

Cardiovascular Cell Therapy Research Network



Manual of Operating Procedures (MOP)

for the **CONCERT-HF** Protocol

Stage 2 Main Trial

A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, and Efficacy of Autologous Mesenchymal Stem Cells and c-kit⁺ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects with Ischemic Heart Failure

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CCTR N CONCERT-HF PROTOCOL

I. Executive Summary – Main Trial (Stage 2)

- Full Title:** A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, and Efficacy of Autologous Mesenchymal Stem Cells and c-kit⁺ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects with Ischemic Heart Failure
- Short Title:** CONCERT-HF
- Sponsor:** CCTRN Data Coordinating Center- University of Texas-Houston School of Public Health
- Sites:** Subjects enrolled in this study will be recruited from all of the sites participating in the National Heart, Lung, and Blood Institute (NHLBI) CCTRN: Texas Heart Institute, Houston Texas; University of Florida, Gainesville Florida; Minneapolis Heart Institute Foundation, Minneapolis Minnesota; University of Louisville, Louisville, Kentucky; University of Miami, Miami, Florida; Stanford University, Stanford, California; and Indiana University-Purdue University, Indianapolis, Indiana; Data Coordinating Center: University of Texas-School of Public Health, Coordinating Center for Clinical Trials, Houston, Texas
- Investigators:** Cardiovascular Cell Therapy Research Network (CCTR N)
- Test Agent:** Autologous human cells (MSCs alone, c-kit CSCs alone, or the combination of MSCs and c-kit CSCs, obtained from subjects via bone marrow aspiration and cardiac biopsy, respectively)
- Population:** Male and female subjects with documented coronary artery disease with evidence of myocardial injury, left ventricular dysfunction, and clinical evidence of heart failure, and eligible to undergo cardiac catheterization/NOGA
- Sample Size:** 144 randomized subjects
- Duration:** Following discharge from the hospital, subjects will be assessed at week 1, and months 1, 3, 6, and 12
- Objective:** The purpose of this study is to assess feasibility, safety, and efficacy of autologous bone marrow-derived mesenchymal stem cells (MSCs) and c-kit⁺ cardiac stem cells (CSCs), both alone and in combination, administered by transendocardial injection in subjects with heart failure (HF) of ischemic etiology
- Safety:** The following safety data will be collected and analyzed by therapy group between baseline and a) 6 months and b) 12 months:
- Major adverse cardiac events (MACE) including: death, hospitalization for worsening HF, and/or exacerbation of HF (non-hospitalization)

- Other significant clinical events including: non-fatal stroke, non-fatal myocardial infarction, coronary artery revascularization, ventricular tachycardia/fibrillation, and/or pericardial tamponade
- All adverse events that are at least grade 2 in severity

Feasibility: The number and percent of subjects who have:

- Events between randomization and SPI that preclude the subject from getting SPI
- Failed bone marrow aspiration procedure
- Failed endomyocardial biopsy procedure
- Failed release criteria (including minimum number of cells) for receiving the MSC product
- Failed release criteria (including minimum number of cells) for receiving the CSC product
- Less than 15 injections during the SPI procedure
- At least one cardiac MRI endpoint measure that is uninterpretable due to issues related to the device, including, but not limited to, inability to undergo the procedure

Efficacy: To assess the overall effect of the cell types used in CONCERT-HF, multiple endpoints have been selected from different categories of effects (domains). Each having the same priority for the efficacy analyses, the domains and endpoint measures for CONCERT-HF are:

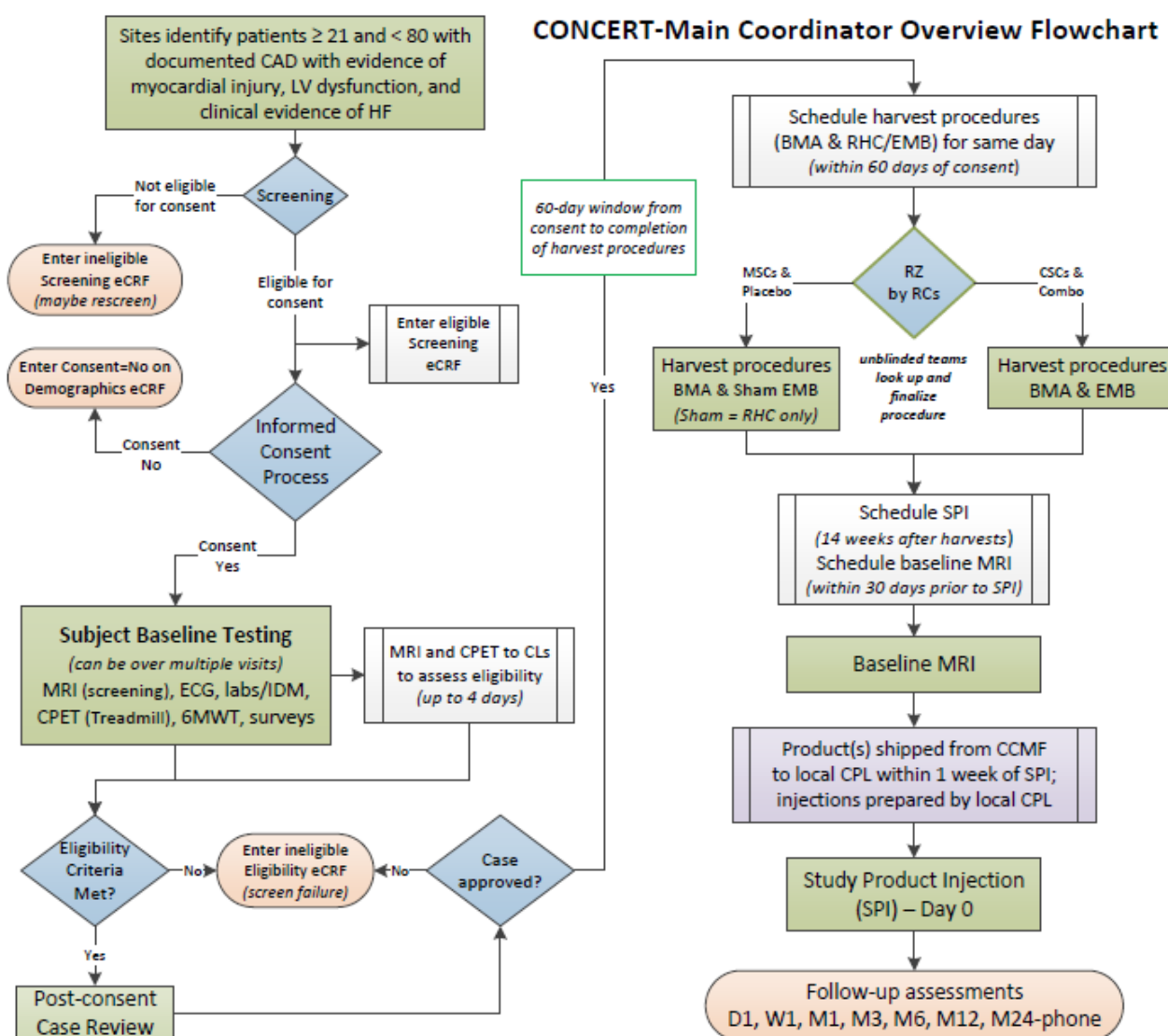
- Myocardial evaluations by cardiac MRI (cMRI) over time:
 - Function:
 - Change in LVEF
 - Change in global and regional strain (HARP MRI)
 - Structure:
 - Change in LVEDVI
 - Change in LVESVI
 - Change in LV Sphericity Index
 - Morphology:
 - Change in infarct/scar volume (DEMRI)
- Functional capacity over time:
 - Change in VO₂ max (treadmill)
 - Change in exercise tolerance (6MWT)
 - Change in MLHF Questionnaire (subject reported)
- Clinical outcomes over time:
 - MACE
 - Cumulative days alive and out of hospital
- Biomarkers over time:
 - Change in NT-proBNP

II. Stage 2: Randomized, Placebo-controlled Phase Overview

Upon successful review of Stage 1 by the DSMB, the investigation will proceed to Stage 2. Stage 2 is a phase II, double-blind, placebo-controlled trial consisting of one hundred forty-four (144) subjects who meet all inclusion/exclusion criteria and will be randomized 1:1:1:1 to one of four treatment strategies:

1. Group A (36 subjects) – Combination of autologous MSCs and CSCs (“Combo”): Target dose is a mixture of 150×10^6 (150 million) MSCs plus 5×10^6 (5 million) CSCs delivered in 15 injections each of 0.4 ml volume
2. Group B (36 subjects) – Autologous MSCs: Target dose is 150×10^6 (150 million) MSCs delivered in 15 injections each of 0.4 ml
3. Group C (36 subjects) – Autologous CSCs: Target dose is 5×10^6 (5 million) CSCs delivered in 15 injections each of 0.4 ml
4. Group D (36 subjects) – Placebo: 15 injections each of 0.4 ml cell-free PlasmaLyte-A medium

Subjects will be enrolled across all seven Network centers. Within 60 days of signing informed consent, all subjects will have iliac crest bone marrow aspiration (BMA) and right heart catheterization (RHC), including transvenous right ventricle endomyocardial biopsy (EMB) only for groups A and C. The bone marrow aspirate and endomyocardial biopsy (if applicable) will be transported to a central cell manufacturing facility (CCMF) where MSCs and/or CSCs will be manufactured to yield the target doses. Subjects will return for a cardiac catheterization procedure to receive study product not less than 14 weeks after harvest procedures. Cells or placebo will then be administered via the NOGA[®] XP Mapping and Navigation System (NOGA) and will be targeted to the border zone and the adjacent scarred tissue. Following cell or placebo injections, subjects will be followed at day 1, week 1, and months 1, 3, 6, and 12 to complete safety and efficacy assessments. Figure 1 below outlines study activities from screening to follow-up.

Figure 1. CONCERT-HF Main Trial Overview Flowchart

III. Administrative Tools

All supporting MOP documents are available on the CCTR website (www.cctrn.org) in “Member Resources” in the corresponding locations (see below), and the initial printouts are located in the corresponding binder section number and header (see below). Updated documents will be uploaded to the website, and email notifications will be sent out when revised documents are available.

A. Coordinator Checklists

The complete schedules of procedures and schedules of lab tests for Stage 2 can be found in Section 6 of the protocol. To help you organize study related activities a procedures checklist template is available and can be modified by the site coordinator to meet the needs of the specific

center. The Stage 2 procedures checklist template, a.k.a. Coordinator Checklist for CONCERT-HF Main Trial (Stage 2), is located in:

- [Member Resources/CONCERT/MOP Documents/Stage 2/2-Procedures Checklist Template](#)
- [MOP Binder Section 2, Coordinator Checklist \(Procedures Checklist Template\)](#)

B. Workbooks

CONCERT-HF case report forms (CRF) workbooks for Stage 2 are located in:

- [Member Resources/CONCERT/MOP Documents/Stage 2/4-CRF Workbooks](#)
- [MOP Binder Section 4, CRF Workbooks](#)

C. FAQs

Frequently asked questions (FAQs) regarding study procedures are located in:

- [Member Resources/CONCERT/MOP Documents/Stage 2/6-FAQs](#)
- [MOP Binder Section 6, FAQs](#)

D. eCRF Users Guide

Refer to the CONCERT-HF (main trial) Electronic Case Report Forms (eCRFs) Users Guide (a.k.a. [eCRFs Users Guide](#)) for complete instructions on submission of eCRFs in the CCTR database. This document is located in:

- [Member Resources/CONCERT/eCRF Users Guides/Stage 2](#)

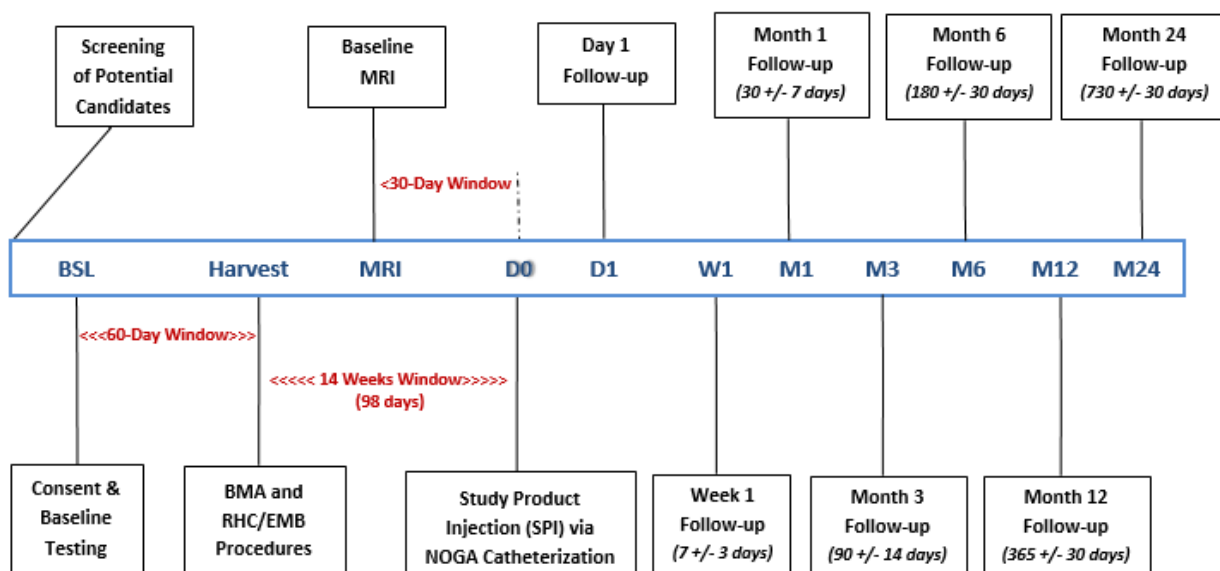
E. Other Resources

Refer to SharePoint / Member Resources for a variety of helpful tools:

- [Member Resources/CONCERT](#) (Confirmed Harvest Calendar)
- [Member Resources/CONCERT/Protocol & IB](#) (Current protocol, ICF and Investigator Brochure)
- [Member Resources/CONCERT/Coordinator Resources](#) (Expected Events handout and AE/CE Coversheet)
- [Member Resources/CONCERT/Core Labs](#) (Manuals and supporting documents for procedures related to Biorepository, CPET (MVO2), and MRI)
- [Member Resources/CONCERT/Recruitment](#) (Study Overview Presentation and Advertising Templates)
- [Member Resources/CONCERT/Training](#) (6MWT materials and Protocol/Safety slides)

IV. Procedures (Stage 2) – Screening thru Eligibility Determination

Figure 2. Timeline



A. Screening

The screening phase pertains to the initial review of potential subject characteristics based on available data (i.e., medical records review). Limited demographic information and eligibility criteria based on available data are recorded on the Screening form (see workbook in *MOP Binder Section 3, CRF Workbooks*) to capture the population approached for the study, how subjects first found out about the study and, when applicable, reason(s) for not consenting the screened subject.

Screening of subjects includes reviewing medical records and imaging studies for inclusions/exclusions prior to consent. From the review of subjects' medical records and imaging studies on file, subjects who are determined to have a diagnosis of chronic ischemic LV dysfunction secondary to MI, have EF $\leq 40\%$, are candidates for cardiac catheterization, and have NYHA class of I, II or III, as stated in Section 4.3, and also do not have evidence in their medical record of study exclusions stated in Section 4.4, are eligible to be consented to the study.

In addition, EF $\leq 40\%$ can be defined by gated blood pool scan (MUGA), cMRI, left ventriculogram, or EF $\leq 35\%$ by two-dimensional echocardiogram.

NOTE: Imaging studies (cMRI, ECG, SPECT, MUGA, echo, and/or left ventriculogram) are acceptable within 12 months prior to consent, and the PI will determine the need to repeat any standard of care imaging modalities to use for screening.

NOTE: Sites should bring any questions or concerns surfacing during the review of potential study candidates to the Network Investigators for discussion.

According to Exclusion criterion #1, subjects on the heart transplant list must not have high likelihood of transplant prior to collection of the 12 months study endpoint. Candidates cannot be UNOS status 1A or 1B, and they must have documented low probability of being transplanted (see p.17, *Post-consent Case Reviews* for documentation requirements).

1. Screening Form

A Screening form should be completed for potential subjects when they meet the following conditions:

1. Candidate meets the first two inclusion criteria: 1. “are ≥ 21 and < 80 years of age” and 2. “have documented CAD with evidence of myocardial injury, LV dysfunction, and clinical evidence of HF”; **AND/OR**
2. Site has taken a (site-defined) “serious look” at the patient which may include a request for medical records.

All eligibility criteria do not need to be answered to submit the Screening form for a candidate who will be ineligible to consent to the trial. Screening forms for candidates who meet the above conditions should be entered on a weekly basis to keep screening numbers accurate for reporting to the Steering Committee. Potential subjects can be screened more than once with multiple screening forms entered for the same candidate before they are consented.

2. Study ID

A Study ID will be generated by submission of the first screening eCRF and the screening date will also appear to assist you with selecting the same candidate should you choose to rescreen someone for the study. ***It is very important that you track the database-generated Study ID and screening date in a manner such that you can retrieve the individual’s information should they be re-screened in the future (another Screening form would be entered at that time using the same Study ID).*** Tracking could be achieved for example, by either keeping an internal log or a separate binder to house the screening forms. In order to accurately count the number of people screened for the study, we must have only one Study ID for each candidate screened no matter how many times you screen them. You cannot screen a subject more than once per day.

The Study ID and screening date will be used to identify the subject on screening records.

a) Stage 1 Subjects

Subjects randomized to the standard of care (SOC) control group in Stage 1 have the option to be evaluated for enrollment in Stage 2. To participate in Stage 2, they will need a new Study ID. If a candidate screened previously (or participated) in Stage 1, please enter Stage 1 Study ID on the Stage 2 Screening form (in Comments).

MRIs from the CONCERT lead-in phase, which were acquired using the CCTR N MRI protocol, are acceptable for use as the screening MRI in the main portion of the trial ***provided that the following are met:***

1. Image was acquired within the past twelve months.

2. The site must be able to rename the Stage 1 MRI images with correct Stage 2 study ID and time point and then resend the images to the MRI Core Lab.
3. No MACE event has occurred since the Stage 1 MRI images were acquired.
4. No medication doses have been increased or new medications started that could affect EF since the Stage 1 MRI images were acquired.
5. There have been no other significant changes in the patient's medical status that might affect MRI measures since the Stage 1 MRI images were acquired.

B. Consent

1. The informed consent process

All Stage 2 subjects (including former Stage 1 SOC subjects) will be consented under a Stage 2 consent form outlining all study related procedures, all possible risks, the time commitment, and the potential for randomization to a placebo group. Candidates identified as eligible for enrollment via the Screening form will be approached by one of the investigators or research coordinators to discuss their interest in participating in the trial after discussion with the individual's primary physician, if applicable. The informed consent will provide information regarding standard alternative heart failure therapies and will include information regarding potential risks and benefits of participation. Potential subjects will be asked to consent to the Biorepository Core (BRC) and the possibility of future genetic testing as part of the informed consent process.

Necessary elements of the informed consent process are included below:

1. Confirm the consent being provided to/reviewed with the subject is a current and IRB-approved consent form.
2. Allow the individual time to read the entire written consent form.
3. Explain the various components of the study to answer initial questions. This includes directed conversations regarding voluntary participation, time requirements, the possibility of assignment to a placebo condition and what that means, a detailed explanation of the risks involved, and confidentiality of research data.
4. Invite and encourage the individual to discuss the consent form with family or loved ones to enable him/her to make a decision with support of these individuals.
5. Ask the individual for an explanation of what the research involves and what is required. Review this information until the individual can provide a clear explanation of the research.
6. Elicit from the individual if there are any further questions about the research being considered.
7. The written consent form is signed/dated by the individual and a research coordinator.
8. One copy of the signed consent form is given to the subject.
9. The original signed consent form is kept in the subject's research record.

For those not wishing to participate in the program:

1. Inform the individual that refusal to participate will not result in negative consequences.
2. Collect specific reason why individual does not want to participate, and document this on the **Screening eCRF** or on the **Demographics eCRF** if an eligible Screening eCRF was entered prior to decision not to participate.
3. Thank the individual for their time and consideration of the research program.

NOTE: Details of the informed consent process will be documented in the subject's medical record. This information will include the date/time the subject was approached for the study, listing of family members/other individuals present for the consent, the date/time the subject signed the consent, and any specific items of concern addressed with the subject.

2. Demographics Form and Acrostic Generation

For individuals who are eligible based on the Screening form and consent to be in the study, a **Demographics form** will be accessible on the eCRF menu. Successful completion of this form will result in the subject Acrostic. An **Acrostic** is a second unique identifier. The acrostic is a combination of six letters which come from the subject's name. It is the first three letters of the last name, first two letters of the first name, and the middle initial. There are cases in which the acrostic may be only 5 letters (e.g. subject has no middle initial). DO NOT include spaces and/or punctuation marks in subject's name, as this can be a problem in acrostic generation.

The Study ID and Acrostic will be used to identify the subject on all study documents other than the screening records.

3. Procedure for generating acrostic for VA subjects

Research data in the VA will be coded using the following format. To prevent any letters of the subject's name being used, the following procedure will be used: First, an acrostic will be developed using the first 3 letters of the subject's last name followed by the first 2 letters of the subject's first name. For example, John Smith would become SMIJO. Next, consonants will be changed to the next consonant in the alphabet and vowels will be changed to the next vowel in the alphabet. In this example, SMIJO would become TNOKU. Only the VA acrostic would need to be entered into the database, in lieu of the subject's name.

C. Baseline Testing and Eligibility Determination

After assignment of Study ID, successful screening, consent, and acrostic generation in the database, the research coordinator collects the baseline assessments per protocol to determine whether the individual truly is a viable candidate for study inclusion. The baseline testing period extends 60 days from the date the ICF is signed. The baseline evaluations cannot begin until after the informed consent has been signed.

1. Baseline Testing and Endpoint Assessment Considerations

a) Six Minute Walk Test (6MWT)

6MWT considerations are listed below:

1. Testing within an hour after a meal will be avoided.
2. Two tests will be done at each visit separated by at least 30 minutes. If the percent change between test 1 and test 2 for total distance walked is >10%, a third test will be done.
3. If 6MWTs and Cardiopulmonary Exercise Test (CPET) are done on the same day, they must be done in consistent order at each visit and at consistent intervals, with 6MWTs completed either at least 30 minutes before or starting at least 1 hour after the CPET.
4. Follow-up 6MWTs should be performed at the same time of day as baseline (within 2hr window) and by the same tester (blinded to RHC with or without EMB) when possible.

Please refer to the 6MWT training materials. The materials can be found on www.cctrn.org at Member Resources/CONCERT/MOP Documents/Stage 2/3-6MWT, and in *MOP Binder Section 3*.

b) Cardiopulmonary Exercise Test (CPET) (Treadmill Test)

Treadmill testing considerations are listed below:

1. If 6MWTs and Cardiopulmonary Exercise Test (CPET) are done on the same day, they must be done in consistent order at each visit and at consistent intervals, with 6MWTs completed either at least 30 minutes before or starting at least 1 hour after the CPET.
2. If a participating laboratory has more than one treadmill or metabolic cart, the same equipment should be used for each test in a given subject. This should be the equipment the CPET core certified.
3. Email CPET Core Laboratory (cpetcore@partners.org) when a subject is scheduled for their baseline test.
4. Provide subjects with pre-test instructions (see manual).
5. Review of contraindications to exercise testing (see manual).

Please refer to the CPET Core Lab Manual. The manual can be found on www.cctrn.org at Member Resources/CONCERT/Core Labs/CPET (MVO2)

c) MRI Testing and EP Training / Qualification for Assessing Devices for MRI Contraindication

MRI Testing and Device considerations are listed below:

1. Dotarem is the required gadolinium-based contrast agent for the study.
2. Subjects with devices will be assessed carefully. Site staff will be trained by MR core to assess devices and work with the MR core to determine eligibility of subjects with devices.
3. MR core trained staff with pacemaker/ICD expertise will be directly involved to oversee device disabling and re-enabling, pre- and post-can measures, subject monitoring, etc.

4. EP Training will be done prior to the first subject with a device who consents to the study. Unless otherwise indicated by the MR core lab, EP Qualification will be done with the first subject with a device who consents to the study.
5. ICD interrogation will be done before and after every MRI as part of MRI protocol.
6. Advanced Cardiovascular Life Support (ACLS) trained personnel and a “crash cart,” including defibrillator, available throughout the procedure to address an adverse event.

Please refer to the MRI Core Lab Manual. The manual can be found on www.cctrn.org at Member Resources/CONCERT/Core Labs/MRI

MRI Core Lab EP/Device contact information: Saman Nazarian, MD, Phone: 443-604-8399
Saman.Nazarian@uphs.upenn.edu. Please copy Dr. Ostovaneh on all emails to Dr. Nazarian

2. Baseline Testing Schedule

Due to the challenges of completing all subject activities, Research Coordinators (RCs) should schedule baseline visits as early in the 60 day window as possible.

NOTE: MRI and CPET core lab reviews take up to 4 days for eligibility determination.

The MRI core lab will review the screening MRI for eligibility as well as clinically for LV thrombus and pericardial effusion, noting statuses on the screening MRI report.

Once the baseline CPET and screening MRI are scheduled, RCs notify MRI & CPET cores (and copy the DCC) of test schedule; indicate the date of the test and center ID.

Contact information:

- CPET Core Lab contact information: cpetcore@partners.org
- MRI Core Lab contact information: Mohammad Ostovaneh, MD mostova1@jhu.edu
- DCC contact information: Michelle Cohen Michelle.L.Cohen@uth.tmc.edu

If the subject screen fails before a scheduled test, please send email update.

Baseline Testing

*(60-day window from consent to completion of harvest procedure(s);
 Baseline testing can be over multiple visits as long as meet 60-day window)*

Demographics (includes date of signed consent)
History and Physical/vitals (with NYHA and CCS classifications)
Medications and Allergies
ECG
Labs (including infectious disease tests)
Cardiac MRI
ICD interrogation (if applicable, before & after cMRI)
Transmit screening images to MRI core
CPET (Treadmill)
Transmit test documentation to CPET core
Six minute walk—Test 1 (T1)

(Must be conducted at least 1 hour after last meal)
Six minute walk—Test 2 (T2) (Must be conducted at least 30 mins after T1)
Six minute walk—Test 3 (done ONLY if % change b/t T1 and T2 >10%) (Must be conducted at least 30 mins after T2)
MLHF questionnaire
Sexual function questionnaire
Post-consent case review

Wait to enter Eligibility, Eligibility Checklist, and Randomization eCRFs until after infectious disease tests results received and post-consent review decision.

Baseline visit notes:

- *Hematocrit and eGFR are required labs in conjunction with each MRI. SOC labs are acceptable under the following conditions:*
 - *eGFR measure taken prior to the date of the scheduled MRI can be used if it meets institution guidelines (usually within 30 days);*
 - *hematocrit measured at the time of the scan or as close as possible to the scan is preferred, though if not feasible in some cases, hematocrit within 30 days prior to the MRI scan is acceptable except for: premenopausal females, subjects with blood loss for any reason, or those having an invasive procedure between the hematocrit measure and MRI scan.*
 - *Record hematocrit and eGFR on MRI worksheet. The values from the lab draw associated with the study visit should be entered on the lab eCRF.*
- *Anticoagulation therapy (ACT): subjects who are on ACT at baseline, see study protocol (Sections 6.2.2 and 6.2.3) for management guidelines during harvest and SPI procedures.*
- *Infectious disease tests: results must be known prior to final eligibility determination. Donor tests are conducted w/in 60 days of harvest(s). If tests expire prior to harvest procedure(s), they must be performed again. Please note, infectious disease test results are not submitted to the DCC unless a subject has a positive test. In the case of a positive test, you must report as an AE. Subjects with inactive markers for Hep C (such as antibody positive, antigen negative, with normal LTF) will need to get clearance from local hematologist for inclusion in study.*
- *Subjects should be advised to not eat, drink, or take supplements (particularly those containing metals such as iron) 4 hours before the MRI. They should consult with the study team on whether or not to take other medications or bring them to take after the test.*
- *If MRI and CPET are done on the same day, care should be taken to ensure there are no lingering effects of sedative medications that may be administered in conjunction with MRI.*

3. Post-consent Case Reviews

Upon completion of baseline testing, receipt of screening MRI report from core, and verification of eligible CPET, the Research Coordinator (RC) will submit records (see process below) for a post-consent case review for subjects who have met eligibility criteria. These data are reviewed prior to final eligibility determination, randomization and harvest procedure(s), which all must occur within 60 days of consent.

Process:

1. by COB Monday of the week to present case:
 - a. RC sends DCC email request for PI to present case review

- b. RC enters the following Baseline eCRFs : **Baseline Risk, PE, Labs, and Medications**
 - c. If candidate is on the transplant list, site sends written documentation to the DCC from the transplant team re: candidate's low likelihood of transplant prior to collection of 12-mo endpoint (i.e., transplant physician note documenting UNOS classification and anticipated time to transplant).
 - d. If applicable, RC notes in the email request any other relevant observations about the candidate (please provide study ID/acrostic) that might be useful in assessing the research risk, e.g. Stress test results (i.e., stress nuclear/pet, stress echo, stress MRI), history of exercise intolerance, history of drug use, comments by others team members, concerns about new findings (e.g., recent weight gain, recent change in NYHA class, etc.).
2. The DCC distributes summary data with the weekly investigator call agenda
 3. Site/study PIs review data prior to call
 4. The Steering Committee discusses cases and comes to consensus if a subject should move forward in the trial

4. Screen failures after consent and re-screening

Subjects may be excluded from the study if any of the baseline testing is not completed or meets an exclusion criterion during this period. If the subject becomes ineligible either during or upon completion of baseline testing and eligibility determination, only two additional forms are required to be submitted in the database: 1) the Eligibility eCRF with the reason for failure, and 2) the End of Study (EOS) eCRF with "screening failure" checked. A total of four eCRFs are necessary for a screen failed patient: 1) Screening, 2) Demographics, 3) Eligibility, and 4) EOS eCRFs. These forms will be monitored. See Section 27.3 of the eCRFs Users Guide for instructions on re-screening subjects post-consent. Please note, **only one screen failure payment will be made per patient**, even if they are reset to attempt baseline testing more than one time.

5. Delays and assessing the need for repeat testing

Please see table to help assess if tests need to be repeated.

Do baseline tests need to be repeated?

	Non-Core Tests		Core Tests
Time frame	No SF	SF	Both (No SF/SF)
Consent—Harvest	Check w/DCC	Redo	Redo only if meets criteria
Harvest—SPI	Check w/DCC	N/A	

SF: Screen Failure

Non-core baseline tests

- If subject has not been entered in the database as a screen failure and there have been no significant changes in the subject's clinical status during the delay, non-core baseline tests will most likely not need to be repeated; *contact the DCC to discuss specifics. You will need*

to file a protocol deviation for going beyond the 60 day window between consent and harvest.

- *If the subject has been entered in the database as a screen failure, you will need to rescreen the subject including repeating the non-core baseline tests.*
- The subject must remain eligible for the study in order to proceed with SPI; this determination may require repeat baseline testing. The Medical Monitor and Center PI will consider on a case-by-case basis whether non-core baseline tests need to be repeated and if so which ones.

Core baseline tests

- Core tests (screening MRI, baseline CPET, baseline MRI) do not need to be repeated ***provided that all the following criteria are met:***
 1. Initial test(s) affected by delay was acquired within the past twelve months.
 2. No MACE event has occurred since the initial test(s).
 3. No medication doses have been increased or new medications started that could affect test measures since the initial test(s) was acquired (particularly heart rate lowering medication; anticoagulation therapy would not trigger repeat MRI).
 4. There have been no other significant changes in the patient's medical status that might affect measures since the initial test(s).
- The protocol says the tests to determine eligibility as well as the harvest procedures will be done within 60 days of signing consent, and that the baseline MRI will be done within 30 days prior to the scheduled NOGA procedure. If a core test(s) meets the criteria above for not needing to be repeated, the DCC will allow the initial test(s) for eligibility determination and/or inclusion of the subject's baseline measures even if the test occurred outside the related window. You will need to file a protocol deviation for going beyond the 60-day window between consent and harvest or the 30-day window between baseline MRI and SPI.

V. Procedures (Stage 2) – Eligibility thru Follow-up

A. Eligibility Form and Eligibility Checklist

Once a subject has been determined eligible and the post-consent review approved, the RC will submit the Eligibility eCRF. In addition, all remaining baseline testing forms will need to be entered at this time. RCs will then submit the Eligibility Checklist eCRF, which allows the web application to perform an automated comparison of eligibility criteria with data from the baseline forms (see exception below) thereby doing a systematic check to help ensure that only eligible subjects are randomized.

The screening EF field on the Eligibility Checklist eCRF is manually entered with the value received on the MRI report from the core. Please enter the exact number from the MRI report.

Baseline testing forms must be entered before the Eligibility Checklist eCRF is functional. The Eligibility Checklist has a checkbox to mark if the subject passed the post-consent case review.

B. Scheduling BMA and RHC Procedures

Subjects determined to be eligible during baseline testing will have a bone marrow aspiration (BMA), as well as a right heart cath (RHC) either with or without endomyocardial biopsy (EMB) depending on randomization assignment. For subjects randomized to the MSCs alone and placebo groups, a RHC without EMB will be performed (a.k.a. sham biopsy). A RHC will include EMB for subjects randomized to the Combo and CSCs alone groups. RCs will coordinate the schedule for the BMA and RHC with their local cell processing lab (CPL), bone marrow harvest team, and EMB teams. The BMA and RHC with or without EMB (RHC/EMB) should be scheduled and completed within the 60-day baseline period after the subject signed consent. All procedures should take place on the same day.

Once the subject has been deemed eligible and the BMA and RHC/EMB date has been confirmed, the RC enters the **Harvest Procedures Schedule eCRF** which will generate an *automated email with scheduled BMA and RHC/EMB date* to: DCC, CPQCL, local CPL, CCMF, BRC, and site. This blind and updateable form must be entered at least 5 business days prior to harvest procedure(s). RCs should notify local CPLs of the confirmed harvest date as well. **This form is updateable should the date change.**

A maximum of 2 harvests can be scheduled per week across ALL centers. *Samples must be received at CMF before noon on Fridays; no weekend deliveries to CMF or BRC*

There are two calendars on SharePoint (located at *Member Resources/CONCERT*) to assist with scheduling harvests, the “Confirmed Harvest Schedule” and the “Working RC Harvest Schedule”. RCs can notify a PM of target harvest dates to be entered on the “Working” calendar. Only one date per study ID will be entered on either calendar. Coordinators should communicate with each other regarding likelihood of target dates being utilized when more than 2 per week are entered on the Working calendar. Subjects must be consented to the trial before they will be entered on the Working calendar. As the DCC receives the automated email notifications of confirmed harvest dates (generated by entry of the Harvest Procedures Schedule eCRF AFTER final eligibility determination), a PM will update the “Confirmed Harvest Schedule” calendar in SharePoint (located at *Member Resources/CONCERT*). After two harvests dates have been confirmed in a given week, the DCC will send a notification to all RCs with a reminder to check the calendars. If an alert is received for a 3rd confirmed harvest scheduled in a week, the site will be contacted about rescheduling.

A “Request for Processing” form must be completed by either the RC or the CPL. This document is sent with other required forms by the CPL to the CCMF once the harvest date has been scheduled.

CPLs provide BM & EMB labels, 300ml transfer pack for BM and spike, EMB vials and conical tube, cooler, cold packs, etc. RCs provide CPL with copies of completed and signed Eligibility and Eligibility Checklist CRFs, as well as a copy of the results of the infectious disease testing.

C. Randomization by Research Coordinator

After entry of Eligibility Checklist, RCs will be able to enter the Randomization eCRF which generates the assignment to one of the four treatment groups. Entry of the Randomization eCRF should take place as close as possible to 7 days prior to harvest procedures. After successful entry of the Randomization eCRF an *automated randomization notification email* will be sent to: DCC, core labs, CPQCL, local CPL, CCMF, BDS, site team, and all PIs. At this time RHC procedure information can be accessed by unblinded study team members with appropriate security credentials. Only cell processing and cell manufacturing staff will have access to actual treatment group (see details next section).

Once randomization has occurred, unblinded study team members (e.g., unblinded RC) with appropriate credentials will be able to look-up the RHC procedure and determine if the subject will have “RHC with EMB” or “RHC without EMB (sham)” (see look-up instructions in *MOP Binder Section 5, RHC/EMB Resources*).

D. Scheduling SPI and Baseline MRI

Once the harvest schedule is secured with all teams (and the subject), the RC will coordinate with the cath lab and NOGA interventionalist to arrange the date of SPI. **Please note the SPI must be scheduled not less than 14 weeks after harvest procedures, and ideally not more than 16 weeks post-harvest.** Please contact the DCC with issues related to scheduling within the 2-week timeframe, though please make every attempt to schedule no more than 16 weeks post-harvest. The RC will also need to contact Biologic Delivery Systems (BDS), **at least 2 weeks in advance**, to arrange for an onsite representative to be available for the SPI.

- BDS contact information: Mark Martin mmarti75@its.jnj.com 717-226-1320; Douglass Suehr dsuehr@its.jnj.com 412-708-1671

The RC will next schedule the subject for Baseline MRI to be collected within 30 days prior to SPI. The MRI Core will review the CONCERT-HF baseline MRIs for endpoint measures as well as do a comparison with the initial “screening MRI” done during baseline testing to demonstrate any change in EF between baseline testing and the intervention. This “baseline MRI” will be used for the baseline measurement. The initial screening MRI is used to determine eligibility.

The site is responsible for having a local read (safety or professional) of baseline MRIs prior to SPI and for making sure there is local documentation on file regarding presence of thrombus and presence of pericardial effusion.

The sites must receive a quality control (QC) email from the MRI Core that says the images passed QC before proceeding with SPI. The Core needs at least 3 business days after they receive the images and form to provide the QC review.

If MACE (see definition in protocol Section 3.5) occurs after the baseline MRI and before Day 0, a new MRI must be performed to ensure subject safety and continued eligibility. In this case the MRI closest to Day 0 will be used for the baseline measurement.

Sites will need to manage baseline MRI and SPI scheduling to accommodate the requirement for local reads/documentation and Core QC review of the baseline MRI prior to SPI. Once scheduling is secured, the RC will submit the **SPI/MRI Procedures Schedule eCRF** which will generate an *automated email with scheduled SPI and baseline MRI dates* to: DCC, CPQCL, local CPL, CCMF, core labs, BRC, BDS, and site.

Please confirm SPI date with BDS before submitting the form.

Please enter the SPI/MRI Procedures Schedule at least 2 weeks before the Day 0 visit window starts. This form is updateable should the date change.

E. Harvest Visit – BMA and RHC/EMB

Both BMA and RHC/EMB will be performed on the same day. See protocol section 6.2.2 for guidelines on anticoagulation therapy (ACT) management during the procedures.

Two 2D echoes will be performed on all subjects on the day of harvest: 1) a pre-RHC/EMB procedure echo to assess for pre-existing pericardial effusion, and 2) a post-RHC/EMB procedure echo within 6 hours to ensure no post-procedure effusion (even if subject is stable).

The CPL will supply the RC with the harvest bag, spike, and labels for the bone marrow harvest as well as the EMB collection vials and labels. The bone marrow label requires subject weight.

Before / During the BMA procedure:

The marrow will be aspirated into pre-heparinized syringes containing preservative-free heparin for a final effective dose of 100 units of heparin / ml of BM prior to the addition of heparin by the CPL to prepare the sample for shipping to the Miami CCMF.

- We offer the following guidance for Cell Processors and/or Research Coordinators to achieve the correct ratio:
 - Prepare the bone marrow collection syringes with heparin:BM ratio *For example, depending what Heparin concentration you use, add 1mL heparin in 20cc syringe (this example assumes Heparin concentration is 1000units/ml)*
 - Pool the collected bone marrow in the 300ml bag provided by the Miami CCMF
 - Do the math to get total heparin:BM ratio in bag and add heparin as needed to achieve 100:1 ratio
- The Bone Marrow bag label provided by the Miami CCMF (see below) should be filled out by the Cell Processors or Research Coordinator such that
 - “mL bone marrow” is the total amount aspirated from the patient and matches what is entered on the Bone Marrow Aspiration form submitted in the EDC
 - The CPLs do not change the BM volume on the Bone Marrow bag label provided by the Miami CCMF (see new procedure below)
 - “units Heparin” is the total amount added to the bone marrow via pre-heparinized syringes and/or added to bone marrow bag NOT INCLUDING the additional heparin added by the CPL to prepare the sample for shipping to the Miami CCMF

BONE MARROW COLLECTION	
FOR AUTOLOGOUS USE ONLY	
Space for bar code label if clinical site uses bar code labeling	
Patient ID _____	Collection Date _____
Acrostic _____	Collection Time _____
Clinical Site _____	_____ ml. bone marrow
Store at 15 to 24°C	_____ units Heparin
	Total volume Heparin _____ mL
NOT EVALUATED FOR INFECTIOUS SUBSTANCES	
Sponsor: CCTRN Data Coordinating Center University of Texas School of Public Health 1200 Herman Pressler, Suite 11009 Houston, TX 77030 713-500-9518	Manufacturer Name and address of Local Collection Facility

- The CPL affixes a separate sticker to the bone marrow bag that states, **“Supplemented with 52ml PlasmaLyte-A, 13ml 25% Buminate & 1750 Units of Heparin”**. This sticker will be modified to include a line for “ml BM in bag for Miami” for the CPL to indicate the final amount of bone marrow in the bag for shipping to the Miami CCMF (after removing samples for QC and biorepository if subject consented).

_____ ml BM in bag for Miami
 BM in bag supplemented with:
 80ml PlasmaLyte-A
 20ml 25% Buminate
 1750 Units of Heparin

Additional guidelines are provided in the CONCERT-HF protocol Appendix A. Subjects on aspirin and Plavix (Clopidogrel) at the time of consent should remain on these medications for the harvest procedures.

During assessment of subject prior to initiation of RHC procedure:
(this could occur prior to both harvest procedures)

Subject should be reevaluated for suitability to continue with the procedure if the following conditions/events occur during subject assessment prior to harvest procedure(s):

- systolic blood pressure (SBP) is <80 mmHg and constitutes a significant change from baseline, e.g., SBP change from ≥ 100 mmHg (at baseline) to <80 mmHg (at harvest);
- heart rate (HR) is >100 and constitutes a significant change from baseline, e.g., HR change from ≤ 80 (at baseline) to >100 (at harvest).

Procedures should be terminated if the subject is determined to have a change in NYHA Class to Class IV prior to harvest procedure(s).

During the RHC procedure (prior to EMB if applicable):

Subject should be reevaluated for suitability to continue with the procedure if the following conditions/events occur during the procedure (pressures should be measured at held expiration end diastole):

- baseline pulmonary artery (PA) systolic pressure is 50-59 mmHg;
- baseline right ventricle (RV) systolic pressure is 50-59 mmHg;
- baseline wedge pressure is 30-34 mmHg (if wedge pressure is >30 mmHg, an O2 sat measure should be taken).

Procedures should be terminated if the following conditions/events occur during the procedure:

- baseline PA systolic pressure is ≥ 60 mmHg;
- baseline RV systolic pressure is ≥ 60 mmHg;
- baseline wedge pressure is ≥ 35 mmHg.

Note:

- All EMB pieces should be divided into 2 cryovials.
- If a procedure is terminated, subjects can be evaluated for rescheduling if condition/event resolves. If a second procedure is undertaken and the conditions again meet the termination threshold, provided the subject is stable, a sham procedure will be performed to maintain subject and staff blinding.
- A script template for the sham biopsy can be found in *MOP Binder Section 5, RHC/EMB Resources*.

Harvest Visit

Biorepository consent status checked and noted
PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and medications updated
Labs (INR only for subjects on ACT)
2D echo <i>pre</i> -RHC/EMB procedure on all subjects
All paperwork for cell processing should be complete
Notify contact at local CP lab when the BMA has begun
Collect approximately 90 ± 10 ml bone marrow for cell processing
Notify contact at local CP lab when the RHC/EMB has begun
2D echo <i>within 6 hours post</i> -RHC/EMB procedure on all subjects
<i>*(if applicable)</i> Collect up to 6 EMB “bites” (~20 mg) of heart tissue for cell processing
<i>*Prepare samples and cooler(s) for cell processors and sign chain of custody forms</i>

**Unblinded RHC Team tasks*

Harvest visit notes:

- *INR required prior to harvest if subject is on ACT; must be <1.6 to proceed.*
- *If not consented to Biorepository, confirm with local CP lab so they will be prepared to dispose of extra aspirate.*
- *At the completion of the BM harvest, an insulated cooler with the labeled sterile BM (including subject weight (kg) is transferred to Cell Processing with appropriate documentation including the*

Chain of Custody form with subject and sample unique identifiers, and a temperature logger. Note: It is acceptable to transfer BM to harvest bag instead of leaving it in the syringe.

- *Work with the CPL to determine who will pick up and/or deliver BM and EMB including supplies (labels, transfer pack for BM and spike, EMB vials, cooler, cold packs, Chain of Custody, etc.).*
- *At the completion of the RHC/EMB procedure, an insulated cooler with or without EMB is transferred to Cell Processing with appropriate documentation including the Chain of Custody form with subject and sample unique identifiers, for transportation on wet ice, or equivalent. If applicable, the EMB samples will be divided into 2 sterile cryovials and placed inside the cooler.*
- *Events associated with the harvest visit are assessed by Unblinded team; entry of event eCRF must be done in blinded fashion; call DCC unblinded contacts for concerns/instruction.*

DCC unblinded contacts:

Shelly Sayre (Shelly.L.Sayre@uth.tmc.edu) 713-500-9529

Judy Bettencourt (Judith.L.Bettencourt@uth.tmc.edu) 713-500-9527

Lara Simpson (Lara.M.Simpson@uth.tmc.edu) 713-500-9503

F. Baseline MRI and Day 0 Visit

See protocol section 6.2.3 for guidelines on ACT management during the SPI procedure.

Baseline MRI Visit

(within 30 days prior to SPI)

Labs (CBC only)
Cardiac MRI with local read for pre-SPI safety review
ICD interrogation (if applicable, before & after cMRI)
Transmit images to MRI core

Baseline MRI visit notes:

- *A local read (safety or professional) of the baseline MRI is required prior to SPI, including local documentation on file regarding presence of thrombus and presence of pericardial effusion.*
- *Hematocrit and eGFR are required labs in conjunction with each MRI. To avoid patient having to come in the day before the MRI, values from an SOC visit are acceptable for the MRI worksheet under the following conditions:*
 - ***eGFR** measure taken prior to the date of the scheduled MRI can be used if it meets institution guidelines (usually within 30 days);*
 - ***hematocrit** measured at the time of the scan or as close as possible to the scan is preferred, though if not feasible in some cases, hematocrit within 30 days prior to the MRI scan is acceptable except for: premenopausal females, subjects with blood loss for any reason, or those having an invasive procedure between the hematocrit measure and MRI scan.*
 - *Record hematocrit and eGFR on MRI worksheet (no lab eCRF).*
- *If MACE (see definition in protocol Section 3.5) occurs after the baseline MRI and before Day 0, a new MRI must be performed to ensure subject safety and continued eligibility. In this case the MRI closest to Day 0 will be used for the baseline measurement.*
- *The interrogation report before the MRI should be assessed by local EP for v-tach / v-fib; RCs will enter AE eCRF if applicable and keep a copy of the report in the research record.*

- *Subjects should be advised to not eat, drink, or take supplements (particularly those containing metals such as iron) 4 hours before the MRI. They should consult with the study team on whether or not to take other medications or bring them to take after the test.*

Study Product Injection (SPI) (Day 0) Visit
(at least 14 weeks (98 days) after harvest procedures)

Pre-SPI:
Institutional Procedural Consent Signed
PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and Medications updated
Labs
<i>(If consented to Biorepository)</i>
Draw 20 ml PB <u>prior to sedation</u> for SPI
Receive cooler with product from cell processors and sign chain of custody
Pre-procedure vitals (including temperature)
ICD interrogation (if applicable) before SPI
SPI: Mapping and delivery of 15 injections, each 0.4 ml and infused over 60 secs
Post-procedure vitals (including temperature)
Post-SPI:
ECG (within 6 hours post-SPI)
2D Echo (within 6 hours post-SPI)
Labs (Troponin I or T within 8 ± 2 hours post-SPI)
Subject monitored on telemetry up to 24 hrs post-SPI or until discharge, whichever is sooner

SPI visit notes:

- *INR required prior to SPI if subject is on ACT; must be <1.6 to proceed.*
- *Pregnancy test must be completed within 36 hours prior to injection to proceed (if applicable).*
- *See BRC SOP for preparation of samples and snap freezing protocol (see **MOP Binder Section 8, Biorepository Procedures**).*
- *All events post-harvest assessed by blinded team.*

1. Delays that might affect study product and/or injection procedure

If there is a delay in the study product injection procedure (e.g., subject unstable) after the cells are shipped to the center, the following scenarios may apply:

- If the cells have not been thawed, they can be stored at the local CPL until SPI is rescheduled.
- If the cells have been thawed and the maximum time from thaw to delivery expires, the cells will be destroyed and the subject will receive placebo product (though remain in the treatment group to which they were assigned according to the intention-to-treat principle). Only unblinded personnel will know what the subject received.

If there is a delay in SPI, the maximum time between harvest and SPI is 12 months. That being said, we very much do *not* want to delay SPI that long if at all possible. The DCC guidance is to get the SPI done ASAP once eligibility is re-established.

2. Circumstances that may affect study product delivery before or during the NOGA Catheterization Procedure

CONCERT-HF protocol, Section 5.13: If any of the following symptoms occur before or during SPI, they could indicate a serious clinical deterioration. If any of the following events/symptoms occurs, the procedure should be temporarily halted and the subject should be reevaluated for suitability to continue with the treatment under investigation:

1. Hypotensive episode defined as a sustained drop in blood pressure exceeding 20mm/Hg not responsive to fluid administration
2. Hemodynamically significant arrhythmia requiring anti-arrhythmic therapy
3. Two episodes of sustained ventricular tachycardia/ventricular fibrillation requiring cardioversion
4. Hemodynamic instability
5. Fever (Temperature increase to $\geq 100.4^{\circ}\text{F}$)
6. Cardiac perforation
7. Clinical signs and symptoms indicating a cerebrovascular accident

G. Day 1 and Discharge

Day 1 (post-SPI)

PE/vitals
ECG (<i>before discharge</i>)
Labs (<i>collected 24 hours post SPI or immediately prior to discharge whichever is sooner</i>)
(<i>If consented to Biorepository</i>) Draw 20 ml PB
AE/SAE assessment and Medications updated
Provide temperature log to subject

Day 1 visit notes:

- *The subject is monitored overnight and provided with a log for monitoring temperature twice a day for the next seven days (see Attachment A for temperature log). This log may be returned at the 1 week visit.*
- *See BRC SOP for preparation of samples and snap freezing protocol (see **MOP Binder Section 8, Biorepository Procedures**).*
- *All events post-harvest assessed by blinded team.*

H. Follow-up Visits

Follow-up visits will take place at regularly scheduled intervals counting from SPI/Day 0. Visits can be done over multiple days as long as all assessments are completed within the visit window.

Follow-up Visits Notes (affect multiple visits):

- *For visits that require BRC blood draws, see BRC SOP for preparation of samples and snap freezing protocol (see **MOP Binder Section 8, Biorepository Procedures**).*
- *All events post-harvest assessed by blinded team.*

Below is a schedule of activities and visit window for each follow-up visit:

Week 1 Follow-Up
(7 days post-SPI $\pm$ 3 days)

PE/vitals
AE/SAE assessment and Medications updated
ECG
Labs
(If consented to Biorepository) Draw 20 ml PB
Collect temperature log from subject

Month 1 Follow-Up
(30 days post-SPI $\pm$ 7 days)

PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and Medications updated
Labs
(If consented to Biorepository) Draw 20 ml PB
Collect temperature log (if not already received)

Month 3 Follow-Up
(90 days post-SPI $\pm$ 14 days)

PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and Medications updated
Labs
MLHF questionnaire

Visit Notes for the Months 6 and 12 visits:

- See pages 13-14 “Baseline Testing and Eligibility Determination”
- MRI technologists will need the baseline MRI completion form, QC form, and to review the images. Techs can access the images from their local PACS, or on WebPAX and as long as they have their site log-on.
- The interrogation report before the MRI will be assessed by local EP for v-tach / v-fib, RCs enter event eCRFs if applicable, and a copy of report should be keep in research record.
- Subjects should be advised to not eat, drink, or take supplements (particularly those containing metals such as iron) 4 hours before the MRI. They should consult with the study team on whether or not to take other medications or bring them to take after the test.
- If MRI and CPET are done on the same day, care should be taken to ensure there are no lingering effects of sedatives that may be administered in conjunction with MRI.
- Hematocrit and eGFR are required labs in conjunction with each MRI. To avoid patient having to come in the day before the MRI, values from an SOC visit are acceptable for the MRI worksheet under the following conditions:
 - eGFR measure taken prior to the date of the scheduled MRI can be used if it meets institution guidelines (usually within 30 days);

- **hematocrit** measured at the time of the scan or as close as possible to the scan is preferred, though if not feasible in some cases, hematocrit within 30 days prior to the MRI scan is acceptable except for: premenopausal females, subjects with blood loss for any reason, or those having an invasive procedure between the hematocrit measure and MRI scan.
 - Record hematocrit and eGFR on MRI worksheet. The values from the lab draw associated with the study visit should be entered on the lab eCRF.
- If applicable, see next section “Heart Transplants, CRT, or LVADs before Months 6 or 12” for instructions.

Month 6 Follow-Up

(180 days post-SPI $\pm$ 30 days)

PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and Medications updated
ECG
Labs
<i>(If consented to Biorepository) Draw 20 ml PB</i>
Cardiac MRI
ICD interrogation (if applicable, before & after cMRI)
Transmit images to MRI core
CPET (Treadmill)
Transmit test documentation to CPET core
Six minute walk—Test 1 (T1) (Must be conducted at least 1 hour after last meal)
Six minute walk—Test 2 (T2) (Must be conducted at least 30 mins after T1)
Six minute walk—Test 3 (done ONLY if % change b/t T1 & T2 >10%) (Must be conducted at least 30 mins after T2)
MLHF questionnaire
Sexual function questionnaire

Month 12 Follow-Up

(365 days post-SPI $\pm$ 30 days)

PE/vitals (with NYHA and CCS classifications)
AE/SAE assessment and Medications updated
ECG
Labs
Cardiac MRI
ICD interrogation (if applicable, before & after cMRI)
Transmit images to MRI core
CPET (Treadmill)
Transmit test documentation to CPET core
Six minute walk—Test 1 (T1) (Must be conducted at least 1 hour after last meal)

Six minute walk—Test 2 (T2) (Must be conducted at least 30 mins after T1)
Six minute walk—Test 3 (done ONLY if % change b/t T1 & T2 >10%) (Must be conducted at least 30 mins after T2)
MLHF questionnaire
Sexual function questionnaire

Month 24 Telephone Contact
(730 days post-SPI ± 30 days)

Assess morbidity and mortality
End of Study

I. Heart Transplants, CRT, or LVADs before Months 6 or 12

If subjects are transplanted, receive CRT, or receive an LVAD prior to the month 6 or 12 visits, collect all endpoint measures (MRI, CPET, 6MWTs, MLHFQ, sexual function questionnaire, NT-proBNP) before the procedure.

Follow subjects for safety, with study visits to include: physical exam, AE/SAE assessment, and medication updates. Enter missing forms for the rest.

All subjects will continue to be followed for safety (provided they are not withdrawn from the study) and seen for study visits, but no further endpoint collection will be completed after the heart transplant, CRT, or LVAD procedure. Adverse event reporting will continue as per section 7.3 of the protocol. For sample collection on explanted hearts, see [MOP Binder Section 8, Biorepository Procedures](#).

J. End of Study

All subjects who are consented to the study will need an End of Study form submitted (see [eCRF Users Guide](#)). If the Reason for Withdrawal is related to an SAE, even if the subject ultimately withdrew consent, please use SAE as the reason. Withdrawal of consent should be used when a subject changes their mind for reasons that don't involve an adverse event.

VI. Missed Visits and Interim Visits

All subjects should be encouraged to complete all scheduled follow-up visits. Subjects should be contacted well in advance of their follow-up visit.

A. Missed Visits and Lost to Follow-up

All subjects should be encouraged to complete all scheduled follow-up visits. Subjects should be contacted well in advance of their follow-up visit. In addition, if a subject misses a follow-up visit,

contact the subject by phone to reschedule the visit in the window. After three failed telephone contacts, send the subject a letter by certified mail, asking them to contact the clinic. Subjects will be considered lost to follow-up after 3 consecutive failed telephone contacts AND one certified letter returned to the site. Be sure to document all attempts to contact a subject and have these available for the Monitor for inspection ([Attachment B – Subject Contact Log](#)). Guidelines for submitting forms for missed visits, including missing form, protocol deviation for the missed visit, and end of study forms can be found in the [eCRF Users Guide](#).

B. Interim Visits

An interim physical exam or lab form should be used when a subject is seen or has tests that are in addition to a scheduled follow-up visit time point. If the visit is for a regularly scheduled follow-up but is outside the window, please use the form that corresponds with that visit and, put a note in the comments as to why it is outside the time window.

VII. Reporting Adverse Events, Unanticipated Problems, and Protocol Deviations/Violations

For detailed information regarding the reporting of adverse events, unanticipated problems, and protocol deviations/violations, please see section 7 of the CONCERT-HF protocol.

There are three eCRF forms to be used for documenting adverse events, unanticipated problems, and deviations/violations from the protocol in the web application (see [eCRF Users Guide](#)). In addition, when these eCRF forms are submitted, **an automatic email will be sent to the DCC personnel** listed below as well as the DCC project managers.

- 1) Dr. Lara Simpson: 713-500-9503; Lara.M.Simpson@uth.tmc.edu
- 2) Dr. Lem Moyé: 713-500-9518; Lemmoye@msn.com

Adverse Events (AEs): An *adverse event* (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study. The event does not need to have a causal relationship with treatment.

Suspected Adverse Reaction (SARs): A *suspected adverse reaction* (SAR) is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting “reasonable possibility” means there is evidence to suggest a causal relationship between the study product/procedures and the adverse event.

Serious Adverse Events (SAEs) or Serious Suspected Adverse Reaction (SSAR): A *serious adverse event* (SAE) or *serious suspected adverse reaction* (SSAR) is defined as an AE/SAR which, in the view of the Investigator or Sponsor, results in: 1) Death; 2) a life-threatening event (i.e. an event in which the subject was at risk of death at the time of the event; it does not refer to an event

which hypothetically might have caused death if it were more severe); 3) inpatient hospitalization of > 24 hours or prolongation of existing hospitalization; 4) a significant disability/incapacity; or 5) a congenital anomaly/birth defect. Other important medical events may be considered SAEs/SSARs if, in the opinion of the Investigator or DCC, they jeopardize the subject or require intervention to prevent one of the other outcomes listed above.

A. Adverse Event Reporting

For all events (AE/SAR and SAE/SSAR), monitoring and reporting to the DCC begins at the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study related procedure and/or receiving investigational product, through and including 30 calendar days after the subject completes the 12 month clinic visit. Only grade 2 and higher events should be submitted on the Adverse Event eCRF. (If your site wishes to capture grade 1 events, a sample event log is included as [Attachment C](#)). **Do not delay the initial reporting of an event in order to obtain resolution or follow up information.** Please group all related signs, symptoms, and abnormal diagnostic procedure results under one diagnosis (a 'possible' or 'presumed' diagnosis is acceptable, such as 'possible influenza' rather than 'fever, severe fatigue, persistent cough, aching muscles'). Only provide signs/symptoms/abnormal test results/procedures performed as the event diagnosis if they are diagnostically unrelated and there is not yet a possible or presumed diagnosis under which they can be classified. The investigator is required to report SAE/SSAR within 24 hours of learning of it. This information can also be communicated via phone, email, or fax (713-486-0981) if necessary. See [Attachment D for SAE/Clinical Endpoint Fax Coversheet](#).

B. Clinical Event Reporting

Per the protocol, the relative safety of the study products will be assessed by collecting and analyzing major adverse cardiac events (MACE) as well as other significant clinical events. AEs that might meet the definition of a clinical event will be adjudicated by the CCTRN Clinical Endpoints Committee. Coordinators will receive a request for supporting documentation for all AEs that are flagged for adjudication ([Attachment D](#)). This request for documentation is the same as what is collected for all SAEs (as described above); however it will also be required in CONCERT-HF for AEs that might meet the definition of a clinical event regardless of seriousness.

C. Unanticipated Problems, Protocol Deviations/Violations, and Protocol Exemptions

Unanticipated Problem: An incident, experience, or outcome that specifically causes increased risk to the study or to its subjects which may be of medical or non-medical etiology. The event is unexpected, definitely, probably or possibly related to participation in the research, and places subjects or others at greater risk of harm than was previously known (e.g. loss/theft of a laptop containing identifiable, sensitive subject information; device failures; incarceration of a study staff member).

Protocol Deviation: A departure from the IRB-approved research plan that does not constitute a threat to the health, safety, and welfare of a research subject, and has no substantive effect on the value of the data collected (e.g. follow up visits which take place outside the specified time outlined in the protocol or blood samples collected at times close to but not precisely at the times specified in the protocol).

Protocol Exemption: A prospectively approved deviation granted by the study sponsor that does not increase the risk to the subject (e.g., minor exceptions to the inclusion/exclusion criteria or an exception to the treatment schedule).

Protocol Violation: A departure from the IRB-approved research plan that jeopardizes the health, safety, welfare, or privacy of a research subject or the integrity of the study (e.g. knowingly or unknowingly delivering study product to the subject which does not meet release criteria or randomizing a subject who does not meet enrollment criteria).

1. Unanticipated problems

Report **unanticipated problems** to the DCC via the database (see [eCRFs Users Guide](#)) within 24 hours of PI or study staff awareness of event.

2. Protocol deviation/violations and exemption requests

Report **protocol deviation/violations** to the DCC via the database (see [eCRFs Users Guide](#)) within 7 days of the PI or staff's awareness of the event. If the departure from the protocol is required to protect the life or physical well-being of a subject, the DCC must be notified within 24 hours.

- Fill out the hard copy Protocol Deviation CRF (workbook) located either in your Manual of Operations binder (see *MOP Binder Section 4*) or printable form from the CCTRn website (www.cctrn.org).
- Enter the information from the workbook into the CCTRn web application Protocol Deviation form (see [eCRFs Users Guide](#)) which describes the event.
 - If the protocol deviation is being completed to request an exemption, you should check the box labeled, "Event has not occurred (exemption request)".
 - If the protocol violation was submitted for an event that has already occurred, the receipt of information will be acknowledged.
- The DCC will complete the bottom portion of the form and enter if the exemption or waiver was granted.
- Copies of all protocol deviation/exemption correspondence should be placed in the corresponding subject's research record for documentation purposes.

For the purposes of IRB and other local regulatory reporting, the DCC will provide each site with regular reports which include enrollment figures; general demographics; and number, frequency, and type of AEs, SAEs, and UPs for the site as well as the overall Network. Reports regarding frequency and type of protocol deviations will also be made available to each individual site.

VIII. Data Clarifications/Data Change Requests (DCCRs)

DCCRs will only be used for requests to eCRFs post-monitoring. Please see the [eCRFs Users Guide](#) for information on entry, verification, or modification to database forms. This document is located at: [Member Resources/CONCERT/eCRF Users Guides/Stage 2](#).

IX. Transferring Subjects between Centers

In the case that a subject needs to transfer between CCTRN centers, please contact a project manager at the DCC to inform them of the situation and they will facilitate this process. Please note: All outstanding data entry and data queries must be completed, reviewed, and applicable forms paid by the DCC prior to activating the transfer. Coordinators at both locations (transferring and receiving) will ensure the transfer of the subject's care and his/her medical and research records.

X. Site and Monitoring Visits

To ensure the highest quality data collection, your site will undergo research monitoring periodically. These visits will take place at the outset of enrollment, at regularly scheduled intervals during the trial, and at the close of the study. These visits are to ensure that you, your Principal Investigator, and the Network are collecting the best available data while protecting the subject's interest. All visits should be scheduled several weeks in advance to ensure that all required research team staff are available to meet with the monitor.

Monitoring visits consist of: Interim Monitoring Visits (IMVs), Close-out Visits (COVs), and a biennial full regulatory document review.

A. Interim Monitoring Visit (IMV)

1. Remote Monitoring

The site will send (via PDF/email) all the relevant source documents to the Clinical Monitor for 100% source data verification (SDV) by remote monitoring of baseline, harvest, and treatment eCRFs to help ensure that the site is following the protocol and completing eCRFs and workbooks appropriately. Each center will send documentation for two Stage 2 subjects unless documentation from two subjects including at least 1 Combo subject was sent during Stage 1. If this criteria is not met in Stage 1, i.e., if < 2 subjects enrolled during Stage 1 or only SOC subjects, then the process will be completed with Stage 2 subjects.

The complete list of documents required for initial remote monitoring are listed in [Attachment E-CONCERT Remote Monitoring Checklist Fax Coversheet](#). **BE SURE TO DE-IDENTIFY ALL DOCUMENTS.** All documents should be sent to the DCC within 5 business days after study product injection (Day 0). The Clinical Monitor or designee will review this documentation within 72 hours.

The DCC may place a site on hold until any identified issues are resolved before continuing enrollment.

In other remote monitoring situations, the Clinical Monitor or designee will respond within 5 business days after remote monitoring has been performed, sending correspondence to site coordinator, listing which eCRFs were reviewed and any action items.

2. Onsite Monitoring

During the first on-site monitoring visit, which will be scheduled within six weeks of the first subject treatment (Day 0), the Clinical Monitor will review the original source documents for baseline through treatment to ensure they match the documents that were sent for remote monitoring.

Interim Monitoring Visits (IMVs) will occur periodically depending on site enrollment. The Clinical Monitor, in consultation with the PM or designee, will determine the necessity and frequency of additional IMVs based on site performance and adherence to SOPs. Visits are announced in a confirmation letter. **PI attendance is requested at least semiannually.** Action items are included in a follow-up letter. It is expected that the average duration of each IMV will be 1 to 3 days per protocol (depending on the number of subjects to be reviewed and any outstanding issues at that visit).

Additional IMVs may be required prior to a Data and Safety Monitoring Board (DSMB) meeting. These additional visits would allow for the collection of all data up to a specified date to ensure completeness of DSMB reports. The dates and data requirements for this meeting will be conveyed to the Monitor by the PM or designee.

3. Final Monitoring / Close-out Visit (COV)

Close-out Visits (COVs) may be completed after all subject data queries are resolved. COV's are within the discretion of the PM or designee. If an Interim Monitoring Visit (IMV) is conducted at the same time of the COV, a separate IMV report may be completed.

4. Biennial On-site Regulatory Document Review

Full regulatory document review (hard copy or electronic) will be conducted at the site biennially. Reviews may be conducted simultaneously with an IMV; in this case, separate reports will be filed.

XI. Biorepository Sample Collection

This protocol includes peripheral blood (PB) collections for the Biorepository Core (BRC) at several time points during the trial. In addition, a sample of bone marrow (BM) will also be sent to the BRC with appropriate consent. RCs will be responsible for assuring accurate collection, processing, storing, and shipment of the PB samples to the Biorepository.

In order to minimize study costs, RCs will be responsible for ensuring the local CPL receives the first shipment of BRC supplies for BM collection as these supplies will be sent to the coordinators with initial shipment of BRC study supplies. To make the process as efficient as possible, the BRC will send self-contained BM kits that can be passed on to the CPL without having to assess supplies. The CPL will then be responsible for ordering re-supplies directly from the BRC.

The standard operating procedure for the management of these samples is included in *MOP Binder Section 8, Biorepository Procedures*.

XII. Subject Care Reimbursement

A. Form Payments

Payments to centers are made on a per form basis. A payment schedule by form is included in *MOP Binder Section 7, Payment Information*. As eCRFs are submitted in the CCTR web application, they are checked for errors, and the form is marked for payment by the DCC. Submitted forms that meet payment criteria are paid automatically on a monthly basis. Sites will receive a check every month along with a detailed invoice with itemized payments for forms that have been submitted via the electronic CRFs in the web application. The invoice will be organized by study so all payments for each study are listed together with a subtotal if the site is participating in multiple CCTR studies. This system for payment alleviates site billing departments' administrative burden of having to generate monthly invoices. Please contact a DCC project manager if you need a reprint of a payment voucher.

B. Subject Travel Stipends (in-town residents)

Subject travel stipends can be provided to subjects to reimburse them for reasonable expenses incurred for travel to and from the center for study visits (e.g., gas, parking, etc.). ***Please note that these are travel reimbursements and NOT payment for participating in the study.*** The money for subject reimbursements should be used from surplus infrastructure funds at the site. The following guidance should be applied when developing the reimbursement strategy: 1) Reimbursements should be provided in a uniform and consistent manner, though actual mileage ranges and reimbursement amounts can be center specific; and 2) Reimbursements should be based on the distance the subjects must travel and use a flat rate for each distance category.

For example, a center might use the following strategy:

Miles from center	Reimbursement per visit
<25	\$25
25-50	\$50
51-100	\$100

>100	\$150
------	-------

All subject travel stipend reimbursement payments should be kept on a log with subject ID, acrostic, study visit(s), distance traveled (miles) and amount paid. See [Attachment F for In-Town Travel Stipend Reimbursement Log](#).

C. Subject Travel Reimbursements (out-of-town residents)

CCTRN recognizes that for some clinical trial participants the cost of traveling to the clinical center may be a significant obstacle, and that reimbursement for reasonable travel expenses may be appropriate. Based on discussions with the NHLBI Program Director, use of NHLBI CCTRN RO1 grants for this purpose is permitted. Accordingly, for the CONCERT-HF trial, clinical centers will be allowed to use funds from their CCTRN budgets to help offset patient travel costs with the provisos listed below.

PLEASE NOTE: DCC review of consent language, and subsequent approval by your IRB of the consent language, is REQUIRED prior to providing any travel reimbursements.

1. Stipulations for travel reimbursements:

- Reimbursements may not be made for international travel.
- Sites should be diligent in reviewing patient records prior to inviting potential participants to the center. In other words, there must be reasonable evidence that the individual would be a likely candidate for the trial. For example, if there is no recent evidence of LV dysfunction in a patient's chart, one would want to see a standard-of-care imaging assessment, to confirm that the time/travel/expense is justified.
- Sites will be responsible for paying the travel reimbursements and keeping appropriate records in the participants file or CRF; this includes collection and tracking of the receipts and reimbursements to the patient, as well as for making pre-approval determinations as is outlined in the ICF language below.
- There is no retroactive reimbursement for travel. Please discuss with the potential participant prior to establishing an initial appointment.
- Sites are responsible for obtaining IRB approval for the consent wording associated with reimbursement (see template below). Sites that do not have sufficient funds for patient travel reimbursement are not required to add this language to their consent documents.
- Sites will be responsible for working with the study schedule to maximize the individual's participation while minimizing the time it takes to collect the data. In other words, if a visit can be collected on one day, a best effort should be made to collect the data in one day and not spread it out any further than is needed to accurately/safely collect the data.

2. Consent form wording:

"If you are an out-of-town resident (greater than 150 miles), travel and lodging expenses will be reimbursed on the basis of written receipts with a maximum amount of \$700 per visit. Hotel

accommodations are authorized for a standard room and should not exceed \$200 per night without prior written approval. Prior written approval also is required for hotel accommodations exceeding more than 1 night. Air travel is authorized for economy class on a common carrier and should be booked at least 14 days in advance. You will receive reimbursement by check upon receipt of flight and hotel invoices. You will not receive reimbursement for any expenses after you are no longer in the study. While you are in the study, you should continue to get regular medical care. You (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not a part of this study.”

Attachment A – Week 1 Subject Temperature Log

The purpose of this temperature log is to monitor you for infection following your injection procedure. Please record your temperature twice daily. Signs and symptoms of infection include: fever, malaise (feeling tired), disorientation, chills, being extra sleepy or rapid heart rate (over 110 beats per minute). If you have any elevation in temperature, please notify <Insert Coordinator Name Here> at <Insert Contact Info Here>.

Study ID Number: _____ Acrostic: _____

Date of Study Product Injection: _____

Week 1

Date	AM	PM

Attachment B – Subject Contact Log

[illegible]

Attachment C – Grade 1 Event Log

Acrostic Identifier:											
Study ID:											
Adverse Event Log											
Outcome Status	Serious	Expectedness	Severity	Relationship to Study / Study Product:	Outcome Attributed to AE						Study Status
1=Resolved (must have an end date) 2=Ongoing	1=Not Serious 2=Serious	1=Expected 2=Unexpected	1=Mild 2=Moderate 3=Severe 4=Life threatening or permanently disabling 5=Fatal	1=Definite 2=Probable 3=Possible 4=Unlikely 5=Unrelated	1=Resolved, no treatment, no sequelae 2=Resolved, no treatment, with sequelae 3=Resolved with treatment, no sequelae 4=Resolved with treatment and sequelae 5=Still present, no treatment 6=Still present, being treated						1=Continuing in Study 2=Withdrawn
Description of Event (Diagnosis)			Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Outcome Status	Serious	Expectedness	Severity	Relationship to Study/Study Product	Outcome Attributed to AE	Study Status
1.											
2.											
3.											
4.											



Attachment D – Serious Adverse Event/Clinical Endpoint

FAX Coversheet

FAX NUMBER: 713-486-0981

ATTENTION: Dr. Lara Simpson or Project Management Team

TOTAL NUMBER OF PAGES (INCLUDING THIS PAGE):

TODAY'S DATE:

SITE:

EVENT REFERENCE NUMBER:

(↑IMPORTANT – FROM COMPLETED EVENT FORM IN EDC)

STUDY ID:

ACROSTIC:

EVENT NAME (DIAGNOSIS):

DATE OF EVENT:
(ONSET)

DATE OF SAE REPORT
IN DATABASE:

SITE REPRESENTATIVE NAME:

SIGNATURE:

☐

INITIAL SUBMISSION

☐

FOLLOW-UP SUBMISSION

FOLLOWING ARE THE NOTED DOCUMENTS FOR THE SERIOUS ADVERSE EVENT(S)/CLINICAL ENDPOINT(S):

DOCUMENTATION	INCLUDED	PENDING	N/A	EXPLAIN (IF NEEDED & NOT INCLUDED)*
CLINIC NOTES FROM LAST PATIENT CONTACT				
CONSULTATION REPORT(S) – CARDIOLOGY, NEUROLOGY, ETC.				
DEATH CERTIFICATE				
DEATH SUMMARY				
DISCHARGE SUMMARY				
EKG REPORT(S)				
ER REPORT				
HISTORY & PHYSICAL				
IMAGING REPORTS: INCLUDING X-RAY, CT, MRI, ECHO, US, ETC.				
INTERROGATION REPORT				
LABS: CHEM, CBC, CARDIAC ENZYMES, ETC.				
OFFICE/CLINIC NOTE(S)				
OPERATIVE REPORT(S)				
TISSUE PATHOLOGY REPORT(S)				

*PLEASE REFER TO THE CONCERT CLINICAL ENDPOINTS AND DEFINITIONS DOCUMENT FOR LISTING OF NEEDED/REQUIRED DOCUMENTATION FOR SAFETY & CLINICAL ENDPOINT REVIEW

ADDITIONAL COMMENTS:

Attachment E – Remote Monitoring Checklist-CONCERT-HF

****DE-IDENTIFY ALL RECORDS BEFORE SENDING TO THE DCC****



CONCERT-HF (Stage 2) Remote Monitoring Checklist

Attention: Uchechi Nwosu (Uchechi.U.Nwosu@uth.tmc.edu)

Sibi Mathew (Sibi.R.Mathew@uth.tmc.edu)

Total number of pages (including this page):

Today's Date:

Site:

Study ID:

Patient Acrostic:

Site Representative Name:

Signature:

Please attach the following workbook forms and source documents from Eligibility through Study Product Injection (SPI).

- | | |
|---|--|
| ☐ Eligibility | ☐ Bone Marrow Aspiration (BMA) |
| ☐ Baseline Physical Exam | ☐ Right Heart Catheter (RHC) |
| ☐ Medication/Allergy List | ☐ Study Product Injection (SPI) |
| ☐ Six Minute Walk | ☐ Other: _____ |
| ☐ Baseline Labs | |
| ☐ Infectious Disease Lab Reports | |
| ☐ Baseline Risk | |
| ☐ Eligibility Checklist | |

All forms and documents should be sent within five working days of Study Product Injection (SPI).

Comments:

Attachment F – In-Town Travel Stipend Reimbursement Log

Study ID	Acroscopic	Study Visit	Reimbursement Amount	Travel distance (miles)
Example 01-1234-01	ACRPUE	1 week f/u	\$50.00	56 miles