

Cardiovascular Cell Therapy Research Network



Manual of Operating Procedures for the TIME Protocol

Transplantation in Myocardial Infarction Evaluation (TIME) Protocol: A Phase II, Randomized, Controlled, Double-Blind Trial Evaluating the Effect of Timing on the Administration of Bone Marrow Mononuclear Cells (BMMNCs) versus Placebo in Patients with Acute Myocardial Infarction

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CCTRN TIME PROTOCOL

I. Study overview

Introduction: This will be the first clinical trial to administer a single target dose of cells to all the patients in the treatment group (150×10^6 Bone Marrow Mononuclear Cells (BMMNC) via an investigational device [PTCA catheter (*Maverick*, Boston Scientific)]

Study Design: The TIME trial is a randomized, Phase II, two factor experiment. The two factors are therapy (active versus placebo therapy) and timing (3 days versus 7 days). The principal interest is whether the effect of cell administration timing influences the relationship between BMMNC infusion and cardiac function. The endpoints are global and regional left ventricular function determined by cardiac MRI.

Target population: 120 male and female participants who have no contraindication to BMMNC delivery and who have: 1) moderate to large anterior infarctions, 2) no prior history of coronary artery bypass grafting (CABG) or myocardial infarction (MI) that resulted in left-ventricle (LV) dysfunction, and 3) initial ejection fraction $\leq 45\%$ following revascularization measured by echocardiography.

Enrollment Period: All five centers of the Cardiovascular Cell Therapy Research Network (CCTRN) will enroll for two years.

II. Description of Study Phases

A. Screening of Potential Candidates: The screening phase of the study pertains to an initial review of potential participant characteristics based on available data (i.e. medical record review). This information is reviewed 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 Time-of-Therapy Assignment: Individuals who are screened and appear to meet eligibility requirements can then be approached (with their physician's knowledge) and invited to participate in the study. The research coordinator reviews the informed consent (process is detailed in section III B) and submits information into the CCTRN web-based database to obtain a study ID, acrostic, and a time-of-therapy assignment (i.e., either 3-day or 7-day).

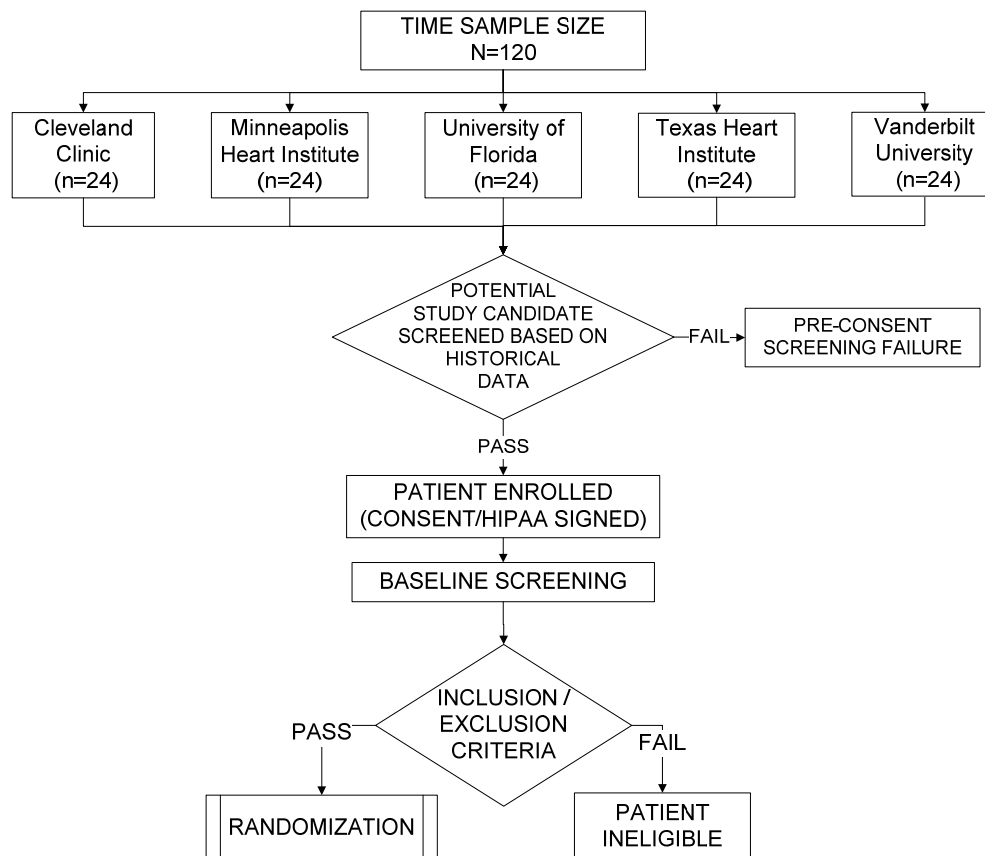
C. Baseline Testing: After obtaining a study ID, acrostic, and time-of-therapy assignment, the research coordinator collects a series of baseline assessments (within the allotted time) to determine whether the individual truly is a viable candidate for study product infusion.

D. Randomization to Study Product: Individuals who have successfully met eligibility criteria via initial screening, baseline assessments, final review of the Treatment Checklist, and whose bone marrow cells have met the cell processing release criteria, are then randomized to a study product assignment (cell therapy or placebo).

E. Intervention: Bone marrow aspiration, cell processing, and study product infusion follow in accordance with time-of-therapy assignment (3-day or 7-day post revascularization). 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-, 3-, 6-, 12-, and 24-months post intervention.

Enrollment Flowchart



III. Procedures by Study Phase

A schedule of all study procedures for the TIME 3-Day group can be found in [Attachment 7](#). A schedule of all study procedures for the TIME 7-Day group can be found in [Attachment 8](#).

A. Screening of Potential Candidates

For frequently asked questions (FAQs) related to screening candidates, see [MOP Binder Section 6](#). These documents are also available on the CCTRN website (www.cctrn.org); navigate to “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).

A patient would only be entered on both the TIME and Late TIME screening logs if s/he became ineligible to participate in TIME, i.e., if s/he misses the window for TIME. The patient would not go on the Late TIME log until s/he became ineligible for TIME.

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.

Special Notes: Although a single date of treatment (three or seven days) has been stipulated, a two-day allowance has been created for each treatment time to accommodate for weekends, holidays and other circumstances that would preclude treatment delivery on Day 3 or Day 7. Thus, those patients randomized to the early group (Day 3) could receive treatment on Day 2 or Day 4, while those patients randomized to the later group (Day 7) could receive cells on Day 6 or Day 8. This will ensure that the two time points remain separated for the entire cohort.

When considering an individual for the TIME protocol, if there is a likely chance that baseline testing cannot occur within the 2-4 day timeframe, or if other complications such as multiple patient bone marrow harvests and/or multiple patient cell processing procedures will occur on the same day, you should not consent the patient to TIME. These patients can be approached for the Late TIME study and encouraged to return in 2-3 weeks for evaluation.

Patients consented to TIME, who for various reasons do not reach the point of randomization to cell therapy or placebo, can be administratively withdrawn from TIME and approached for Late TIME.

B. Consent and Time-of-Therapy Assignment

i. Consent

The informed consent process is as follows:

All participants enrolled in this clinical trial will have presented to a clinical site or approved satellite hospital with an acute myocardial infarction and will have undergone successful percutaneous revascularization of the infarct-related artery. 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^F 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.

‡ 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 addressed with the participant, and any explanations concerning delayed dates/times of witness or person obtaining consent signatures.

ii. Time-of-Therapy Assignment

To maximize the likelihood that effects observed at the end of the study are due to the therapy, active or placebo treatment is assigned randomly, i.e., independent of the participant's characteristics. In this protocol, there are two randomizations; **1) randomization to Time-of-Therapy (Day 3 or Day 7)** which occurs following evaluation of eligibility criteria and consent by the research coordinator and **2) randomization to study product (cell therapy or placebo)** which takes place at the end of cell processing, and is carried out by the cell processing technician.

iii. Procedures to Complete Enrollment & Randomization to Time-of-Therapy (Day 3 or Day 7) See *Attachment 6* for a list of eCRF form names and codes (CNBxxx)

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 TIME forms.
4. Complete "Screen/Demographics" eCRF (**CNB099**) which will result in computer generated participant acoustic and patient study ID.
5. Complete "Eligibility" eCRF (**CNB001**).
 - 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 and receive the time-of-therapy assignment if the participant is eligible.
 - b. The computer will check whether all inclusion/exclusion criteria have been met and display the time-of-therapy assignment. Note that assignment to the 3-day group or 7-day group, although randomly assigned, is not blinded. Both the research coordinator and the participant will know what day the patient is to receive the intervention.

C. Baseline Testing and Treatment Checklist

Once consented and a study ID and acronym have been assigned, the participant can proceed with baseline testing. The TIME Protocol Schedule Matrix ([Attachment 1](#)) provides a simple guide for determining when intervention will take place based on the day of the week the participant suffered his/her MI. The baseline evaluations cannot begin until after the informed consent has been signed. Tests that were part of standard care in the post-myocardial infarction evaluation (within last thirty days) also can be used for evaluation once the participant has signed consent.

NOTE: All patients will be advised to take aspirin and Plavix (clopidogrel) 75mg for 24 months

i. Baseline Review and Testing during Consent Visit (Day 0 to Day 2)

- Consent signed
- Inclusion / Exclusion Review
- Complete Medical History and Medication Review
- *Physical Exam*: including vital signs, height, weight and pulse oximetry
- *Laboratory Tests*: complete blood count (CBC) with diff, lipid panel, renal panel, hepatic panel, troponin T or I, CK, CK-MB, hsCRP, BNP level, and pregnancy test (women of childbearing age)
- **Infectious Disease Testing*: 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 pallidum (by serology) are collected per local site's standard operating procedure ([see Attachment 9](#)).
- ****Echocardiogram (LVEF <45%)**
- 12 lead ECG

**To reduce patient discomfort, samples for infectious disease testing can be drawn at the same time as the biorepository peripheral blood samples (study product infusion day). 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 CNB041).*

***This result can come from an echo performed as part of standard care in the post-myocardial infarction evaluation. The optimum time to measure LVEF is 24-48 hours post PCI. If LVEF results are reported as a range, enter only the upper bound of the range in the CCTR web application.*

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

1. **CNB099** Screening/Demographics (if not already entered)
2. **CNB001** Eligibility (if not already entered)
3. **CNB005** Baseline Physical Exam
4. **CNB021** Baseline Labs
5. **CNB007** Treatment Checklist* (entered after forms 1-4 have been entered)

The other baseline forms should be entered as soon as possible:

1. **CNB003** Baseline Risk Factors and other cardiac history

2. **CNB004** Medical History
3. **CNB006** PCI
4. **CNB012** Medication Allergies
5. **CNB011** Medication List[‡]
6. **CNB024** Baseline ECG

* The treatment checklist allows the web application to match eligibility criteria with data from the baseline physical exam and labs thereby doing a computerized systematic check to help ensure that only eligible participants are randomized. The time constraint between the completion of the informed consent and the bone marrow aspiration may make it difficult to enter all baseline forms into the database in this small time interval. However, please be sure to enter the Screening/Demographics form (**CNB099**), the eligibility form (**CNB001**), the baseline labs (**CNB021**), the baseline physical exam (**CNB005**), followed by the treatment checklist (**CNB007**) **prior to scheduling bone marrow aspiration.**

[‡] 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.

ii. Day 3 or Day 7 (Study Product Infusion)

- *Physical Exam*, including vital signs, height and weight
- Assessment of NYHA class
- Vital signs pre and post bone marrow harvest and study product infusion
- Bone marrow aspiration ([Attachment 3](#))
- Study product infusion in catheterization laboratory
- Troponin T or I, CK, CK-MB collected one time on the morning following infusion
- Telemetry after procedure (18-24hrs)
- Cardiac MRI (baseline) – All patients undergo cardiac cMRI at Day 3 and those patients randomized to therapy on Day 7 will undergo repeat cMRI on Day 7.
- Five 10 ml venous blood (purple top tubes) for biorepository FACS analysis, one 10 ml venous blood (green top heparin tubes) for biorepository plasma cryostorage (see Peripheral Blood Procedures in [MOP Section 3](#))
- One 3 ml yellow top tube (*anti-coagulated with acid citrate dextrose*) for preparation/blinding of the placebo product when applicable*
- Review of medications for changes
- Assess for AEs /serious adverse events (SAEs)

* **Please note: To aid in the blinding of the placebo product, one 3 ml yellow top tube (anti-coagulated with acid citrate dextrose) of peripheral blood will be collected from each patient immediately prior to bone marrow harvest with the other blood collected and delivered to the cell processing laboratory.**

D. Randomization to Study Product

This is the second of the two randomizations that each individual must complete to be a participant in this study ([Attachment 2](#)). This second step takes place after the patient **1**) has been successfully randomized to Day 3 or Day 7 therapy, **2**) has completed a successful bone marrow aspiration ([Attachment 3](#)) **3**) the bone marrow aspirate has been processed by the site's cell processing lab using the Sepax system, and **4**) the resulting product has passed release criteria (i.e., is safe to infuse). Study product randomization is carried out by the unblinded cell processing technician. Conducting study product randomization just before infusion 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 (**CNB029**) 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 (e.g., an adverse event or an unanticipated problem), 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 into 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 received cell therapy. Note, you will also need to fill out an AE or SAE form.

Events precluding delivery of the study product that could occur before cell processing are as follows:

1. Hypotensive episode
2. Hemodynamically significant arrhythmia requiring antiarrhythmic therapy
3. Hemodynamically unstable
4. Fever (Temperature increase to $\geq 100.4^{\circ}\text{F}$)
5. Excessive bleeding from the bone marrow harvest site
6. Cardiac perforation

F. Manual procedure for receiving Study ID/Acrostic, Time-of Therapy-Assignment, 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

Infusion of BMMNC or placebo will be performed in the cardiac catheterization laboratory a minimum of four hours after bone marrow aspiration and within the randomized time points for either Day 3 or Day 7 therapy. **The total maximum out-of-body time (from bone marrow aspiration to study product infusion) for the cells is 12-hours.** The study product will be infused in six aliquots (five ml) over two minutes during each balloon inflation at low pressure (three to four atm). Two minutes of reperfusion will occur following each cycle of study product infusion. When treatment has been delivered, the research coordinator will need to complete and enter the Study Product Infusion eCRF (**CNB031**) 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 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. Some visits require additional testing. Below is a schedule of activities for each follow-up visit:

i. First Post Treatment Follow-up Visit Day 4 or Day 8 (Day after infusion)

- Basic follow-up physical exam and labs (**CNB005, CNB021**)
- 12 lead ECG (**CNB024**)
- 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 one month following infusion 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 100.0° F.)

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

ii. MONTH 1 (30 days +/- 7 days)

- Basic follow-up physical exam and labs (**CNB005, CNB022**)
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository (core)
- 12 lead ECG (**CNB024**)
- 24 hour Holter (**CNB023**)

iii. MONTH 3 (90 days +/- 14 days)

- Basic follow-up physical exam and labs (**CNB005, CNB022**)
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository (core)

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

- Basic follow-up physical exam and labs (**CNB005, CNB022**)
- Echocardiogram** (Limited) (core)
- Two 10 cc purple top tubes and one 10 cc green top tube for the biorepository (core)
- 12 lead ECG (**CNB024**)
- Cardiac MRI (core)

*the MRI in the endpoint analysis will still be used if it is outside the window

**The site will use its clinical judgment to determine if echo contrast (as an aid in visualization of the ventricular endocardial border definition) will be obtained, following the guidelines outlined in the protocol

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

- Basic follow-up physical exam and labs (**CNB005, CNB022**)
- Cardiac MRI

vi. MONTH 24 (720 days +/- 30 days)

- Basic follow-up physical exam and labs (**CNB005, CNB022**)
- Cardiac MRI

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 ([Attachment 4](#)).

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 TIME protocol. A brief overview of eCRF completion is provided below.

There are four eCRF forms to be used for documenting 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 Pillar: 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 signs consent through and including 30 calendar days after the subject completes the study) that occur regardless of whether you believe the cell therapy caused the event. **All SAE's must be followed until they resolve. Do not delay the initial reporting of a serious adverse event in order to obtain resolution or follow-up information.**

- i. Report **adverse events** to the DCC via the database using **Form CNB041**. 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 CNB042**. The investigator is required to report the event within 24 hours of learning of it. This information can also be communicated via phone, email, or fax if necessary (See [Attachment 5](#) 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 or infusing study product into a vessel that was not patent at the time of delivery).

- i. Report **unanticipated problems** to the DCC via the database using **Form CNB043** within 24 hours of PI or study staff awareness of event.

- ii. Report **protocol deviation/violations** to the DCC via the database using **Form CNB044** 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 **CNB044** 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 fax it to the DCC (please use the DCC Fax Coversheet [Attachment 5](#)).
- **All data queries should be faxed 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.
- The DCC will initial/date the changes were made, sign the form and fax a copy back to the site for your file.

Tips for Identifying forms on the Data Query Report:

- In the Data Query Report, a form name “Labs (Panels)” refers to the Baseline or Day After Infusion lab form while a form name of “Labs (Follow-up)” refers to one of the follow-up time points.
- 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 lab or ECG form from a drop down menu, you will see a list of all submitted lab or ECG forms 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 (see [Attachment 10](#)) will be accessible via the Research Coordinator 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. 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 and data queries must be completed, 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 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 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 Maverick over-the-wire PTCA catheter (Boston Scientific). The devices will be shipped from the Data Coordinating Center 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") and the logs will be made available to the CCTRN monitor during scheduled monitoring visits. Questions regarding device shipments or to request additional devices should be directed to the Data Coordinating Center. Requests for additional shipments should be made by contacting the DCC project managers or the DCC regulatory specialist.

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-TIME Protocol Schedule Matrix

Randomized to Day 3

Day 0 (MI)	Sunday	Monday	Tuesday	Wednesday ##	Thursday #	Friday **	Saturday
Day 1	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 2 (consent*)	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday
Day 3	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday
BMA/Therapy Administered	Wednesday	Thursday	Friday	Friday	Monday	Monday	Tuesday

*Could consent on day 1

**Unless you have someone “on call” over the weekend you would miss the Friday patients because they would not be consented in time to randomize.

Would need to consent on Day 1 in order to randomize these patients on time unless you have someone taking call over the weekend.

Would need to consent on Day 1 in order to randomize on day 1 for a possible day 2 BMA/Therapy administration.

Randomized to Day 7

Day 0 (MI)	Sunday	Monday	Tuesday	Wednesday ##	Thursday #	Friday **	Saturday
Day 1	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 2 (consent*)	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday
Day 3	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday
Day 4	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday
Day 5	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday
Day 6	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday
Day 7	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
BMA/Therapy Administered	Monday	Monday	Tuesday	Wednesday	Thursday	Friday	Friday

*Could consent on day 1

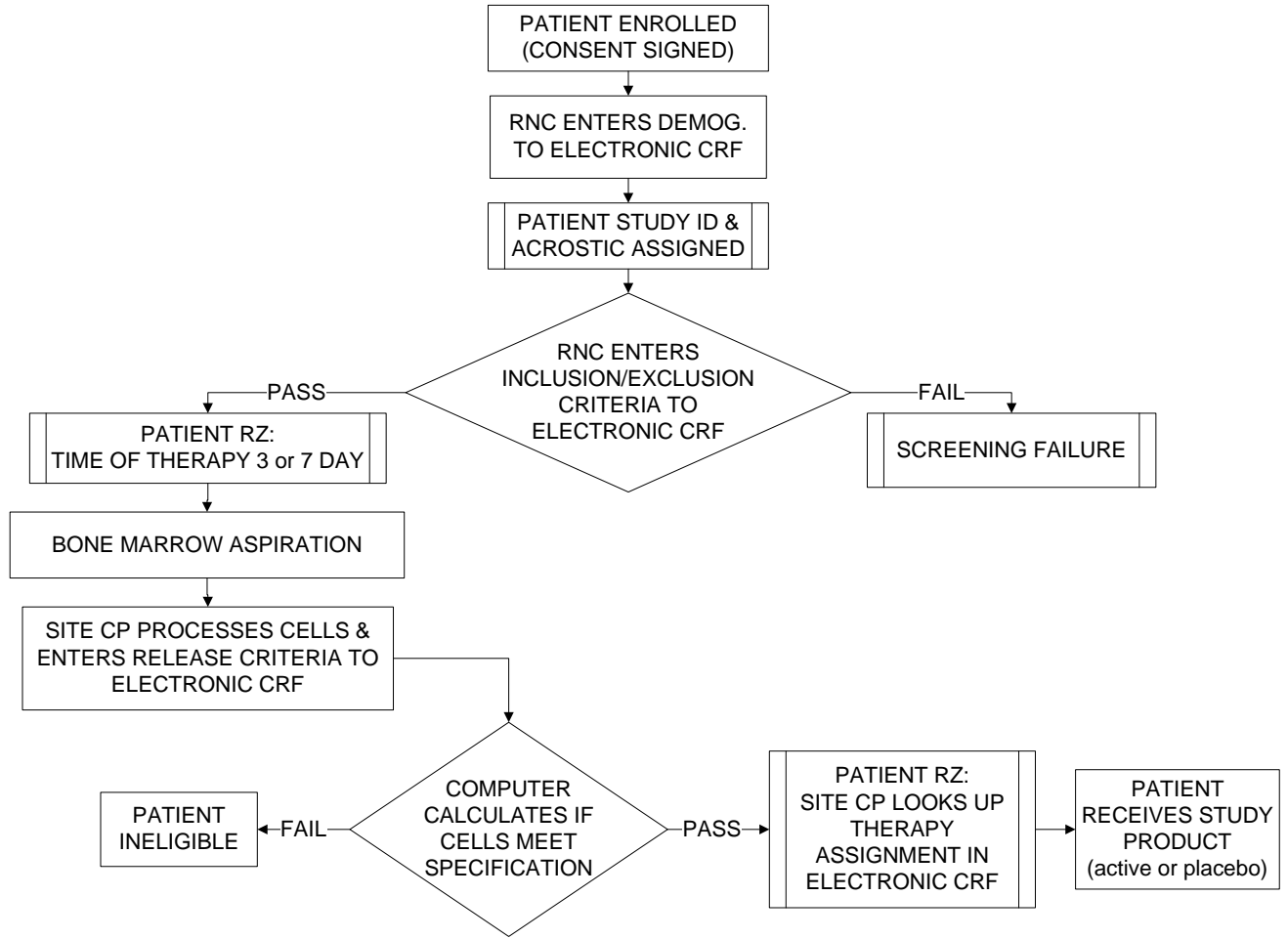
**Unless you have someone “on call” over the weekend you would miss the Friday patients because they would not be consented in time to randomize.

Would need to consent on Day 1 in order to randomize these patients on time unless you have someone taking call over the weekend.

Would need to consent on Day 1 in order to randomize on day 1 for a possible day 2 BMA/Therapy administration.

Attachment 2- Randomization

RANDOMIZATION & UNBLINDING



Attachment 3- 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.

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. Patients on aspirin and Plavix (clopidogrel) at the time of consent should remain on aspirin and Plavix (clopidogrel) for the bone marrow aspiration procedure. Continuance or discontinuance of other medications at the time of bone marrow aspiration, (e.g. Coumadin) are left to the discretion of the Study Physician.
6. 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 take 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 Infusion 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 infusion site.

Attachment 5- CCTRN Fax Cover



[Enter today's date]

FAX

To: Rachel Vojvodic or Shelly Sayre or
Judy Bettencourt

Phone: 713-500-9528 or 713-500-9529 or 713-
500-9527

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 6 – List of eCRF Form Names and Codes

FORM #	DESCRIPTION of TIME FORMS
CNB099	Screening/Demographics
CNB001	Eligibility
CNB003	Baseline Risk Factors & Other Cardiac Hx
CNB004	Baseline Non Cardio. Med. Hx
CNB005	Physical Exams
CNB006	Index Event (Revascularization)
CNB007	Treatment Checklist
CNB011	Medication List
CNB012	Medication Allergies
CNB021	Labs (Panels)
CNB022	Labs (F/U)
CNB023	Holter
CNB024	ECG
CNB026	Labs (Interim)
CNB029	Bone Marrow Aspiration
CNB031	Study Product Infusion
CNB041	Adverse Event
CNB042	Serious Adverse Event
CNB043	Unanticipated Problem
CNB044	Protocol Deviation
CNB045	Schedule of Procedures
CNB047	Data Glossary
CNB048	Missing Form
CNB051	End of Study

Attachment 7 – Schedule of Procedures TIME 3-Day Group

Schedule of Procedures TIME 3-Day Group	
Procedures	Time Window
Screening/Baseline	
Screen/Demographics Eligibility (Inclusion/Exclusion criteria) Revascularization/PCI Baseline PE Baseline Lab Panels Baseline Non-Cardiovascular History Baseline Risk Factors Baseline Allergies Baseline Medications Baseline EKG Baseline Echo (core)	
Aspiration/Infusion (SPI)	PCI + 3 days +/- 1 day
Day of Infusion PE Treatment Checklist Biorepository blood draws Bone Marrow Aspiration Baseline cMRI (core) Cell Processing Cell Processing - Post Release Study Product Infusion	
Day after Infusion	SPI + 1
Day after Infusion PE Biorepository blood draws Day after Infusion Lab Panels Day after Infusion EKG	
1 Month	SPI + 30 days +/- 7 days
PE Labs (F/U) Biorepository blood draws EKG Holter	
3 Month	SPI + 90 days +/- 14 days
PE Labs (F/U) Biorepository blood draws	
6 Month	SPI + 180 days +/- 30 days
PE Labs (F/U) EKG Biorepository blood draws Echo (core) cMRI (core)	
12 Month	SPI + 360 days +/- 30 days
PE Labs (F/U) cMRI	
24 Month	SPI + 720 days +/- 30 days
PE Labs (F/U) cMRI End of Study	

Attachment 8 – Schedule of Procedures TIME 7-Day Group

Schedule of Procedures TIME 7-Day Group	
Procedures	Time Window
Screening/Baseline	
Screen/Demographics Eligibility (Inclusion/Exclusion criteria) Revascularization/PCI Baseline PE Baseline Lab Panels Baseline Non-Cardiovascular History Baseline Risk Factors Baseline Allergies Baseline Medications Baseline EKG Baseline Echo (core)	
Day 3	PCI + 3 days +/- 1 day
Baseline cMRI (core)	
Aspiration/Infusion (SPI)	PCI + 7 days +/- 1 day
Day of Infusion PE Treatment Checklist Biorepository blood draws Bone Marrow Aspiration cMRI Cell Processing Cell Processing - Post Release Study Product Infusion	
Day after Infusion	SPI + 1
Day after Infusion PE Biorepository blood draws Day after Infusion Lab Panels Day after Infusion EKG	
1 Month	SPI + 30 days +/- 7 days
PE Labs (F/U) Biorepository blood draws EKG Holter	
3 Month	SPI + 90 days +/- 14 days
PE Labs (F/U) Biorepository blood draws	
6 Month	SPI + 180 days +/- 30 days
PE Labs (F/U) EKG Biorepository blood draws Echo (core) cMRI (core)	
12 Month	SPI + 360 days +/- 30 days
PE Labs (F/U) cMRI	
24 Month	SPI + 720 days +/- 30 days
PE Labs (F/U) cMRI End of Study	

Attachment 9 – Clarification for Infectious Disease Testing

As per the requirement of Infectious Disease Testing at baseline for each patient that will participate in the TIME and Late TIME protocols, 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 infusion 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 10- 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: _____