Cardiovascular Cell Therapy Research Network

Manual of Operating Procedures for the FOCUS Protocol

Randomized, Controlled, Phase II, Double-Blind Trial of Intramyocardial Injection of Autologous Bone Marrow Mononuclear Cells under Electromechanical Guidance for Patients with Chronic Ischemic Heart Disease and Left Ventricular Dysfunction

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CCTRN FOCUS PROTOCOL

I. Study overview

Introduction: Congestive heart failure (CHF) is a cardiovascular problem worldwide that continues to increase in frequency, causing major morbidity and has a 5 year mortality rate of 50% in patients with end stage disease. Existent therapies are not adequate to prevent the progressive increase in the problem. Selected bone marrow-derived mononuclear cells have the unique ability to differentiate into new blood vessels and cardiac myocytes. This study will be an extension of a previous trial using an endocardial delivery platform to evaluate a larger number of bone marrow-derived mononuclear cells (dose range: 80×10^6 to 110×10^6) in a patient population with CHF.

Study Design: This is a randomized, Phase II, double blind, placebo controlled clinical trial that will assess the effect of autologous bone marrow mononuclear cells delivered transendocardially to patients with CAD, LV dysfunction, and limiting heart failure and/or angina. Myocardial perfusion, LV contractile performance, and maximal oxygen consumption are primary efficacy measures. Patient safety of this cell-based therapy will also be determined.

Target population: 87 individuals (58 cell treated and 29 receiving placebo); male and female, who have no contraindications to bone marrow cell infusions and who have coronary anatomies unfavorable for coronary artery surgery or percutaneous coronary artery interventions, LV dysfunction (LVEFs ≤45%) and limiting heart failure and/or angina.

Enrollment Period: Enrollment will be continuous at all five centers until the sample size of 87 is reached (includes placebo and active groups). Final endpoint determination will occur six months after enrollment. Participants will be followed for an additional 4.5 years for efficacy.

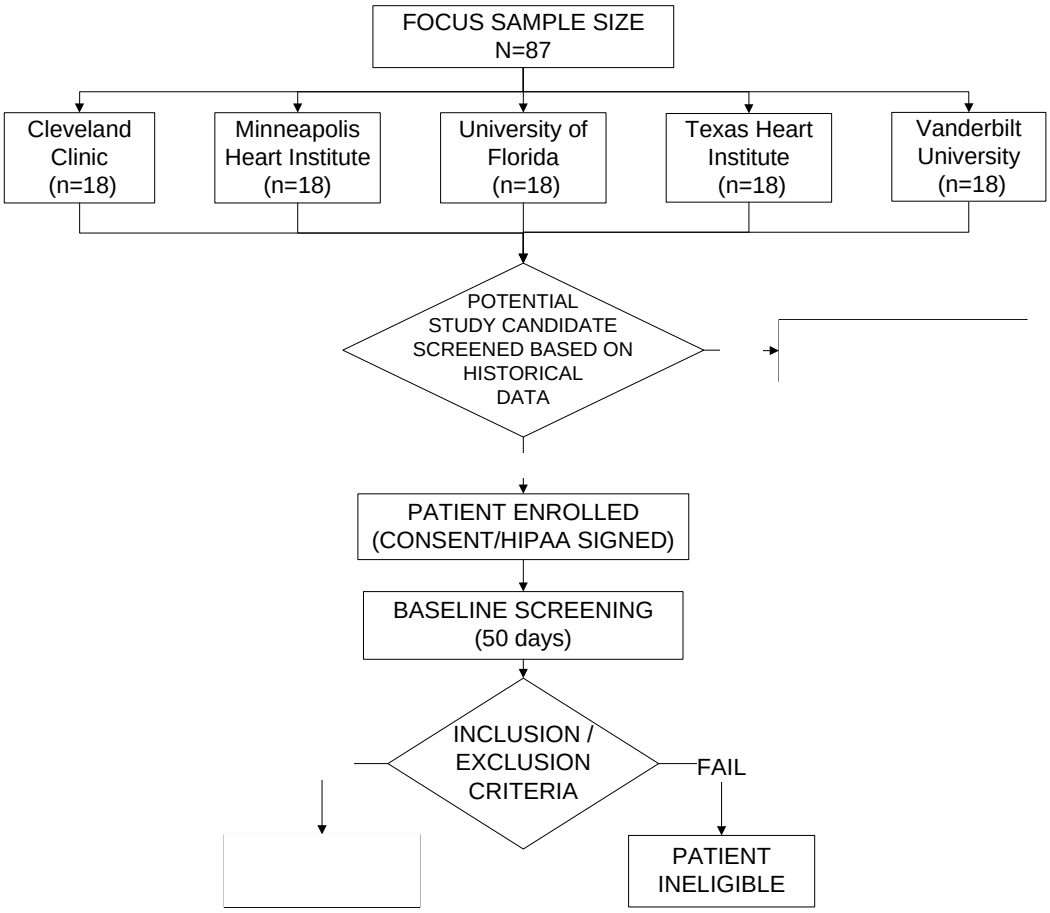
II. Description of Study Phases

A. Screening of Potential Candidates: The screening phase of the study reviews potential participant characteristics based on available data (i.e., medical record review). This information is evaluated prior to consenting to the study. Limited information is recorded on the screening log (see example Screening Log in MOP Binder Section 2) to capture the population approached for the study. See details for completing this log in Section III below.

B. Consent and Enrollment: Individuals who are screened and appear to meet eligibility requirements can then be approached and invited to participate in the study. If the candidate

is identified while in the hospital, the individual may be approached with his/her physician's knowledge. Individuals who have learned about the study through external sources (internet, private physician, etc.) and initiate contact with the clinical center can be invited to provide additional medical information to determine eligibility. Such individuals should be asked to have their physician fax relevant medical records (see example letters via the *Research Coordinator Resources/Common Resources* section of the CCTRN website.) to the clinical center to complete preliminary screening. Those individuals who appear to be eligible candidates would then be scheduled for consent and baseline screening (3-4 day period). The research coordinator would then review the informed consent (process is detailed in section III B) with the eligible candidate, obtain consent and enter demographic information into the CCTRN web-based database to enroll the individual and obtain a study ID and acrostic.

Enrollment Flowchart



C. Baseline Testing: After obtaining a study ID and acrostic, the research coordinator collects a series of baseline assessments (within the 50 day screening period) to determine whether the individual truly is a viable candidate for study product injection. Enrolled subjects (i.e., those who qualify following baseline assessment) would be scheduled for the bone marrow aspiration and mapping/injection procedures at a future date (but within the 50 day screening period).

D. Randomization to Study Product: Individuals who meet the following criteria: 1) initial screen demonstrates that they have successfully met eligibility criteria, 2) all baseline assessments are complete, 3) passed the Treatment Checklist, and 4) bone marrow cells have met the cell processing release criteria, are then randomized to a study product assignment (cell therapy or placebo) (Attachment 1).

E. Intervention: Bone marrow aspiration, cell processing, and mapping/study product injection procedures follow the assignment to cell therapy or placebo. The participant is monitored overnight and, with physician authorization, is discharged within 24 hours.

F. Follow up Visits: Participants are asked to return to the clinical center for follow up visits at 1- and 4- weeks, 3-, 6-, and 12-months. Participants will receive an annual telephone call at Years 2-5 post intervention.

III. Procedures by Study Phase

A schedule of all study procedures for the FOCUS trial can be found in Attachment 6.

A. Screening of Potential Candidates

Frequently asked questions (FAQs) related to screening candidates will be developed and distributed to each center (see MOP Binder Section 6). This document will also be made available on the CCTRN website (www.cctrn.org) by navigating to the Research Coordinator Resources/Common Resources link.

Completing the Screening Log (See example Screening Log, MOP Binder Section 2):

At a minimum, the following information must be collected on all individuals considered for participation: race/ethnicity, gender, date of screening, and reason for screen failure (if applicable). If the individual fails to meet the inclusion criteria, please note the reason for screen failure on the log (using the coding provided in the instructions on the log). For individuals who sign consent and have subsequent data entered in the database, please note the assigned study ID on the screening log. The completed screening log should therefore represent a comprehensive list of all individuals considered for the study (i.e. both pre-consent screen failures and consenting participants).

The information entered on the screening log should be kept on-site for review by the Clinical Research Associate during monitoring visits. A copy of the cumulative log will be emailed to the Data Coordinating Center every Monday and Network-wide reports will be presented during the regular Steering Committee teleconferences.

B. Consent and Enrollment

i. Consent

The informed consent process is as follows:

All participants enrolled in this clinical trial will have presented to a clinical site hospital with coronary artery disease, left ventricular dysfunction, and limiting heart failure and/or angina. These individuals have coronary anatomies unfavorable for coronary artery surgery or percutaneous coronary artery interventions. If identified in the hospital, potential participants will be approached by one of the investigators or research coordinators after discussion with the individual's primary physician. The information provided to the potential participant is included in the informed consent. The informed consent includes all possible risks to participants. Necessary elements of the informed consent process are included below:

1. Allow the individual time to read the entire written consent form.
2. 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.
3. 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.
4. 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.
5. Elicit from the individual if there are any further questions about the research being considered.
6. The written consent form is signed by the individual. The form is also signed by a third party witness[Ŧ] from the clinical research site (not affiliated with the study) who has observed the consent procedure and/or has spoken with the individual to affirm that all questions related to the study were answered during the informed consent process, that he/she understands the components of the study and how they differ from usual care, that he/she understands his/her rights and responsibilities, and that he/she was not coerced into participation.
7. One copy of the signed consent form is given to the participant.
8. The original signed consent form is kept in the participant'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. Thank the individual for their time and consideration of the research program.

[Ŧ] The informed consent form must also be signed by an impartial witness. For the purposes of this trial, a witness is considered an individual employed by the clinical facility but not associated with the study (e.g. research intermediary, floor nurse, etc.).

NOTE: Consent form signature (all signing parties) will include both the date and time (indicating am/pm or record using military time). Details of the informed consent process will be documented in the participant's medical record. This information will include the date/time participant was approached for the study, listing of family members/other individuals present for the consent (including the witness name and affiliation with the institution), the date/time the participant signed the consent, any specific items of concern raised by the participant, and any explanations concerning delayed dates/times of witness or person obtaining consent signatures.

ii. Procedures to Complete Enrollment

See Attachment 5 for a list of eCRF form names and codes (CNAxxx)

1. Coordinator completes initial review of the inclusion and exclusion criteria (screening).
2. A signed, witnessed informed consent is obtained for the participant.
3. Log onto the CCTRN Web application (www.cctrn.org) and select Data Management from the top navigation bar, then access FOCUS, Patient Data.
4. Complete "Screen/Demographics" eCRF (**CNA099**) which will result in computer generated study ID and acrostic.
5. Complete "Eligibility" eCRF (**CNA001**).
    a. A research coordinator must authenticate this form either by logging in and entering this eCRF or, if an assistant has entered the form, by verifying the data is correct and entering his/her Coordinator user name and password to add it to the database to verify the subject is eligible.
    b. The computer will check whether all inclusion/exclusion criteria have been met.

C. Baseline Testing and Treatment Checklist

Once consented and a study ID and acrostic have been assigned, the participant can proceed with baseline testing. The baseline evaluations cannot begin until after the informed consent has been signed.

i. Baseline Review and Testing following Consent

- Consent signed
- Inclusion / Exclusion Review
- Complete Medical History and Medication Review
- *Physical Exam*: including vital signs, height, weight, pulse oximetry, and a neurological evaluation (NIH stroke scale)

- *Laboratory Tests:* complete blood count (CBC) with differential and platelet count, Chemistry-8 panel (Na+, K+, Chloride, CO_2, Glucose, BUN, Creatinine, Calcium), hepatic panel, troponin T or I, CK, CK-MB, hsCRP, BNP level, urine pregnancy test (women of childbearing age), and PTT, PT/INR
- **Infectious Disease Testing:* assays for the detection of Infectious Disease Labs: HIV, hepatitis B (HBV), hepatitis C virus (HCV) , human T-lymphotropic virus (HTLV) I/II antibody, rapid plasma regain (RPR),cytomegalovirus (CMV) , ABO group, Rh status, West Nile virus and serum protein electrophoresis are collected per local site's standard operating procedure (see Attachment 7).
- **Echocardiogram (LVEF ≤45%) (Contrast 2D with strain rate imaging) **(core)**
- 12 lead ECG
- SPECT Imaging **(core)**
- Treadmill Testing with myocardial oxygen consumption (MVO2) determination **(core)**
- 24 hour Holter monitoring
- ICD Interrogation (if applicable)
- Quality of Life Assessments (Minnesota Living with Heart Failure and the SF-36)
- Chest X-Ray
- Cardiac MRI performed on Day of Study Product Injection (if not contraindicated) **(core)**
- Six Minute Walk Test

To reduce patient discomfort, samples for infectious disease testing can be drawn at the same time as the biorepository peripheral blood samples. Please note, infectious disease test results are not submitted to the DCC unless a patient has a positive test. In the case of a positive test, you must submit an AE eCRF (Form CNA041**).*

*** If LVEF results are reported as a range, enter only the upper bound of the range in the CCTRN web application.*

Once baseline testing has been completed, the following forms must be entered into the web application before the bone marrow aspiration:

1. **CNA099** Screening/Demographics (if not already entered)
2. **CNA001** Eligibility (if not already entered)
3. **CNA003** Baseline Risk Factors and other cardiac history
4. **CNA004** Baseline Non Cardiovascular Medical History
5. **CNA005** Baseline Physical Exam
6. **CNA011** Medication List¥
7. **CNA012** Medication Allergies
8. **CNA021** Baseline Labs
9. **CNA023** Baseline Holter
10. **CNA024** Baseline ECG
11. **CNA027** Baseline Six Minute Walk Test
12. **CNA062** SF-36 (Quality of Life Questionnaire)
13. **CNA061** MLHFQ (Quality of Life Questionnaire)
14. **CNA007** Treatment Checklist* **(entered after forms 1-13 have been entered)**

¥ For medications that have a dose that changes frequently, update the medication with the current dose and then put the number of doses, dates of changes and/or dose range in the comment field. There is one comment field for each drug. Please remember to update the form with changes to medications that take place between follow-up visits.

* The treatment checklist allows the web application to match eligibility criteria with data from the baseline physical exam, labs, and medications thereby doing a computerized systematic check to help ensure that only eligible participants are randomized. The treatment checklist should be completed after entering all baseline forms and prior to scheduling bone marrow aspiration. The treatment checklist programming will search for Coumadin/Warfarin on the medication list if the PT/INR is too high. If this medication has not been added when the treatment checklist is accessed, you will have to cancel the form and enter Coumadin to the medication list. Then click on the treatment checklist. The data for the treatment checklist pulls from forms already entered.

Biologic Delivery Systems (BDS) requires approximately 2 weeks notice to provide personnel to be on site for each intervention. Please contact Mark Martin to coordinate BDS representation with study product mapping/injection procedure.

Mark Martin
Manager, Field Operations
Biologics Delivery Systems, Cordis Corporation
office: 909.839.7229
mobile: 717.226.1320
email: mmarti75@its.jnj.com

Technical support for the use of the NOGA console and associated software is available at:
1-866-473-7823

ii. Day 1 (Study Product Injection)

- *Physical Exam*, including vital signs, height and weight and a neurological evaluation (NIH stroke scale)
- Assessment of NYHA class and CCS class
- Vital signs pre and post bone marrow aspiration and study product mapping/injection
- Bone marrow aspiration (see Attachment 2)
- Baseline cardiac MRI (if not contraindicated) (core)
- Study product mapping/injection in cardiac catheterization laboratory
    - Angiography
    - Electromechanical Mapping (EMM)
- Troponin T or I, CK, CK-MB collected at 8, 16, and 24 hours post injection
- Telemetry after procedure (18-24hrs)
- 12 lead ECG

- Five 10 ml venous blood (purple top tubes) for biorepository FACS analysis and one 10 ml venous blood (green top heparin tubes) for biorepository plasma cryostorage (see Peripheral Blood Procedures in MOP Section 3)
- 2 Echocardiograms (one immediately after procedure in cath lab and one 4-6 hours after procedure)
- 24 hour Holter
- Review of medications for changes
- Assess for AEs /serious adverse events (SAEs)

D. Randomization to Study Product

Randomization takes place after the patient **1)** has completed a successful bone marrow aspiration (See Attachment 2) **2)** the bone marrow aspirate has been processed by the site's cell processing lab using the Sepax system, and **3)** the resulting product has passed release criteria (i.e., is safe to inject). Study product randomization is carried out by an unblinded cell processing technician. Conducting study product randomization just before injection minimizes the number of participants who are randomized to the intervention but do not receive the intervention. When the bone marrow aspiration is complete, please enter the bone marrow aspiration form (**CNA029**) into the web application.

E. Events Precluding Delivery of Study Product

If an event occurs before cell processing will (or might) be completed that would preclude the delivery of the study product, the **RC must call the cell processor ASAP and notify them to suspend data entry of cell processing release criteria into the CCTRN web application.** Once a patient's release criteria have been entered and submitted in the database, the computer automatically randomizes the patient and produces a therapy assignment. At that point, the patient must be followed and all data must be included in the analysis according to the randomization assignment regardless of whether he/she actually underwent the injection procedure. Note, you will also need to fill out an AE or SAE form.

<u>Guidance for NOGA Catheter Usage</u>

There are events that may occur either during LV mapping with the NOGA XP System or during endocardial injections with the MyoStar Injection Catheter that could indicate a serious clinical deterioration.

The procedure should be temporarily halted, and the patient should be reevaluated, in the event of:

• persistent complaints of chest pain;
• complaints of cardiac pain associated with injections;
• persistent hypotension;
• complaints of shortness of breath;
• ICD shocks to stop ventricular tachycardia (VT);
• DC cardioversion or defibrillation for VT;
• any question as to the location of the catheter tip in relation to vasculature or the LV
• any unanticipated change in level of consciousness or neurological status.

The procedure will be terminated in the event of:

- sustained hypotension not responsive to fluid administration;
- clinical signs and symptoms indicating acute coronary syndrome;
- clinical signs and symptoms indicating a cerebrovascular accident;
- cardiac tamponade being strongly suspected or confirmed;
- hemipericardium requiring pericardiocentesis
- two episodes of sustained ventricular tachycardia requiring cardioversion or administration of an antiarrhythmic;
- the patient experienceing one episode of ventricular fibrillation (VF);
- identification of thrombus in the LV or the Aorta that was not previously present on echo or left ventriculogram;
- an aortic dissection being suspected or confirmed.;
- cardiac perforation;
- excessive bleeding from the bone marrow harvest site;
- fever of 99.4 degrees or higher;
- hemodynamically unstable.

F. Manual procedure for receiving Study ID/Acrostic or Therapy Assignment

1. Call from Site personnel to DCC
2. Medical Monitor (or designee) will confirm valid need for obtaining study information, obtain caller contact information, and call Site personnel back shortly with requested information
3. Website access for Center and Satellites will be terminated by the DCC to avoid automatic computer generation of duplicate information at unaffected locations (i.e., if website access is a local impediment)
4. The DCC will update the database with manually-derived assignments when electronic capability has been reestablished
5. Website access for Center and Satellites will be reinstated by the DCC

G. Intervention

Injection of BMMNC or placebo will be performed in the cardiac catheterization laboratory a minimum of four hours after bone marrow aspiration. **The total maximum out-of-body time (from bone marrow aspiration to study product injection) for the cells is 12-hours.**
Coronary and LV angiography and LV EMM will be performed to locate the target area to be injected. All cell injections will be performed in areas of a SPECT defect (fixed or reversible) associated with viability, as per NOGA criteria. The target myocardial area must display points that show electrical viability, defined as a unipolar voltage of > 6.9 mV, thus representing viable myocardial tissue. In the case of divergent results between the perfusion imaging test and EMM regarding the target ischemic area, the coronary anatomy will be taken into account. EMM will be relied on for point source viability for the injections.

When treatment has been delivered, the research coordinator will need to complete and enter the Study Product Injection eCRF (**CNA031)** in the web application**.** The research coordinator is also responsible for assuring the peripheral bloods collected for the biorepository (core) are labeled and delivered to the cell processing lab to be included with the excess cells in the shipment to the biorepository core lab.

H. Follow-up Visits

Follow-up visits will take place at regularly scheduled intervals. Each visit includes a medical history, physical exam, and a blood draw. Female participants of childbearing potential will also have a pregnancy test at 4 week, 3, 6, and 12 month visits. Some visits require additional testing. Below is a schedule of activities for each follow-up visit:

i. First Post Treatment Follow-up Visit Day 2 (Day after injection)

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA021**)
- 12 lead ECG (**CNA024**)
- Review of past 18-24 hours of Telemetry
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository **(core)**
- Review of medications for changes
- Assess for AEs /serious adverse events (SAEs)

(Note that participants will take twice-daily measurements of temperature for two weeks following injection of product. The participants will be required to see their primary physician or one of the Investigators within 48 hours if the participant develops a persistent fever greater than 99.5° F.)

The index date for the following visit timing and window is the day of study product injection.

ii. WEEK 1 (7 days +/- 2 days)

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA021**)
- 12 lead ECG (**CNA024**)
- 24 hour Holter (**CNA023**)
- Echocardiogram
- Assess for AEs / serious adverse events (SAEs)

iii. WEEK 4 (30 days +/- 5 days)

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA021**)
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository **(core)**
- 12 lead ECG (**CNA024**)

- 24 hour Holter (**CNA023**)
- Assess for AEs / serious adverse events (SAEs)

iv. MONTH 3 (90 days +/- 7 days)

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA021**)
- Echocardiogram
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository **(core)**
- 12 lead ECG (**CNA024**)
- 24 hour Holter (**CNA023**)
- ICD interrogation (if applicable)
- Quality of Life Assessments (**CNA061, CNA062**)
- Assess for AEs / serious adverse events (SAEs)

***v. MONTH 6* (180 days +/- 30 days)**

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA021**)
- Echocardiogram **(core)**
- SPECT imaging **(core)**
- TMT with MVO_2 **(core)*** note: this Month 6 should be completed at the same time of day ± 2hrs as the baselineTMT test (see baseline physical eCRF in database)
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository **(core)**
- 12 lead ECG (**CNA024**)
- 24 hour Holter (**CNA023**)
- Six minute walk test (**CNA027**)
- ICD interrogation (if applicable)
- Quality of Life Assessments (**CNA061, CNA062**)
- Assess for AEs / serious adverse events (SAEs)
- Chest X-Ray
- Cardiac MRI **(core)**

vi. MONTH 12 (360 days +/- 30 days)

- Follow-up Physical Exam, including a neurological evaluation (NIH stroke scale) (**CNA005**)
- Labs **(CNA022**)
- 12 lead ECG (**CNA024**)
- Assess for AEs / serious adverse events (SAEs)
- Quality of Life Assessments (**CNA061, CNA062**)

vii. ANNUAL FOLLOW-UP PHONE CALL (Years 2-5 +/- 30 days)

- Phone call follow-up and complete the eCRF (**CNA070**)

All participants should be encouraged to complete all scheduled follow-up visits. Participants should be contacted well in advance of their follow-up visit. In addition, if a participant misses a follow-up visit, contact the participant by phone to reschedule the visit in the window. Should this fail, send the participant a letter by certified mail, asking them to contact the clinic. Be sure to document all contact attempts to contact a participant and have these available for the Monitor for inspection (see Attachment 3).

I. Interim Visits

An interim physical or lab form should be used when a patient 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, for physicals, check the box that says "visit is outside the time window" and give a reason. For labs, put a note in the comments.

IV. 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 FOCUS protocol. A brief overview of eCRF completion is provided below.

There are four eCRF forms to be used for documenting adverse events, serious adverse events, unanticipated problems, and deviations/violations from the protocol in the web application. 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. Linda Piller: 1-713-500-9507; Linda.B.Pillar@uth.tmc.edu
2) Dr. Lem Moyé: 1-713-500-9518; Lemuel.A.Moye@uth.tmc.edu

A. Adverse Events and Serious Adverse Events

You must report all AE's and SAE's (from the time the participant receives the infusate through the 12 month follow-up visit) that occur regardless of whether you believe the therapy caused the event. **All SAE's must be followed until they resolve.**

i. Report **adverse events** to the DCC via the database using **Form CNA041.** Please group all signs, symptoms, and abnormal diagnostic procedure results under one diagnosis.
ii. Report **severe adverse events** to the DCC via the database using **Form CNA042.** Deaths, MIs, and strokes (related or not) must be reported within 24 hrs of the event. All other SAEs should be reported within five calendar days of discovery. This information can also be communicated via phone, email, or fax if necessary (See Attachment 4 for Fax Cover).

B. 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 participants and may be of medical or non-medical etiology. The event is unexpected, probably or possibly related to the research, and places patients 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 participant, 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 participant (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 participant or the integrity of the study (e.g. knowingly or unknowingly delivering study product to the patient which does not meet release criteria).

i. Report **unanticipated problems** to the DCC via the database using **Form CNA043** within 5 calendar days of PI or study staff awareness of event**.**

ii. Report **protocol deviation/violations** to the DCC via the database using **Form CNA044** 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 participant, the DCC must be notified within 24 hours.

- Fill out the hard copy Protocol Deviation workbook located either in your Manual of Operations binder or printable form from the CCTRN website (www.cctrn.org).
- Enter the information from the workbook into the CCTRN web application Protocol Deviation form **CNA044** which describes the event.
- Fax the complete and signed workbook form to a Project Manager at the DCC using the DCC Fax Coversheet.
    - 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 (waiver granted).
  - The DCC will complete the bottom portion of the form and enter if the exemption or waiver was granted.
  - The DCC will fax the complete and signed workbook back to the site.
  - Copies of all protocol deviation/exemption correspondence should be placed in the corresponding participant'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.

V. Data Query Reports and Data Clarifications/Data Change Requests

A. Data Query Reports

- A form that has been submitted with entries that have created data queries will show up in CCTRN web application the top navigation menus with a "p" for pending. (Forms that are complete and have no pending queries will show as green with a check mark and will be automatically submitted for payment.)
- In order to resolve the data queries so that the forms can be completed and paid, follow the process below:
  - RCs run Data Query Reports each week for forms that have generated data queries. To run the report:
    1. From main CCTRN website, select Data Management
    2. Select "Reports and Invoices"
    3. Select "Generate a List of Unresolved Data Queries"
  - Print the form and verify the queries with the source documents.
  - Initial/date next to the correct entries.
  - If the entry needs correction, fill in the value to be changed, initial and date.
  - Sign the report and either fax it to the DCC (please use the DCC Fax Coversheet Attachment 4) or scan it and email to a DCC project manager as a .pdf attachment.
  - **All data queries should be sent to the DCC by the 15th of each month for processing of payment.**
  - An individual at the DCC will mark the fields for change in the web application. A batch process is run routinely to actually change the entries in the database and set the status code to "verified" for records that have had all data queries resolved. This process will also change the form in the top navigation bar to green with a check mark.

Tips for Identifying forms on the Data Query Report:

- In the Data Query Report, a form name "Labs (Panels)" refers to all time points except Month 12 labs where a form name of "Labs (Follow-up)" is seen.
- In the CCTRN web application, select Patient Form Status from the "Other" menu. This form includes the statuses all forms for a given patient and will be displayed as follows:
    1. Incomplete
    2. Complete
    3. Pending (data queries exist and have not been corrected)
    4. Complete-verified (data queries existed and have been verified or corrected)
    5. Missing
- In the CCTRN web application, when you select a repeatable form such as a lab, ECG, Holter, 6-minute walk, or quality of life form from a drop down menu, you will see a list of all previously submitted forms of that type and their form status will be displayed as one of the following:
    1. Incomplete
    2. Complete
    3. Verify errors (data queries exist and have not been corrected)
    4. Verified complete (data queries existed and have been verified or corrected)

B. Data Clarifications/Data Change Requests (DCCRs)

The DCCR form (Attachment 8) will be accessible via the Research Coordinator Resources/Common Resources section of the CCTRN website. The DCCR form can be generated by the Sponsor, the Clinical Monitor, or a Site Research Coordinator. The DCCR process is the following:

1. Data Change Request:
    - The top half of the form is to be completed by a site RC when an eCRF previously submitted as complete requires a change.
        - Ex. A request indicating that on the Baseline Lab form, the blood sample was actually drawn on 2/13/08 and not on 2/3/08 as was indicated on the submitted eCRF.
    - The action is a request that requires the DCC to respond.
    - Print DCCR form, fill out, sign and fax to the DCC with a DCC fax cover sheet
    - The DCC makes the change in the database, initials the DCCR form and faxes it back to the site with signature.
    - The site maintains a copy and the DCC maintains a copy.
2. Data Clarification Request:
    - The bottom half of the request is typically completed by the DCC or Clinical Monitor (CRA) when there is a question about submitted or pending data.
    - The action is a question that requires the Site to respond.

    - Ex. RC's patient has completed all baseline eCRFs except the ECG. The DCC notices this form is missing and faxes a DCCR form to the site requesting clarification (did the subject complete the ECG procedure? RC would indicate the resolution (complete the ECG eCRF or complete a missing form eCRF).
  - The Site receives the form from the DCC or Monitor.
  - Complete the form, initials/date the clarification, sign and fax the form back to DCC with a DCC fax cover sheet.
  - The site maintains a copy and the DCC maintains a copy.
3. The CRA will verify all data change/data clarification requests with source documents during the monitoring visit.

VI. Transferring Participants Between Centers and Satellites

There may be occasions when participants transfer from center to center, center to satellite facility, or from one satellite facility to another. In order to activate a transfer, the coordinator at the subject's current facility must complete the CCTRN Transfer Request. This form will be accessible via the Research Coordinator Resources/Common Resources section of the CCTRN website. The request form should be completed with the information of the effective date of transfer, the destination center/satellite facility, and signature of the principle investigator. Please note: All outstanding data entry/eCRF forms and data queries must be completed, submitted, reviewed, and paid by the DCC prior to activating the transfer. Coordinators at both locations (transferring and receiving) will ensure the transfer of the patient's care and his/her medical and research records.

VII. Site 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 participant'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.
It is expected that the average duration of each visit will be 1 to 2 days per protocol (depending on the number of participants to be reviewed and any outstanding issues at that visit). The DCC clinical monitor or project manager(s) should be contacted with any questions concerning the amount of time to schedule for a particular monitoring visit. The visit duration may be adjusted as needed.

VIII. Device Accountability and Disposition Logs

The device used for study product delivery in this protocol is the NOGA Myostar injection catheter. The devices (both mapping and injection catheters) will be shipped from the Biologics Delivery Systems (BDS)to the designated clinical center personnel. The clinical center is responsible for accounting for the receipt and use of each catheter. Such information will be logged (see MOP Binder Section 2 "Subject Screening and Catheter Accountability Log"). The PI should sign the log, following each procedure, and fax back to BDS at 909-839-7335. The logs will also be made available to the CCTRN monitor during scheduled monitoring visits.

If a catheter received in shipment is defective, please call 1.866.473.7823 to issue an RGA# before you return the catheter. Questions regarding device shipments or to request additional devices should be directed to Wendy Collett at WCollett@its.jnj.com.

Please cc the Data Coordinating Center project managers (below) on the correspondence.

Project Manager, Rachel Vojvodic:	713-500-9528 Rachel.W.Vojvodic@uth.tmc.edu
Project Manager, Shelly Sayre:	713-500-9529 Shelly.L.Sayre@uth.tmc.edu
Project Manager, Judy Bettencourt:	713-500-9527 Judith.L.Bettencourt@uth.tmc.edu

IX. Biorepository Peripheral Blood/Plasma Collection

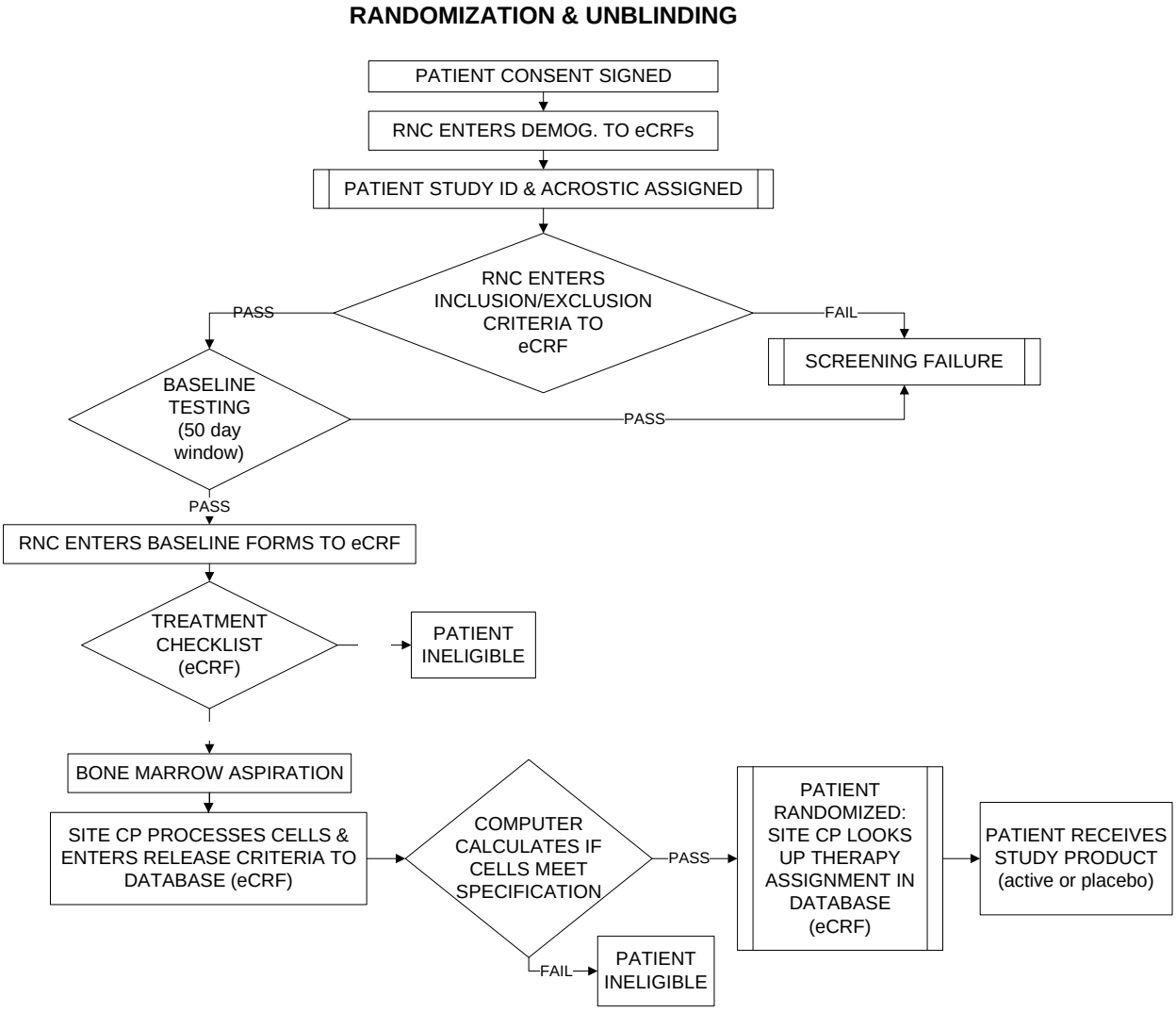
This protocol includes peripheral blood/plasma collections for the biorepository at several time points during the trial. The research coordinators will be responsible for assuring the accurate collection, processing, storing, and shipment of these samples to the biorepository.
The standard operating procedure for the management of these samples is included in MOP Binder Section 3 "Peripheral Blood/Plasma Sample Procedures".

X. Payment

Payments are made on a per form basis. As eCRF forms are submitted in the CCTRN web application, they are checked for errors. When a form's data query process is complete, the form is marked for payment by the DCC. Submitted forms that meet payment criteria are paid automatically on a monthly basis. A check and a copy of detailed invoices are mailed to each center. The invoices will also be available for view by site personnel with a proper security role via the CCTRN website. This system for payment alleviates site billing departments' administrative burden of having to process monthly billings. Payment will be transparent as sites will receive a check every month along with a detailed invoice for services that have been submitted via the electronic CRFs in the web application. To view the invoices, follow the process below:

- From main CCTRN website, select Data Management
- Select "Reports and Invoices"
- Select "View Payment Vouchers"
- Select Invoice Date

Attachment 1- Randomization



Attachment 2- CCTRN Bone Marrow Aspiration Standard Operating Procedure

The following standard operating procedure (SOP) is for carrying out bone marrow aspirations for patients recruited in the Cardiovascular Cell Therapy Research Network (CCTRN) protocols.

CCTRN patients will undergo one and only one bone marrow aspiration to harvest cells for a protocol. One exception will be if a clinical circumstance arises which, after the bone marrow aspiration, results in an inability to deliver cells. When the clinical circumstance has resolved, a second bone marrow aspiration could be granted at the patient's request.

Purpose:

Bone marrow aspiration is a scheduled procedure performed by a trained Physician (e.g., hematologist, pathologist, or hematopathologist). Only physicians with substantial experience in carrying out bone marrow harvesting procedures (more than forty previous successful procedures) will perform the procedure. Other medical personnel trained in bone marrow aspiration procedures (e.g. registered nurses, nurse practitioners, and medical technologists) will assist in the collection to ensure proper sample collection, preparation and processing of the specimen. The bone marrow aspiration is indicated for research regarding stem cell therapy for cardiovascular conditions.

Scope:

This SOP refers to bone marrow collections at the five stem cell therapy centers involved in the CCTRN. The five centers are as follows:

1. Texas Heart Institute Stem Cell Center
2. Minneapolis Heart Institute Foundation
3. University of Florida Department of Medicine
4. Cleveland Clinic Lerner College of Medicine
5. Vanderbilt University Medical Center

PROCEDURE

Supplies and transportation:

1. Bone marrow aspiration supplies will comply with the site-specific institutional procedures and practices.
2. All equipment, supplies, and reagents used in the process of bone marrow collection must be sterile with a lot number and date of expiration noted and able to be recorded on site-specific institutional data forms.
3. Study personnel will notify the site-specific cell processing lab at the following time points: 1) when a patient is enrolled and randomized, 2) when a patient's bone marrow aspiration has been scheduled, 3)when the bone marrow aspiration has begun.
4. Bone marrow aspiration specimen transportation to the cell processing laboratory will be treated as a STAT procedure.

Patient preparation and specimen collection performed by Physician:

1. Verify patient identification with the patient.
2. Explain the risks and benefits of bone marrow aspiration. Give patients an opportunity to ask questions and be able to verbalize understanding.
3. A separate consent form specific for the bone marrow aspiration procedure is signed by patients to document the informed consent process and to permit the physician to perform the aspiration.
4. Medication of patients for the bone marrow aspiration will be left to the discretion of the performing or overseeing Physicians with the exception of general anesthesia which will not be covered by the study.
5. All collection procedures must be performed with universal precautions and sterile aseptic technique.

Bone marrow aspiration procedures:

1. The media container and/or heparin vials must be opened with sterile technique and media prepared with the appropriate amount of anticoagulant. The final concentration of heparin will be 10-25 units of heparin/ml of bone marrow.
2. After the administration of medication (sedatives and/or analgesics) and prior to collection, the donor will be evaluated while in the prone position to be safely positioned without pressure compromise on arms, brachial plexus, breasts, genitalia, knees, vascular structures or other body parts.
3. The donor shall be prepped and draped in the usual manner using alcohol, Betadine and sterile draping.
4. Prior to insertion of collecting needles, the landmarks and sites of aspiration shall be reviewed and confirmed by both the Physician and Assistant.
5. A total of 80-90 mls of bone marrow product will be obtained. So that the samples are comparable across the five centers, physicians will aspirate no more than 5 ml of product per needle puncture into the marrow space. Approximately 5 mls of marrow is aspirated with each aspirate. Although there are multiple needle punctures in the bone marrow spaces, there are generally 1-2 skin punctures on the iliac crest.
6. An incision is made in the iliac crest and a needle is advanced through the periosteum and into the marrow space. A minimum of one skin puncture and 16 needle punctures into the marrow space are required to aspirate 80 ml of bone marrow. The number of skin punctures or needle punctures must not be so frequent as to require general anesthesia.
7. Physicians will perform the aspiration on one side. The only time aspiration will takes place in the contralateral site is if the initial site produces a dry tap.
8. In the event that no marrow is aspirable, then pressure will be applied to the injection site until hemostasis is achieved. A dressing will then be applied.
9. Patients will be on anticoagulant medications, thus pressure will be applied to the injection site until hemostasis is achieved. A sterile dressing will be applied. A pressure dressing will be applied if persistent venous oozing is present.
10. All bone marrow collections will be sent to the site's cell processing laboratory using site-specific institutional transportation procedures. Bone marrow aspiration transportation to the cell processing laboratory will be treated as a STAT procedure and arrive at the cell processing lab as soon as possible following the bone marrow aspiration procedure.

Reporting requirements:

1. Label the CCTRN Study Product Injection form and all specimens with the patient acrostic, study ID, date and time of collection, and label the form with the amount aspirated.

Site-specific chain of custody forms must be used to document the chain of custody of the bone marrow aspirate from the site of the procedure to the cell processing laboratory to the study product injection site.

Attachment 3- Participant Contact Log

Study ID	Acrostic	Date/Time of Contact	Type of Contact (mail/phone)	Purpose of Contact	Outcome
Example 01-1234-02	ACRPUE	03/31/2008 15:30	Phone	Schedule 3mos fu	Appt set

Attachment 4- CCTRN Fax Cover

[Enter today's date]

FAX

To: Rachel Vojvodic, Shelly Sayre, or Judy Bettencourt

Phone: 713-500-9528 (RV), 713-500-9529 (SS), or 713-500-9527 (JB)

Center Name: Data Coordinating Center- CCCT

Fax: **713-500-9530**

From:

Phone: [Type the sender phone number]

Center Name: [Type the sender center name]

Fax: [Type the sender fax number]

Number of Pages: [Type the number of pages sent]

COMMENTS:

Attachment 5 – List of eCRF Form Names and Codes

FORM #	DESCRIPTION of FOCUS FORMS
CNA099	Screening/Demographics
CNA001	Eligibility
CNA003	Baseline Risk Factors & Other Cardiac Hx
CNA004	Baseline Non Cardio. Med. Hx
CNA005	Physical Exams
CNA007	Treatment Checklist
CNA011	Medication List
CNA012	Medication Allergies
CNA021	Labs (Panels)
CNA022	Labs (M12)
CNA023	Holter
CNA024	EKG
CNA026	Labs (Interim)
CNA027	Six Minute Walk Test
CNA029	Bone Marrow Aspiration
CNA031	Study Product Injection
CNA041	Adverse Event
CNA042	Serious Adverse Event
CNA043	Unanticipated Problem
CNA044	Protocol Deviation
CNA045	Schedule of Procedures
CNA047	Data Glossary
CNA048	Missing Form
CNA051	End of Study
CNA061	Minnesota Living with Heart Failure Questionnaire
CNA062	SF-36
CNA070	Phone Call Follow-up

Attachment 6 – Schedule of Procedures

Schedule of Procedures FOCUS	
Procedures	**Time Window**
Screening/Baseline	**Consent + 50 days**
Screen/Demographics Eligibility (Inclusion/Exclusion criteria) Baseline Labs Baseline Non-Cardiovascular History Baseline Risk Factors Baseline Allergies Baseline Medications Baseline PE Baseline Chest xray Baseline 6 min walk test Quality of Life Questionnaires Baseline EKG Baseline Holter ICD Interrogation (if applicable) Baseline TMT with MVO2 (core) Time of Test: _____ Baseline SPECT (core) Baseline Echo w/contrast (core) Treatment Checklist	
Aspiration/Injection (SPI)	**SPI**
Day of Injection PE Biorepository blood draws (if consented) Bone Marrow Aspiration Baseline cMRI (if applicable) (core) Cell Processing Cell Processing - Post Release Study Product Infusion EKG Holter Routine Echo immediately post procedure Routine Echo 4-6 hrs post procedure	**SPI + 14 days**
Day after Injection	**SPI + 1 day**
Day after Injection PE Biorepository blood draws (if consented) Labs EKG	
1 Week	**SPI + 7 days +/- 2 days**
PE Labs Holter Routine Echo EKG	
4 Weeks	**SPI + 30 days +/- 5 days**
PE Labs Biorepository blood draws (if consented) EKG Holter	
3 Month	**SPI + 90 days +/- 7 days**
PE Labs Biorepository blood draws (if consented) Holter ICD Interrogation (if applicable) Routine Echo EKG Quality of Life Questionnaires	

6 Month	SPI + 180 days +/- 30 days
PE Labs EKG Biorepository blood draws (if consented) Holter Echo w/contrast (core) Chest xray 6 min walk test Quality of Life Questionnaires cMRI (if applicable) (core) TMT with MVO2 (core) SPECT (core) ICD Interrogation (if applicable)	
12 Month	**SPI + 360 days +/- 30 days**
PE EKG Labs Quality of Life Questionnaires	
24 Month	**SPI + 720 days +/- 30 days**
Telephone F/U	
36 Month	**SPI + 1080 days +/- 30 days**
Telephone F/U	
48 Month	**SPI + 1440 days +/- 30 days**
Telephone F/U	
60 Month	**SPI + 1800 days +/- 30 days**
Telephone F/U End of Study	

Attachment 7 – Clarification for Infectious Disease Testing

As per the requirement of Infectious Disease Testing at baseline for each patient that will participate in the FOCUS protocol, the sponsor (CCTRN) has clarified at each of the five CCTRN clinical sites listed below, where this function is performed and by whom.

This testing will consist of the following standard tests for infectious diseases; assays for the detection of HIV and HCV (by nucleic acid testing), anti-HIV I/II, anti-HTLV I/II, anti-HBc antibody (Ab), HBsAg, anti-HCV, and Treponema palladium (by serology).

Blood samples should be drawn prior to study product injection according to local institutional policy (see below). To reduce discomfort to the patient, these samples can be drawn at the same time as the initial peripheral bloods for the Biorepository (immediately preceding bone marrow aspiration).

1) **Texas Heart Institute- Texas Heart Institute Stem Cell Center**

   The blood tubes are transported for Infectious Disease testing (baseline) to the cell processing lab and the cell processing laboratory will send this out with other samples for testing

2) **Cleveland Clinic- Cleveland Clinic Lerner College of Medicine**

   a) Anti HIV I/II will be done in the microbiology lab
   b) The HTLV I/II are sent to our lab then are sent out to a lab in California called Specialty Labs
   c) The Hepatitis screening Anti HBc, HBsAg, Anti HCV and Treponema Palladium IgG are done in the immunology lab

3) **Minneapolis Heart Institute Foundation**

   At the time that the marrow is harvested, the blood samples are collected and sent to the MHIF. The Coordinators send the samples to Memorial Blood Center in Minneapolis who does the testing and sends reports to the cell processing lab.

4) **University of Florida Department of Medicine-SHANDs**

   All of the infectious disease tests are conducted by the local community blood center, (which uses FDA approved kits, CLIA licensed). The patient's blood is drawn by the RN and delivered to the Stem Cell Processing Lab. Couriers transport the blood to the blood center for testing.

5) **Vanderbilt University Medical Center**

   For autologous donors, the nurses send the blood to the Diagnostic Clinical Laboratory at Vanderbilt University Medical Center

Attachment 8- **CCTRN- Data Change/Clarification Request**

Site:	**Patient ID:**
Date of request:	**Patient Acrostic:**

Request initiated by: **Sponsor** ☐ **Monitor** ☐ **Site** ☐

Change Request (complete this portion if requesting a change to previously submitted data)

Form	Field Name/Description	Change Action	Change Complete Sponsor initials/date

Clarification Request (complete this portion if requesting clarification on submitted or pending data)

Form	Field Name/Description	Clarification (note: if response results in change, complete change action above)	Resolution	Clarification Complete Site initials/date

Signature for File:

Sponsor representative signature & date: _____ **Site representative signature & date: _____**