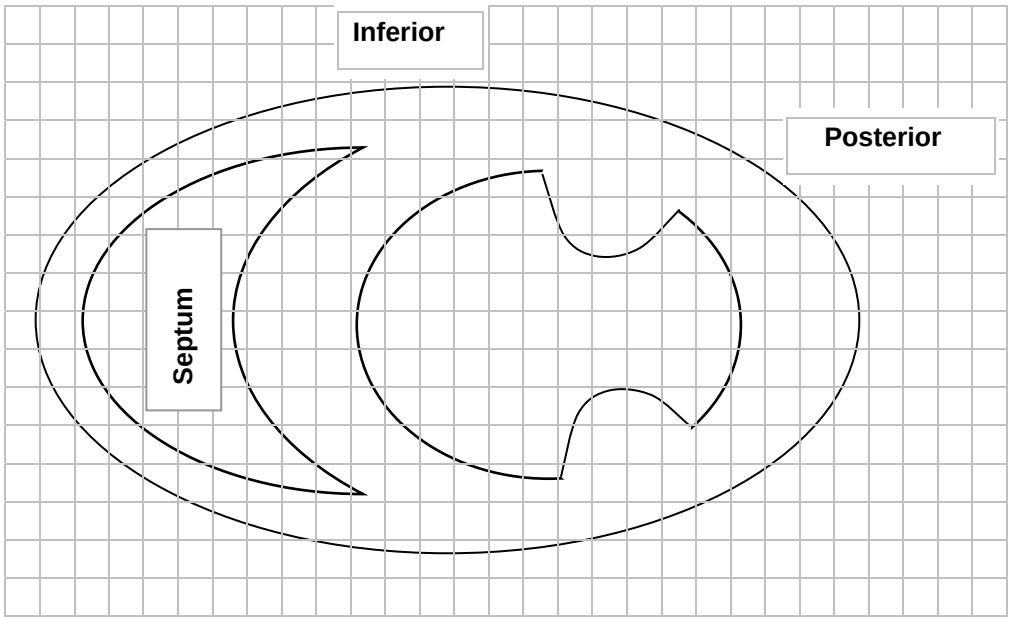
The location of each injection delivered and the timing of the injections will be documented on the Intervention Injection Verification CRF (LVAD18) by the operating surgical investigator immediately following the treatment intervention. The date, time intramyocardial injections were initiated and completed, the number and locations of injection sites and total volume injected will be recorded. **The Intervention Injection Verification CRF must be signed by the surgeon and faxed to the DCC at 212-731-7373 within 48 hours following VAD implantation.** The original copy of the form will be kept in the participant's source document binder.

The Intervention Injection Verification form asks that the operating surgical investigator document the approximate location of each area injected by marking X's on the schematics on the following diagrams:

Basal Short Axis View



Mid Short Axis View



C. *LVAD Implant and Management*

Any permanent surgically implanted non-pulsatile **LVAD approved by the FDA for BTT or DT** for end-stage heart failure may be implanted at the discretion of the surgeon for patients enrolled in this trial. Implantation and management will be performed according to

the **Directions for Use for the specific LVAD**. Long term LVAD management should include optimization of hemodynamic off-loading of the left ventricle to target: (1) reduction of LVEDd to 5.5-6 cm; (2) reduction of mitral regurgitation to, at most, mild regurgitation; and (3) reduction in mean blood pressure to < 100 mmHg.

XVI. POST-INTERVENTION DATA COLLECTION

With the exception of the 12 (± 4) hours and 1 (+ 1) day data collection, all post-intervention data collection is calculated from the date of randomization. The 12 (± 4) hour and 1 (+ 1) day data collection is calculated from the time of intramyocardial study product injection and LVAD implantation.

A. *Surgical Procedure*

Must be completed within 24 hours of initial LVAD implant procedure

Data associated with the initial LVAD surgery and type of LVAD implanted will be recorded.

- Type of VAD implanted
- Location of pump
- Surgical procedure start times
    - Skin incision
    - Sternotomy or Thoracotomy
    - Initiation of CPB
    - Aortic cross clamp
- Surgical procedure stop times
    - Aortic cross clamp release
    - Termination of CPB
    - Sternotomy or Thoracotomy Closure
    - Skin closure
- Intraoperative pharmacologic therapies
- Blood transfusion, if applicable
    - Reason for transfusion
    - Estimated blood loss
- Brief narrative of the surgical procedure

B. *Hospitalization*

At initial hospitalization for LVAD implant

The following information will be collected regarding the participant's index hospitalization:

- Date of hospital admission
- Date of hospital discharge
- Number of cumulative days in intensive care unit setting (i.e., OHRR, CCU, MICU, SICU)
    - Calculate ICU days after intervention
- Reason for admission
- Disposition at time of discharge

C. *Laboratory Assessment*

12 (±4) hours post-intervention, and 7(±3), 21 (±3), 45 (±7), 60 (±7), and 90 (±14) days post randomization, and every 60 (± 14) days thereafter until cardiac transplantation (as applicable) or 12 months, whichever comes first

- CBC with differential and platelets
  - White blood cell count (10^3/mL) , Red blood cell (10^3/mL), Hemoglobin (g/dL), Hematocrit (%), Platelet count (10^3/mL), Neutrophils (%), Lymphocytes (%)
- Chemistry Panel
  - Sodium (mM/L), Potassium (mM/L), HCO_3 or CO_2 (mM/L), Blood Urea Nitrogen (mg/dL), Creatinine (mg/dL), Total Bilirubin (mg/dL)
- Liver function test
  - Alanine Aminotransferase (ALT; U/L), Aspartate Aminotransferase (AST; U/L), Alkaline Phosphatase (IU/L), Albumin (g/dL) and Lactate dehydrogenase (LDH; U/L)
- Coagulation profile
  - Prothrombin Time (PT/sec), Partial Thromboplastin Time (PTT/sec), International Normalized Ratio (INR)
  - Plasma Free Hemoglobin (PFH)

D. *Biospecimen Analyses*

Collection of specimens for cytokines, cell phenotyping and function will be collected at the time points specified below and shipped to the Biospecimen Core Laboratory at the Texas Heart Institute monthly. Complete instructions for collection, processing and shipping can be found in the Biospecimen Core Laboratory Manual.

- Chemo- and Cytokine Quantification
  1 (+1) day post-intervention, 7 (±3), 30 (±7), 60 (±14), and 90 (±14) days, and at 6 and 12 months post randomization
  - IFN-γ, IFN-α, IP-10, Eotaxin, MIP–1α, MIP-1β, RANTES, TNF–α, MIG, IL–1RA, GM–CSF, IL–1β, IL–2, IL–4, IL–5, IL–6, IL–2R, MCP–1, IL–7, IL–8, IL–10, IL–12 (p40⁄p70), IL–13, IL–15, IL–17 (pg/ml), VEGF, ANG-1, ANG-2, SDF-1, PDGF, and SCF (pg/ml).
- Phenotypic Assessments and Colony Forming Capacity of Peripheral MPCs
  1 (+1) day post-intervention, 30(± 3), and 90(± 14) days post randomization
  - Stro1+, CD3, CD11b, CD14, CD19, VEGFR2, CD31, CD34, CD45, CXCR4+, and CD133.

E. *Immunologic Assessment*

30 (±3) and 90 (±14), and at months 6 (±14 days) and 12 (±14 days) months post randomization

An anti-HLA antibody serum sample will be collected and sent to the Biospecimen Core Laboratory using the procedures described in the Biospecimen Core Laboratory Manual. The Biospecimen Core Laboratory will direct these samples to the Immunologic Core Laboratory for analysis. Immune reactivity results for % IgG Class I and IgG Class II and anti-murine and anti-bovine antibodies will be recorded by the Immunologic Core Laboratory.

Coordinators will record whether the samples were obtained, the date the samples were collected and the date the samples were shipped to the core laboratory.

If the samples were not collected, the reason for missing the collection will be specified. Please create a protocol deviation form for the missing assessment as well.

F. *Physical Examination*

1 (+1) day post-intervention, 7 (±3), 21 (±3), 45 (±7), 60 (±7), and 90 (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

Physical examination will include the following:

- Anthropometrics (weight only)
- Vital signs, including temperature and respiratory rate
- Neurologic exam
- Cardiovascular exam
- Respiratory exam
- Abdominal exam
- Extremity exam
- Nutritional assessment

G. *Medications*

1 (+1) day post-intervention, 7 (±3), 21 (±3), 45 (±14), 60 (±7), and 90 (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

The following medications that the patient is receiving at the time of data collection will be recorded:

- Cardiovascular therapy
- Inotropic or Vasoactive therapy
- Anticoagulation
- Antiplatelets
- Antibiotic therapy

H. *Early Stopping Events*

At LVAD implantation, 12 (±4) hours and 1 (+1) day post-intervention, 7 (±3), 21 (±3), 45 (±14), 60 (±7), and 90 (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

Information regarding the occurrence of any event that triggers the early stopping rule, regardless of the seriousness of the event, will be collected as they occur (event driven), and will be confirmed at each study visit.

If an event has occurred, the following information will be collected:

- Type of event
- Date of occurrence
- Date site first aware of the event
- Date DCC was notified of the event

In addition, the site will have to complete the following requirements:

- Notify the DCC
- Complete Early Stopping Event form in EDC
- Fax preliminary de-identified documentation to the DCC to Regulatory Manager
- Notify site IRB

I. *Hemodynamics*

60 days (±7), and 90 days (±14) post randomization*

Hemodynamics by right heart catheterization are to be performed during LVAD wean ***only at centers where this is standard practice for clinical LVAD wean monitoring.*** *Dobutamine right heart catheterization is performed for* ***all patients at 90*** *(± 14) days.* ****The 60*** *(±7)* ***day post-randomization dobutamine right heart catheterization is optional and may only be conducted at centers where it is standard clinical post-LVAD practice.***

Full hemodynamic assessment by right heart catheterization will be collected as a baseline and repeated on Dobutamine infused at 10 µg/kg/min. Pressures will be measured 10 minutes after the maximum dose of Dobutamine has been reached. The VAD will remain at the same rate during this procedure.

The following hemodynamics will be recorded:

- Central venous pressure (CVP)
- Pulmonary artery pressures
  - Systolic (PA_S)
  - Diastolic (PA_D)
  - Mean (PA_M)
- Pulmonary capillary wedge pressure (PCWP)
- Transpulmonary gradient
- Cardiac output (CO)
- Cardiac index (CI)
- Pulmonary artery oxygen saturation (PAO_2 sat)
- Pulmonary vascular resistance (PVR measured in Wood Units)

J. *Echocardiography*

30 (±3), 60 (±7) and 90 days (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

Baseline echocardiographic parameters will be assessed at each time point listed with the LVAD at full flow prior to the wean. Selected measurements will be repeated at 1, 5 and 15 minutes following successful wean from LVAD support (while LVAD flow remains weaned), and immediately following the six minute walk test, as tolerated by the participant. The echocardiograms will only be performed if the patient is able to tolerate the LVAD wean (up to each time point). Only the baseline (pre-wean) echocardiogram will be performed for patients who do not tolerate LVAD wean. The complete echocardiography procedures and instructions can be found in Appendix IV of the protocol.

The echocardiograms will be read by the Echocardiography Core Lab. The values below will be calculated from the measurements obtained by the site.

- Comprehensive Echo Assessment on full support, at 15 minutes following successful wean from LVAD support, and immediately following the 6 minute walk, as tolerated by the patient
    - Left ventricular (LV) end-diastolic and end-systolic dimensions
    - LV fractional shortening
    - LVEF by Simpson's Rule (when possible)
    - LVEF by visual assessment
    - Regional wall motion score index (WMSI) (at limited time points only).
    - Right ventricular (RV) function (Qualitative: normal, mild, moderate, severe)
    - RV systolic pressure (RVSP) from tricuspid regurgitation jet
    - Global and regional strain from speckle tracking
- Limited Echo Assessment following 1 and 5 minutes following successful wean from LVAD support
    - Left ventricular (LV) end-diastolic diameter
    - LV end-systolic diameter
    - LV ejection fraction (2D LV dimension measurements or visual assessment)
    - LV fractional shortening will be obtained from the above measurements

If an image was not performed, a protocol deviation will be documented and reason for missing the assessment will be recorded.

K. *LVAD Wean Assessment*

30 (±3), 60 (±7) and 90 days (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

Participants with an INR of < 2.0 on the day of the assessment will receive 10,000 units of intravenous unfractionated heparin at least 5 minutes prior reducing the pump speed. Patients will not receive any additional anticoagulation during the wean following the initial bolus as detailed in Appendix III of the protocol. Complete LVAD Wean instructions are detailed in Appendix III of the protocol.

Sites should wean the LVAD in increments of 1,000 until the low-speed of 6,000rpm is reached. Once the patient has been weaned to 6,000rpm, data should be collected for the 0-minute time point and the clock should begin. The wean time points specified in the protocol are all taken based on when the clock is started following a wean to 6,000rpm.

Sites should follow their institutional policies for location of LVAD wean. Typically, the LVAD wean is done in the cardiac catheterization laboratory or in designated echocardiology space. Sites should employ their own portable base units during the LVAD wean. The site personnel required to attend the LVAD weans are the Study Coordinator, LVAD Coordinator, Echocardiology Technician and/or Echocardiology Attending and LVAD Cardiologist.

Blood pressure and heart rate measurements will be taken prior to the wean and every 5 minutes thereafter throughout the wean. Sites should use the assessment tools they are most comfortable for assessing blood pressure in this population. Trial sites have reported the use of a Terumo Turbo cuff or Doppler for assessing blood pressure.

The LVAD Cardiologist will determine the patient's ability to wean. Sites are not required to complete a protocol deviation for not completing a wean assessment if the patient is too sick. A protocol deviation is required if the assessment is simply missed. If the patient is too sick to be weaned, complete the wean assessment CRF (LVAD23) by checking that the wean was not attempted and specify the reason as "patient too sick" on question 2.

The assessment of any signs and symptoms listed below will be conducted every 5 minutes during the wean and recorded. An absolute change in blood pressure alone, in the absence of the clinical signs and symptoms listed, will not necessitate terminating the LVAD wean.

- Light headedness
- Dyspnea
- Fatigue
- Pulmonary edema
- Chest pain – complete a 12 lead ECG immediately

The guidelines for early termination of device turn down during echocardiography and six minute walk test dictate that the LVAD will be returned to full LVAD flow if the patient develops symptoms of low cardiac output or vascular congestion.

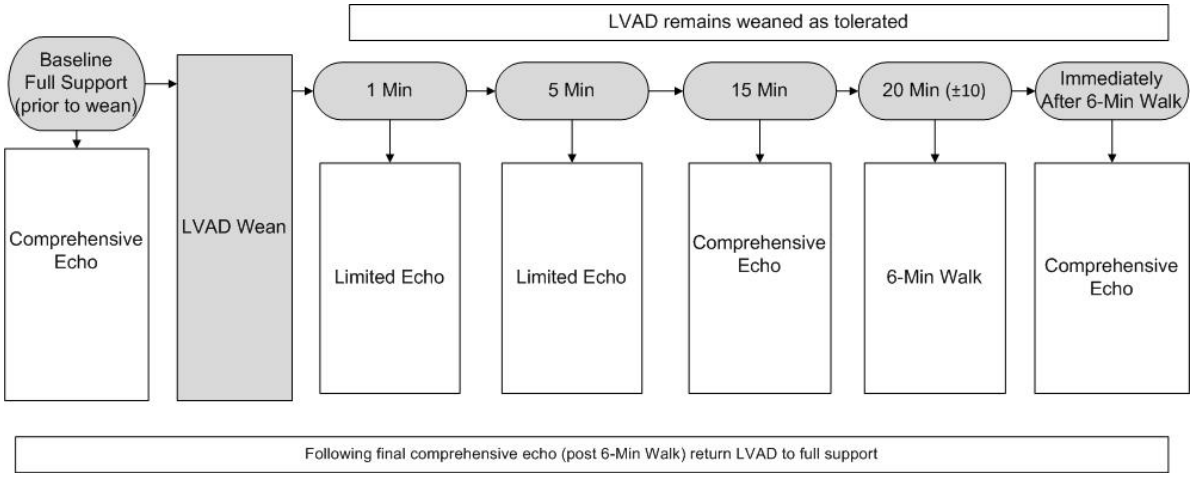
If a patient is not able to tolerate the LVAD wean for the full 30 minutes, then it would be considered an attempted but failed wean. Any echocardiograms that were completed should be uploaded and the electronic wean CRF completed in the EDC system. The CRF contains a section to detail the specific events that resulted in a failed wean. Sites should also refer to the wean worksheets to assist in conducting the weaning procedures.

The LVAD wean will continue until the patient:

- Reaches 30 minutes off LVAD support, *and*
- Completes the echo and 6 minute walk (if this takes longer than 30 minutes and the patient remains stable), *or*
- Fails the wean (See Appendix III of the protocol)

Once the final echocardiographic parameters are complete, the VAD coordinator should increase the pump speed to the original pre-testing settings by increments of 1000 rpm. Ensure that both the main and extended alarm resets are OFF and that both controllers are on original settings.

Timeline of Functional Assessments Completed During LVAD Wean:



Note: Sites are not required to complete the 6-minute walk test if the patient fails the wean. However, all sites should complete the baseline echocardiogram at full support, even if the wean is not attempted.

L. *Six Minute Walk*

30 (±3), 60 (±7) and 90 days (±14) post randomization, and every 60 days (±14) thereafter until cardiac transplantation or 12 months, whichever comes first

If the patient tolerates the wean to 6000 rpm, and is stable at the completion of the 15 minute echo, the six minute walk should be performed. **Take the participant's spare batteries and second controller with you during the walk. Ensure the second controller is easily accessible.**

The test should be performed in an enclosed corridor, preferably free from distractions, on a course that is 60 feet long. The distance walked will be recorded (in feet), regardless of number of times stopped or the rate of ambulation. Detailed instructions for performing the Six Minute Walk can be found in Appendix V of the protocol.

The following information will be recorded:

- Distance walked (feet)
- Date of test
- Test time
- Reason for not completing six minute walk, if applicable

M. *Neurocognitive Testing*

90 days (±14) post randomization, but not during LVAD wean

Please follow the instructions in Appendix IX of the protocol for completing the assessments listed below.

Cognitive performance will be assessed using the following battery of tests:

- Hopkins Verbal Learning Test
- Trailmaking Form A and B
- Digit Span

- Digit Symbol
- MCG Complex Figures
- Controlled Oral Word Association (COWA)

The testing will take a total of 45 minutes and will be administered by study personnel trained and certified by the Duke University Neurocognitive Core Laboratory. Results from these tests will be independently scored by investigators from the Neurocognitive Core Laboratory. All neurocognitive batteries will be tape recorded and the de-identified recordings sent to the core lab for quality assurance evaluation.

Coordinators are asked to record the whether the test was completed, the date of the testing and the date the tests were sent to the core laboratory.

The Trailmaking Part B assessment of the Neurcognitive battery is required by both this study protocol and the INTERMACS registry at the pre-implant and 90 day post-randomization time points. The battery should only be administered once at any given time point. The results from the Trailmaking Part B performed as part of the trial can be used to meet the requirements of the INTERMACS registry.

N. *Cardiac Histology*

At native heart explant for cardiac transplantation or at autopsy (if applicable)

Histologic samples will be collected and sent to the Biospecimen Core Laboratory for analyses according to the specifications outlined in the Biospecimen Core Laboratory Manual. Sites should coordinate specimen procurement in advance with their pathology department, following all applicable laws and institutional guidelines.

Coordinators are asked to record the following information:

- Time point of collection
  - Cardiac Transplantation
  - Autopsy
- Number and location of tissue samples
- Date of shipment to core laboratory
- Time in 10% buffered formalin, where applicable

XVII. EVENT DRIVEN DATA COLLECTION

A. *Adverse Events*

Event Driven within 24 hours of knowledge of event

Detailed information regarding the event and the event classification will be recorded.

- Date of onset and resolution
- Type of adverse event
  - Neoplasm
  - Major Bleeding (not intra-operative)
  - Intraoperative bleeding
  - Cardiac arrhythmias

  - Pericardial fluid collection
  - Inflammatory reaction
  - Device malfunction
  - Hemolysis
  - Hepatic dysfunction
  - Major infection
  - Myocardial infarction
  - Myocardial rupture
  - Neurological dysfunction
  - Psychiatric episode
  - Acute renal dysfunction
  - Chronic renal dysfunction
  - Right heart failure
  - Atrial non-CNS thromboembolism
  - Venous thromboembolism event
  - Wound dehiscence
  - Vasodilatory state
  - Unexpected other serious adverse events
- Reason for resolution
- Seriousness of adverse event
- Relatedness to LVAD implantation
- Brief narrative of the event

B. *Early Stopping Events*

At every study visit and event driven

Information regarding the occurrence of any event that triggers the early stopping rule, regardless of the seriousness of the event, will be collected as they occur (event driven), and will be confirmed at each study visit. Enrollment will be halted should any of these events be observed and deemed related to the study procedures (please see protocol for definitions):

- Infectious myocarditis
- Myocardial rupture
- Neoplasm
- Hypersenstivity reaction
- Immune sensitization

If an event has occurred, the following information will be collected:

- Type of event
- Date of occurrence
- Date site first aware of the event
- Date DCC was notified of the event

In addition, the site will have to complete the following requirements:

- Notify the DCC by entering the event into the EDC
- Complete Adverse Event form
- Fax preliminary de-identified documentation to the DCC to Regulatory Manager

C. *NIH Stroke Scale*

The NIH Stroke Scale will be performed following protocol defined neurological event. Please follow the instructions for completing the NIH Stroke Scale in Appendix VIII of the protocol.

D. *Modified Rankin Scale*

The Modified Rankin Scale will be performed following protocol defined neurological events. Please follow the instructions in the protocol for completing the assessment.

E. *Hospitalization*

Event driven for any hospitalization following the initial LVAD implant

Information pertaining to any hospital admission following the LVAD implant index hospitalization will be collected.

- Date of hospital admission
- Date of hospital discharge
- Number of cumulative days in an intensive care unit setting (i.e., OHRR, CCU, MICU, SICU)
- Reason for admission
- Where hospitalization took place (investigative center or another facility)
- Disposition at time of discharge
- Whether associated with an adverse event

F. *Surgical Procedure*

Event driven within 24 hours of procedure

Data associated with an operation for any reason, including all re-implants, cardiac transplantation, and re-operations, will be captured.

- Type of procedure
- Primary reason for procedure
- Additional surgical procedures performed, if applicable
- Surgical procedure start times
    - Skin incision
    - Sternotomy or Thoracotomy
    - Initiation of CPB
    - Aortic cross clamp
- Surgical procedure stop times
    - Aortic cross clamp release
    - Termination of CPB
    - Sternotomy or Thoracotomy Closure
    - Skin closure
- Intraoperative pharmacologic therapies
- Blood transfusion, if applicable
    - Reason for transfusion
    - Estimated blood loss
- Brief narrative of the surgical procedure
- Whether associated with an adverse event

G. *Medication*

Event driven with the report of one of the following adverse event: Right heart failure, Bleeding, Pump Thrombus, Stroke, Arterial Non-CNS Thromboembolism, and Venous Thromboembolism Event

All prescribed anticoagulation, antiplatelet, inotropes and other medications that the patient is receiving at the time of the adverse event will be captured.

H. *Immunotherapy Medication*

Event driven

All prescribed immunosuppressive treatments that the patient receives following LVAD implantation must be documented.

- Therapy
  - Intravenous Immunoglobulin
  - Plasmapheresis
  - Intravenous Cyclophosphamide
  - Intravenous Rituximab
  - Intravenous OKT3
  - Atgam
  - Thymoglobulin
  - Other (specify)
- Courses/Procedure
- Start date of therapy
- End date of therapy

I. *Mortality*

Event Driven within 24 hours of knowledge of event

The investigator will record the date of death, immediate cause of death, primary underlying cause of death, notation of autopsy being performed, and clinical narrative of the event.

In addition, the site will have to complete the following requirements:

- Notify the DCC
- Complete Mortality form
- Fax preliminary de-identified documentation to the DCC Regulatory Manager

J. *Pump Retrieval and Explant (and/or Postmortem) Examination*

Event Driven

In the event of mortality, all attempts to obtain permission for a full body autopsy should be made. At a minimum, autopsies will be requested of patients who participated in the study in order to evaluate the device, heart and other major organs. Histologic samples of the myocardium will also be obtained and forwarded to the Biospecimen Core Laboratory for analyses, according to the specifications outlined in Biospecimen Core Laboratory Manual.

K. *Missed Visit*

Event Driven

If a patient is unable to return for follow-up before closure of a study visit window, a missed visit form must be completed in the EDC.

XVIII. END OF STUDY DATA COLLECTION

A. *Study Completion/Early Termination*

Event Driven

Date and reason for study completion or early termination will be recorded. If the reason for early termination is heart transplantation, the start time of anesthesia is to be recorded.

Every effort should be made by the Clinical Investigators to have each randomized subject complete all aspects of the study.

B. *Investigator Statement*

At the end of study after eCRF data completion and review

After a complete review of the eCRFs and patient summaries, the Principal Investigator will electronically sign this form to attest to the accuracy and completeness of the data collected.

XIX. SAFETY REPORTING

A. *Event Reporting Timelines*

All investigators conducting clinical studies supported by the NHLBI must report both expected (protocol-defined) and unexpected serious adverse events. All AE reporting should proceed as follows:

Type of Event	**Report to your IRB**	**Enter into EDC**	**Send Initial Source Documents to DCC**	**Send Follow-up Source Documents to DCC**
Early Stopping Event	Within **24** hours of discovery, or as per your IRB's policy, whichever is sooner	Within **24** hours of discovery	Within **72** hours of discovery if event occurred at your site; Within **5** calendar days if event occurred at external site	As soon as possible
Unexpected Serious AE that is **Possibly or Probably** Related to the Study Intervention	Within **24** hours of discovery, or as per your IRB's policy, whichever is sooner	Within **24** hours of discovery	Within **72** hours of discovery if event occurred at your site; Within **5** calendar days if event occurred at external site	As soon as possible
Death	Within **24** hours of discovery, or as per your IRB's policy, whichever is sooner	Within **24** hours of discovery	Within **72** hours of discovery if event occurred at your site; Within **5** calendar days if event occurred at external site	As soon as possible

Type of Event	Report to your IRB	Enter into EDC	Send Initial Source Documents to DCC	Send Follow-up Source Documents to DCC
Unanticipated Problem (UP) that is **ALSO an SAE**	Within **24** hours of discovery, or as per your IRB's policy, whichever is sooner	Within **24** hours of discovery	Within **72** hours of discovery if event occurred at your site; Within **5** calendar days if event occurred at external site	As soon as possible
Unanticipated Problem (UP) that is **NOT an SAE**	Within **5** calendar days of discovery, or as per your IRB's policy, whichever is sooner	Within **5** calendar days of discovery	As soon as possible	As soon as possible
Unexpected SAE that is **Unlikely** Related to the Study Intervention	Within **5** business days of discovery, or as per your IRB's policy, whichever is sooner	Within **5** business days of discovery	As soon as possible	As soon as possible
Expected (protocol defined) **AE**	Within **10** business days of discovery, or as per your IRB's policy, whichever is sooner	Within **10** working days of discovery	As soon as possible	As soon as possible

The DCC will notify the designated NHLBI program staff of any SAEs that are possibly or probably related to the intervention and all deaths (regardless of relatedness and expectedness) via email within 24 hours of receipt of the event. The NHLBI designated program staff will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

DCC REPORTING TO FDA

The DCC will report unexpected SAEs that are possibly or probably related to the investigational intervention to FDA as appropriate. The DCC will send an initial IND safety report communication to the FDA within **2** business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of unexpected SAEs that are possibly or probably related to the investigational intervention for this IND trial.

DCC REPORTING TO MESOBLAST, INC.

The DCC will report unexpected SAEs that are possibly or probably related to the investigational intervention to Mesoblast, Inc. in accordance with the NHLBI-Mesoblast, Inc. Clinical Trials Agreement. The DCC will provide Mesoblast, Inc. with reports on safety data from this trial at least on an annual basis.

DCC REPORTING TO THE OTHER CLINICAL SITES

If, in the course of this trial, an IND Safety Report indicating a serious and unexpected suspected adverse reaction (an adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event) for Revascor™, the DCC will notify all participating investigators and distribute this report to the sites for submission to their local IRBs. Each site should note the submission date and date of IRB acknowledgment on the SAE/IND Safety Report Tracking Log.

B. *Adverse Events*

Definitions for Unanticipated Problems, Adverse Events, Serious Adverse Events and Unanticipated Problems can be found in the protocol.

If a Protocol Defined Event or Unexpected SAE is discovered, the clinical site must follow these three steps for reporting:

1. Report to IRB per local policy
2. Enter into the EDC
    a. This step alerts the DCC of the event
3. Send source documentation to the DCC
    a. Via email to karen.o'sullivan@mountsinai.org or faxed to 212-731-7346
    b. De-identify all source and write PTID on each page of source prior to submission
    c. If source documentation is unavailable within appropriate time frame, complete a PI Initial Report Form. Forms may be found on the trial website and in the EDC.
    d. Add this event to the SAE/IND Safety Report Tracking Log. Note the date of the IRB submission and date of the IRB acknowledgement for each event.

C. *Event Adjudication Committee*

As described in the protocol, all mortalities and protocol defined and serious adverse events will be adjudicated by an independent Event Adjudication Committee (EAC). The DCC will provide de-identified source documentation supplied by the clinical sites to the committee to support each event and mortality to be adjudicated.

The optimal procedure for the clinical site personnel in this process is to file source documentation supporting each reported AE in the Patient Source Binder as the events are reported.

All events will be fully monitored and locked in the EDC prior to presentation to the EAC for adjudication.

XX. STUDY COMPLETION AND CLOSEOUT PROCEDURES

Each site will have close-out conference call with the trial monitor that will occur once the study is completed and all data and finalized CRFs are submitted by the site. During the call, the monitor will also review the DCC policy for maintaining records and completing new tasks identified as part of close-out. The site will receive an electronic report with a summary of the call discussion and any outstanding tasks that need to be completed by the site. Once a site has completed the tasks and all data has been monitored and locked, a final report will be generated by the monitor and sent to the site and NHLBI.

Appendix I: Cell Preparation

STORING REVASCOR™ CELLS

- Each Clinical Site will receive an investigational product cassette stored within a transport Dewar. The cassette rack measures 5 ½ x 11 cm.
- Each investigational product cassette stores 1 study product bag containing either Mesenchymal precursor cells or placebo, the product cassette dimensions are 3.75 inches x 6.25 inches x 0.25 inches
- The unblinded cell technician will be able to view the study product description through a window located on the front of the cassette. This information includes the name of the study product, Labeling Identification Code (CAT#) and Lot number.
- The Investigational product must be appropriately identified and segregated from other products.
- The study products will be stored in a -140º Celsius freezer or in the VAPOR phase of liquid nitrogen at -196 to -140ºC until ready for use. Do NOT submerge the study product into the liquid nitrogen during storage.
- For long-term storage, the product should be maintained in a continuously monitored freezer with adequate security, 24 hour temperature monitoring and an audible alarm. Temperatures must be recorded at least once daily.

SUPPLIES REQUIRED FOR CELL PREPARATION

- Equipment required for preparing the assigned investigational product for injection are:

1 18-gauge Monoject spinal needle supplied by the manufacturer	*70% alcohol wipes*
The FDA requires the use of the 18-gauge spinal needle and may not be substituted with any other product	*1 ziploc plastic bag*
1 10 or 15 cc sterile syringe	*1 sterile plastic bag or wrap for cryobag*
1 sterile female-female luer connector	*1 stopwatch/timer*
4 BD ml luer-lock tip syringes	*1 pack 3M Steri-Strips (E4546)*
4 3/4 inch 23 gauge needles	*37 degree water bath filled with sterile water*
1 sterile marker and labels	*Biological laminar flow hood if that is the standard at your institution for working with human products*
3 small sterile drapes	*Or a compounding aseptic isolator class 100 environment*
2 pairs of sterile gloves	

- A 37 degree water bath filled with sterile water will be used.
- The investigational product is to be prepared under either a Biological laminar flow hood, or the use of a Compounding Aseptic Isolator.
- Sites will have to supply the syringes and steri-strips. The ordering information for the steri-strips being used for the blinding process of the injection syringes is ***¼ inch x 4 inch * 6mm x 100mm 3M Steri-Strips. Ref number E4546 and NHRIC number 833-4546-01***

RANDOMIZATION PROCESS

- The randomization procedure will be performed within 24 hours prior to the LVAD implantation and treatment intervention
- Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system
- Once the randomization form in the EDC has been completed by the study coordinator, the treatment assignment form, under the Pre-Implant tab is activated and is viewable for the unblinded cell technician only
- The treatment assignment form will automatically display the randomization assignment to the Cell Technician based on a randomization sequence designed by the unblinded trial statistician
- The Cell Technician will enter cell or placebo specific information, the labelling identification code and lot number from the front of the cryobag into the EDC.
- The cell technician must certify that the prepared syringes will appear identical, with no distinguishing characteristics to identify the treatment assignment, number 4 in the EDC, and confirm that the treatment assignment has been read and understood, number 5 in the EDC, for confirmation of the treatment assignment. These will appear **red** in the EDC and **must** be completed in order to **sign** the treatment assignment form.
- Save the treatment assignment form by clicking the **Save link** at the top of the screen.
- Electronically sign the form in the system by clicking the **Sign** button on the Cell Technician signature line and then clicking the **Sign button** in the pop-up certification window.
- The study coordinator and cell technician must communicate the exact timing of the intervention. Treatment intervention and LVAD implantation must occur within 24 hours following randomization. This includes confirmation of treatment assignment in the electronic data capture system, study product preparation, injection intervention and LVAD implant.

REVASCOR™ CELL PREPARATION: THAWING OF ASSIGNED INVESTIGATIONAL PRODUCT

- The unblinded cell technician will remove the cassette containing the assigned investigational product from the liquid nitrogen storage.
- Read the investigational product label, verifying that you are removing the assigned study cells or placebo.

- Open the cassette and remove the Cyrobag containing the assigned study product.
- Place the cryobag in a clear plastic bag and immerse into a 37 degree water bath. A timer for the thawing process of 4 minutes should be set.
- With gentle agitation, the cells will be thawed after approximately 4 minutes of submersion. The cryobag should be removed from the water bath just before the last crystal of ice has fully melted.
- A timer should be started once the cells have thawed. The investigational product must be injected within 75 minutes of thawing.
- If any fluid from the cryobag leaks into the plastic bag or if any lacerations or defects to the cryobag are noted, that product should not be used. Instead a designated unblinded member of the investigational site's team should retrieve another identical dose product.

REVASCOR™ CELL PREPARATION: PREPARING TO REMOVE STUDY PRODUCT FROM CYROBAG

- Once determined the study product is in good condition, set up a sterile field using 3 sterile drapes and transfer the sterile needles, spinal needle, *3/4* x 23 gauge sterile needles, alcohol wipes, syringes, steri-strips, sterile bag or wrap, sterile pen and labels to the sterile field

REVASCOR™ CELL PREPARATION: REMOVING ASSIGNED STUDY PRODUCT FROM CYROBAG

- Wearing sterile gloves, place the cryobag into a sterile plastic bag or wrap in a sterile drape to maintain sterility of the person conducting the transfer procedure.
- Twist and remove one of the capped ports on the study cryobag.
- Swab the port with 70% alcohol.
- Place the cryobag onto the sterile field with the ports of the cryobag lying on a sterile 4x4 gauze.
- After placing the cryobag into a sterile bag or sterile wrap, change your sterile gloves.
- Remove the inner cannula from the 18-gauge Monoject spinal needle and attach to the 10 or 15 cc syringe.
- Draw up 10 ml of air into the 10 or 15 cc syringe and gently insert the spinal needle through the membrane within the bag port. The membrane will be firm. Be careful not to puncture the product bag.
- Inject 10ml of air into the cryobag. You will see the study product disperse in the product bag.
- You may insert the spinal needle with the 10 or 15 cc syringe attached OR insert the spinal needle without the syringe attached. Once you have successfully inserted the needle through the membrane, proceed with attaching the syringe.
- Invert the cryobag with the ports facing up or at a 45-degree angle and withdraw the contents of the bag into the 10 or 15 cc syringe. (Prior experience with the study product has shown that some product can get trapped in the bag's unused port when aspirating product at an

upright position. Therefore, Mesoblast has recommended that the product be aspirated at a slight angle for enhanced product recovery.) The product bag contains 5 ml of the study product. If the bag collapses before enough volume is pulled, a second syringe can be added to the other port to add air. Continue to aspirate the study product from the first syringe. Keep the ports facing up to avoid losing product within the other ports.

- Be certain to remove all air bubbles from the 10 or 15 cc syringe.

Although the training video and protocol guides sites to inject 7cc of air into the thawed product bag, more air may be injected to help inflate the bag and retrieve product. Prior to aspirating the product from the bag, sites may invert the bag and slowly inject 10cc of air above the solution line into the thawed product. In addition to inflating the bag, this will also help reduce air bubbles and possibly help in retrieving the product.

REVASCOR™ CELL PREPARATION: PREPARING STUDY PRODUCT FOR INJECTION

- After drawing up the study product, attach the 10 or 15 cc syringe to the female-female luer connector.
- Attach a sterile 5 cc luer lock syringe to the 10 or 15 cc syringe luer connector.
- Draw up 4 ml of study product, equally divided between the 4 sterile 5 cc syringes, drawing up 1 ml of study product into each 5 cc syringe.
- Remove the 5 cc syringe from the luer; gently tap the syringe to remove any air bubbles, attach the 3/4 inch 23 gauge needle to the 5 cc syringe.
- The final 4 syringes must be "gently rocked" to prevent clumping.

REVASCOR™ CELL PREPARATION: BLINDING OF INVESTIGATIONAL PRODUCT SYRINGES

Under the guidance of the CTSN/CCTRN Cell Injection Procedures Working Group Investigators and the study product manufacturers, blinding of the investigational product for the current trial was standardized with the use of a wide steri-strip. Alternative methods to de-identify the investigational product should not be attempted.

- Number the sterile Labels numbers 1 thru 4.
- With the sterile marker, place a line around the plunger of the 5ml syringe. The surgeon will see this line merge up into the syringe as he injects the study product, allowing the surgeon to track the amount of study product he is injecting. You may also pull the plunger back to the 3ml mark and then mark the plunger. *(Please see the three images at the end of Appendix I as an example)*
- Starting at the hub, wrap the lower portion of the 5ml syringe with the 3M Steri-Strips to obscure the lower barrel of the syringe. You will need to use 2 Steri-Strips.
- Using the second Steri-Strip continue to wrap the Steri-Strip around the syringe to the bottom of the black rubber stopper on the plunger.

- These Steri-Strips are wide, flexible and non-transparent. They can easily be stretched around the syringe without difficulty.
- Make any adjustments to the Steri-Strip as needed so not to leave any section of the syringe uncovered and unblinded.
- Mark the Steri-Strip with a marker at the 1ml mark to allow tracking of the amount of study product injected.
- Label the 4 5ml sterile syringes numbers 1 thru 4.

PREPARING INVESTIGATIONAL PRODUCT SYRINGES FOR TRANSPORTING TO THE OR

Note: study product preparation can be done in the OR as long as sterility and blinding is maintained.

- Place the 4 prepared 5ml blinded syringes onto the top opened sterile drape. Gently rock the syringes to prevent clumping of cells as you are placing them into the sterile drape.
- Securely wrap the 4 blinded 5ml sterile syringes inside the top sterile drape.
- Secure the wrapped syringes with a sterile label.
- Wrap the second sterile drape around the securely wrapped sterile blinded syringes.
- Secure the double wrapped sterile blinded syringes with the remainder of the sterile labels for transporting to the OR.
- The study coordinator or cell technician will transport the prepared syringes under sterile conditions to the OR.
- Bring the timer that was set at the time the investigational product was thawed to the OR for time management. The study product must be injected within 75 minutes from the time the study product was thawed.

TRANSPORTING INVESTIGATIONAL PRODUCT SYRINGES TO THE OR

- The prepared syringes must be gently hand rocked while being transported to the OR to prevent clumping.
- Upon arrival to the OR, conduct a time for patient identification.
- Safely unwrap the outer drape then the inside sterile drape containing the 4 blinded sterile syringes.
- The OR scrub nurse will remove the 4 blinded 5ml sterile syringes containing the assigned study product from the inner sterile drape. If the surgeon is not ready to inject the study product at this time, the scrub nurse will continue to gently rock the syringes to prevent clumping until the surgeon is ready for injection.
- After passing the 4 blinded 5ml syringes to the scrub nurse, check the timer for the amount of time remaining before the study product must be injected. Inform the surgeon of the injection time remaining.
- Cells thawed longer than 75 minutes must be discarded.

- The Investigational Product Tracking log must be completed for any product being dispensed, disposed or returned.

Syringe Labeling Instructions