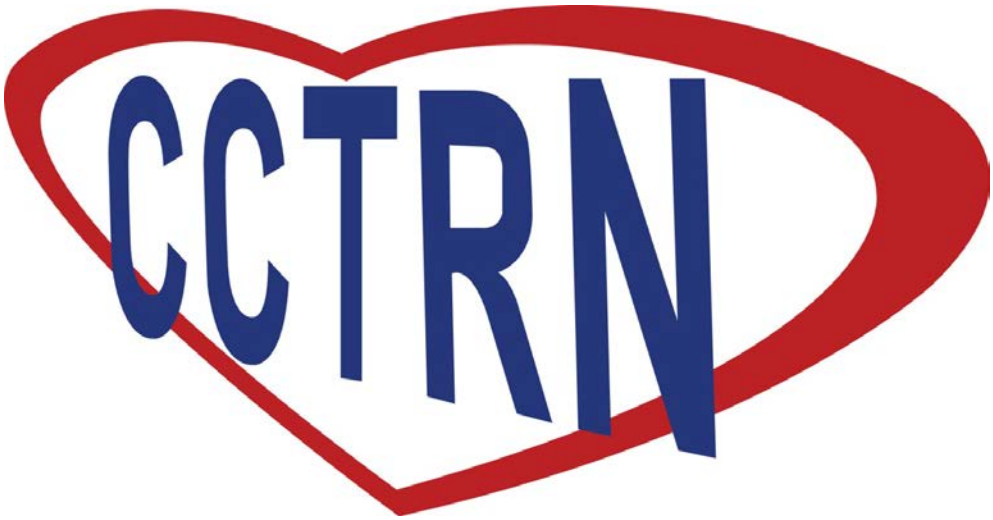
Cardiovascular Cell Therapy Research Network



Manual of Operating Procedures for the PACE Protocol

Clinical and MR Imaging Assessments in Patients with Intermittent Claudication Following Injection of Bone Marrow Derived ALDH Bright Cells

Version 4 – March 23, 2015

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CCTRN PACE PROTOCOL

I. Study Overview

Full Title: Clinical and MR Imaging Assessments in Patients with Intermittent Claudication Following Injection of Bone Marrow Derived ALDH Bright Cells

Short Title: **P**atients with Intermittent Claudication Injected with **A**LDH Bright **Ce**lls (PACE)

Sponsor: CCTRN Data Coordinating Center- University of Texas-Houston School of Public Health

Clinical Sites: Texas Heart Institute, Houston Texas; University of Florida, Gainesville Florida; Minneapolis Heart Institute Foundation, Minneapolis Minnesota; University of Minnesota, Minneapolis, Minnesota; University of Louisville, Louisville, Kentucky; University of Miami, Miami, Florida; Stanford University, Stanford, California; and Indiana University-Purdue University Indianapolis, Indianapolis, Indiana; Data Coordinating Center: University of Texas-School of Public Health, Coordinating Center for Clinical Trials, Houston, Texas

Investigators: Cardiovascular Cell Therapy Research Network (CCTRN)

Test Agent: ALD-301; Autologous Bone Marrow Derived $ALDH^{br}$ cells

Population: A total of 80 patients (40 receiving active and 40 receiving placebo therapies); males and females, who have atherosclerotic peripheral artery disease (PAD) with symptom-limiting intermittent claudication, and presence of significant stenosis or occlusion of infrainguinal arteries including the superficial femoral artery, popliteal artery and/or infrapopliteal arteries as defined by at least 50% stenosis and an ankle-brachial index <0.9 or toe-brachial index <0.70 will be enrolled in the trial.

Treatment: Patients enrolled in this study will be recruited from all of the sites participating in the National Heart, Lung, and Blood Institute (NHLBI) CCTRN. PAD patients with with intermittent claudication are identified at the facilities in which they receive their standard vascular care; this includes the respective hospitals of the Network and referrals from local hospitals affiliated with the Network hospitals. All prospective patients will be screened by the Investigators and study coordinators and will be enrolled in this Phase II, double-blind, placebo-controlled trial after meeting inclusion/exclusion criteria and signing the informed consent form. Subjects will be randomized in a 1:1 ratio to active treatment (ALD-301) or placebo (vehicle) and will undergo bone marrow aspiration (180 mL ± 10mL). For subjects assigned to the active treatment condition, 150mL will be transported from the local site cell processing labs to the Center for Cell and Gene Therapy (CAGT)

(*Houston, Texas*) for cell processing and release-testing at their FDA registered cell processing laboratory. The cell product will be transported back to the respective site cell processing labs to allow for study product injection within 96 hours of the bone marrow aspiration. Placebo product will be provided by CAGT to the local cell processing labs and kept on-site. With appropriate consent, patients randomized to cell treatment will have approximately 30mL of bone marrow sent to the CCTRN Biorepository for further study and patients randomized to the placebo group will have approximately 180mL of bone marrow sent to the CCTRN Biorepository. A 25 gauge needle will be used for 8 injections into the calf muscle and 2 injections into the posterior lower thigh of the index limb. Each injection contains approximately 1 mL of study product (active or placebo). Injections are evenly targeted according to the injection manual diagram (outlined in the appendix of the study protocol).

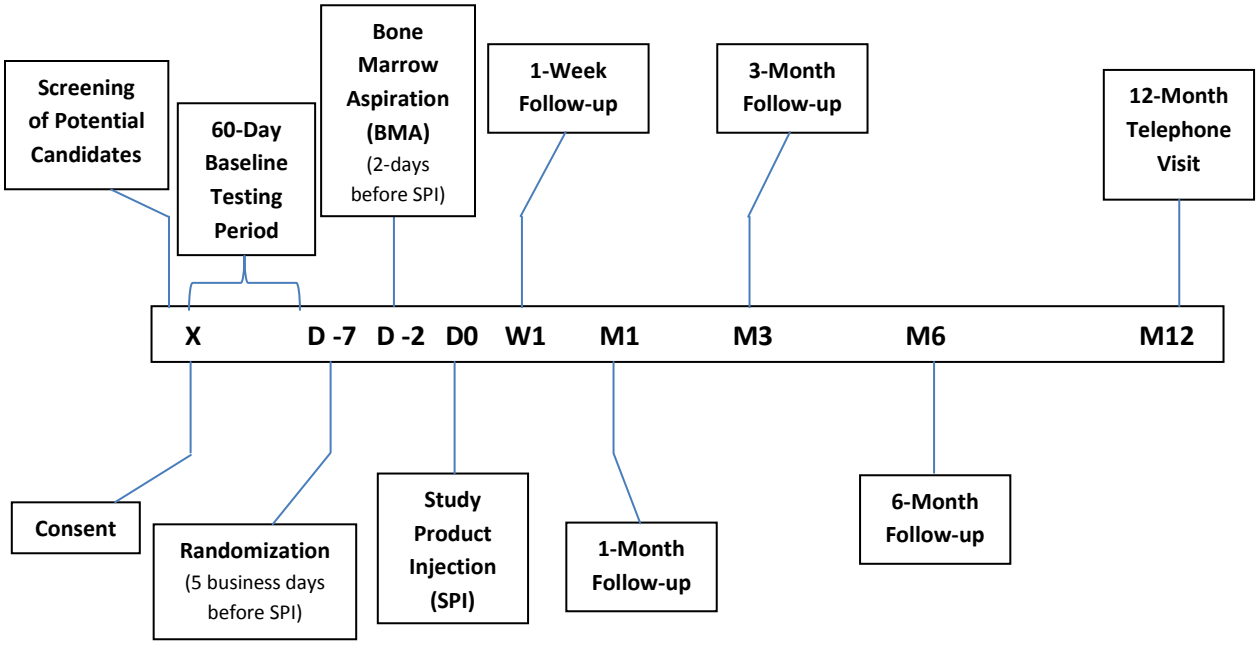
Duration: Subjects enrolled in this study will be followed for 6 months; with a single telephone contact at 12 months post treatment.

Objective: The purpose of this study is to determine the safety and effectiveness of bone marrow-derived stem cell therapy on improving tissue perfusion and/or peak walking time (PWT) in patients with PAD and intermittent claudication. The four primary efficacy endpoints (measured at baseline and at six months) are 1) change in PWT, 2) change in the number of new leg collateral vessels (contrast enhanced MR), 3) change in peak flow (phase-contrast MR), and 4) change in hyperemic flow (perfusion MR). In addition, the relationship between PWT and each of the three MR endpoints will be evaluated, and a comprehensive set of PAD objective and subjective clinical endpoints will be assessed.

Endpoints: The four primary endpoints (reflecting change from baseline to 6 months between groups) are: 1) Peak walking time (PWT), 2) Leg collateral artery anatomy (via contrast enhanced-MR), 3) Vascular flow (phase-contrast MR), and 4) Perfusion (via cuff-induced ischemia using perfusion MR)

Secondary endpoints (reflecting change over time between groups) include: 1) Resting ABI at three and six months, 2) Post-exercise ABI at three and six months, 3) Claudication onset time (COT) at three and six months, 4) PWT at 3 months, 5) assessment of the relationship between PWT and the three imaging based primary endpoints, 6) Walking Impairment Questionnaire (WIQ) at 1,3, and 6 months, and 7) Peripheral Artery Questionnaire (PAQ) at 1,3, and 6 months

II. Flowchart of Study Phases



To help you organize study related activities for each patient, a procedure checklist template **has been provided (see MOP Binder Section 2, Coordinator Checklist) and can be modified by the site coordinator to meet the needs of the specific center. This document, along with all supporting MOP documents are also available on the CCTRN website (*www.cctrn.org*); navigate to Member Resources/PACE/MOP Documents and they are saved under the corresponding binder section number and header.**

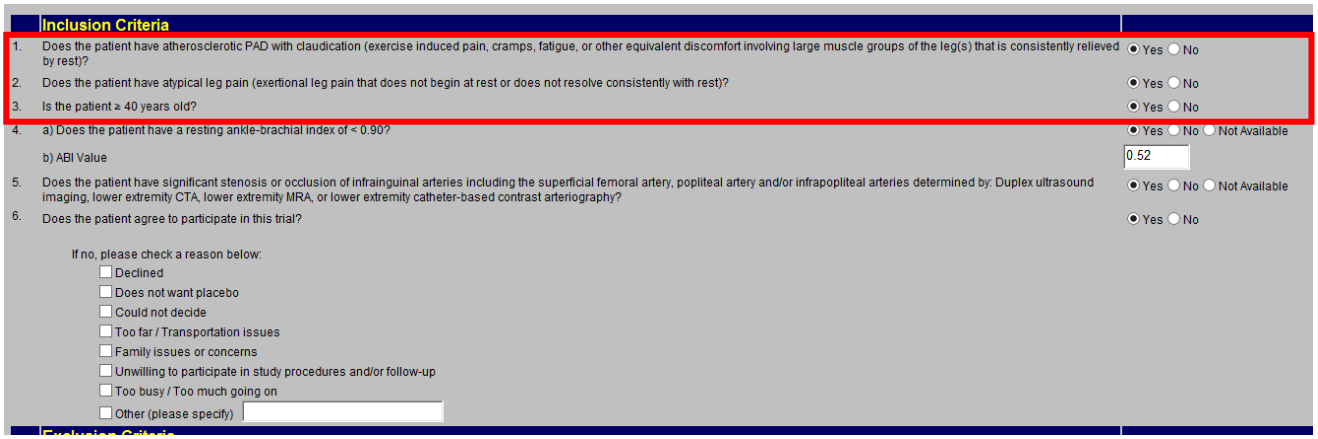
For frequently asked questions (FAQs) regarding study procedures, see MOP Binder Section 7, FAQs.

III.Procedures by Study Phase

A. Screening

The screening phase of the study pertains to the initial review of potential participant characteristics based on available data (i.e. medical records review). This information is reviewed prior to consenting to the study, including review of patients' imaging studies (i.e., duplex, angiography or MRI). Limited demographic information and eligibility criteria based on available data are recorded on the Screening Form (see workbook in *MOP Binder Section 3, CRF Workbooks*) to capture the population approached for the study, how participants first found out about the study and, when applicable, reason(s) for not consenting the screened population. A screening form should be completed for EVERY potential participant that fits the following criteria: PAD with

classic claudication (inclusion criteria #1 on form) and/or atypical leg pain (inclusion criteria #2 on form) and are at least 40 years old (inclusion criteria #3 on form). See sample screening form below:



Inclusion Criteria

1. Does the patient have atherosclerotic PAD with claudication (exercise induced pain, cramps, fatigue, or other equivalent discomfort involving large muscle groups of the leg(s) that is consistently relieved by rest)? — Yes / No
2. Does the patient have atypical leg pain (exertional leg pain that does not begin at rest or does not resolve consistently with rest)? — Yes / No
3. Is the patient ≥ 40 years old? — Yes / No
4. a) Does the patient have a resting ankle-brachial index of < 0.90? — Yes / No / Not Available
   b) ABI Value: 0.52
5. Does the patient have significant stenosis or occlusion of infrainguinal arteries including the superficial femoral artery, popliteal artery and/or infrapopliteal arteries determined by: Duplex ultrasound imaging, lower extremity CTA, lower extremity MRA, or lower extremity catheter-based contrast arteriography? — Yes / No / Not Available
6. Does the patient agree to participate in this trial? — Yes / No

If no, please check a reason below:

- Declined
- Does not want placebo
- Could not decide
- Too far / Transportation issues
- Family issues or concerns
- Unwilling to participate in study procedures and/or follow-up
- Too busy / Too much going on
- Other (please specify)

Additionally, if the patient states s/he was "referred by a friend or other non-medical person", please be sure to also ask if s/he knows how this person became aware of the study. The first source of study awareness would be the best answer to the question. If a patient does not want to participate, it is important to collect the specific reason why and document this on the Screening eCRF. If a participant does not report how they found out about the study, or if they are included from a screening chart review with no personal discussion, please indicate "no response" for this question. All criteria do not need to be answered to submit the form for a patient who will be ineligible to consent to the trial. ***Screening forms should be entered on a weekly basis*** to keep screening number accurate for reporting to the Steering Committee.

PACE Workbooks are available online on the CCTRN website; navigate to Member Resources/PACE/MOP Documents/3-CRF Workbooks

Refer to the CCTRN Electronic Case Report Forms (eCRFs) Users Guide a.k.a. "eCRFs Users Guide" for complete instructions on submission of eCRFs in the CCTRN database. This document is located on the CCTRN website; navigate to Member Resources/PACE/eCRF Users Guide.

Potential participants can be screened more than once with multiple screening forms entered for the same patient before they are consented. A Study ID will be generated by submission of the first screening eCRF and the screening date will also appear to assist you with selecting the same patient should you choose rescreen someone for the study. ***It is very important that you track the database-generated Study ID and screening date in a manner such that you can retrieve the individual's information should they be re-screened in the future (another Screening Form would***

be entered at that time using the same Study ID). Tracking could be achieved for example, by either keeping an internal log or a separate binder to house the screening forms. In order to accurately count the number of people screened for the study, we must have only one Study ID for each patient screened no matter how many times you screen them.

For individuals who are eligible based on the Screening form and consent to be in the study, a Demographics Form will be accessible on the eCRF menu. Successful completion of this form will result in the patient Acrostic. An **Acrostic** is a second unique identifier. The acrostic is a combination of six letters which come from the patient's name. It is the first three letters of the last name, first two letters of the first name, and the middle initial. There are cases in which the acrostic may be only 5 letters (e.g. patient has no middle initial). Do not include spaces and/or punctuation marks in patient's name, as this can be a problem in acrostic generation. The Study ID and Acrostic will be used to identify the patient on all study documents other than the screening records which will be identified in the database by the Study ID and the screening date. You cannot screen a patient more than once per day.

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

B. Consent

<u>The informed consent process is as follows</u>:

All participants enrolled in this clinical trial will be identified as having symptomatic claudication and will be referred from vascular clinics, outpatient care clinics, other physician referrals, self-referrals generated by advertising, or other site-specific recruitment plans. Candidates identified as eligible for enrollment via the Screening form 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 will provide information regarding standard alternative claudication therapies and will include information regarding potential risks and benefits of participation. Potential participants will be asked to consent to the Biorepository and the possibility of future genetic testing as separate consents within the main consent form. PLEASE BE SURE this information is entered correctly in the database, as the Cell Processors will use this information to know how to handle each subject's surplus bone marrow and their peripheral blood.

Necessary elements of the informed consent process are included below:

1. Confirm the consent being provided to/reviewed with the patient is a current and IRB-approved consent form.
2. Allow the individual time to read the entire written consent form.
3. Explain the various components of the study to answer initial questions. This includes directed conversations regarding voluntary participation, time requirements, the possibility of assignment to a placebo condition and what that means, a detailed explanation of the risks involved, and confidentiality of research data.
4. Invite and encourage the individual to discuss the consent form with family or loved ones to enable him/her to make a decision with support of these individuals.
5. Ask the individual for an explanation of what the research involves and what is required. Review this information until the individual can provide a clear explanation of the research.
6. Elicit from the individual if there are any further questions about the research being considered.
7. The written consent form is signed/dated by the individual.
8. One copy of the signed consent form is given to the participant.
9. 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. Collect specific reason why individual does not want to participate, and document this on the Screening eCRF.
3. Thank the individual for their time and consideration of the research program.

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 the participant was approached for the study, listing of family members/other individuals present for the consent, the date/time the participant signed the consent, and any specific items of concern addressed with the participant.

If a subject DOES NOT consent to the Biorepository, please confirm this with your local cell processing lab, so they will know NOT to send any extra bone marrow to the Biorepository. On a related note, **NO peripheral bloods will be drawn for any patient that does not give Biorepository consent.** It may be helpful to flag these charts with a reminder.

C. Baseline Testing

After consent and assignment of study ID and acrostic in the database, the research coordinator collects the baseline assessments per protocol to determine whether the individual truly is a viable candidate for study treatment. The baseline testing period extends from the date informed consent is signed until the day of study treatment. The baseline testing window will not exceed 60 days prior to randomization (Day -4). **Note: Participants may be excluded from the study if any of the baseline testing is not completed or meets an exclusion criterion during the 60 day period.**

The baseline evaluations cannot begin until after the informed consent has been signed. Below is a list of baseline assessments that must be completed within the 60-day testing period. For your convenience, we have listed the assessments in 2 study visits schedules, however, if necessary, participants can complete these assessments at more than 2 visits.

Treadmill Testing

Treadmill testing has several instructions for standardization, as listed below:

1. Treadmill Exercise Test TMET-1 and TMET-2 must be completed at least 72 hours apart, to give the patient time to recover and the Treadmill core lab time to review testing documentation for accuracy. If you must complete the treadmill testing on consecutive days, please contact the Treadmill core lab for prior approval.
2. Participants should be picked up at patient drop-off upon arrival at site and transported by wheelchair to all procedures.
3. Any sedatives given to the participant on the day of a treadmill test (for example, during the MRI) will need to clear the system before completing the treadmill test.
4. Scripts provided by the Treadmill Core Lab should be used during TMETs to standardize language and encourage maximal walking. (Scripts can be found on www.cctrn.org at Member Resources/PACE/Core Labs/Treadmill)

MRI Testing

The MRI testing has several pre-testing instructions for the day of the test, as listed below:

1. Participants should fast for a minimum of 8 hours before scan
2. Participants should be asked to abstain from smoking, taking vasoactive medications (including over the counter medications, such as high-dose niacin, decongestants, vitamins C and E), and vigorous activity

The MRI should be scheduled as the first test in the morning on the day of Visit 2 since it must be done **AT LEAST 2 HOURS BEFORE** the treadmill testing and with the subject fasting.

The complete schedule of procedures can be found in Section 6 of the protocol. Instructions for eCRF entry in the database located on www.cctrn.org can be found in **eCRFs Users Guide**. CRF workbooks can be found in *MOP Binder Section 3, CRF Workbooks.*

In the case that a patient screen fails after consent during the baseline screening process, the End of Study form (EOS) should be completed. The only forms necessary to complete for a screen fail patient are Screening, Demographics, Eligibility, and the EOS. These forms will be monitored. If a center would like to rescreen a screen-fail patient, please contact the DCC to get approval. Once approved, the baseline forms will be reset. Please note, **only one screen failure payment will be made per patient**, even if they are reset to attempt baseline testing more than one time.

1. Baseline Review and Testing - Visits 1 and 2

Visit 1- Baseline Testing

TEST
Demographics (includes date of signed consent)
History and Physical Exam
Medications and Allergies
ECG
Labs-Blood work#
Labs-Infectious Disease†
San Diego Claudication Questionnaire (SDCQ)
Walking Impairment Questionnaire (WIQ)
Peripheral Artery Questionnaire (PAQ)
Patient Expectation Questionnaire (PEQ)
Cuff inflation test procedure*
Treadmill Familiarization¶
TMET 1‡
ABI/TBI pre and post exercise‖

Visit 2 - Baseline Testing
(must be at least 3 days between TMET-1 and TMET-2)

TEST
MRI€
TMET 2‡
ABI/TBI pre and post exercise, if necessary§
Eligibility Form

To manually calculate GFR, the National Kidney Foundation's eGFR calculator is available online (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Enter patient data to calculate GFR and use the "MDRD study equation" for calculated GFR. Enter the result into the lab eCRF. Please screen print the page from the website for the source documentation.

† 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 report as an AE. Results must be known prior to randomization. If patient has inactive markers for Hep C (such as antibody positive, antigen negative, with normal LTF) will need to get clearance from local hematologist for inclusion in study.

**Cuff inflation test procedure is included as Attachment A*

¶ Treadmill Familiarization can occur on the same day as TMET-1, if both tests are AT LEAST 30 minutes apart from each other. For more information about TMETs, please see Treadmill Core Lab procedure manual.

‡ TMET - Treadmill Exercise Test (must be at least 72 hours between TMET-1 and TMET-2)

‖ If ABI is >1.3 or there is documentation of non-compressible vessels, a TBI can be obtained by photoplethysmography (PPG) by a core lab certified vascular tech or sonographer. TBI must be <.0.70 for patient to quality for study. If TBI is used for eligibility, no post-exercise TBI (or ABI) are collected. Please note that ABI/TBI form should be saved incomplete until treadmill core lab has approved ABI/TBI upon which the form can be submitted and finalized in the system.

*€ MRI must be performed **AT LEAST 2 HOURS BEFORE** treadmill testing at Visit 2 due to possible vascular changes from exercise testing.*

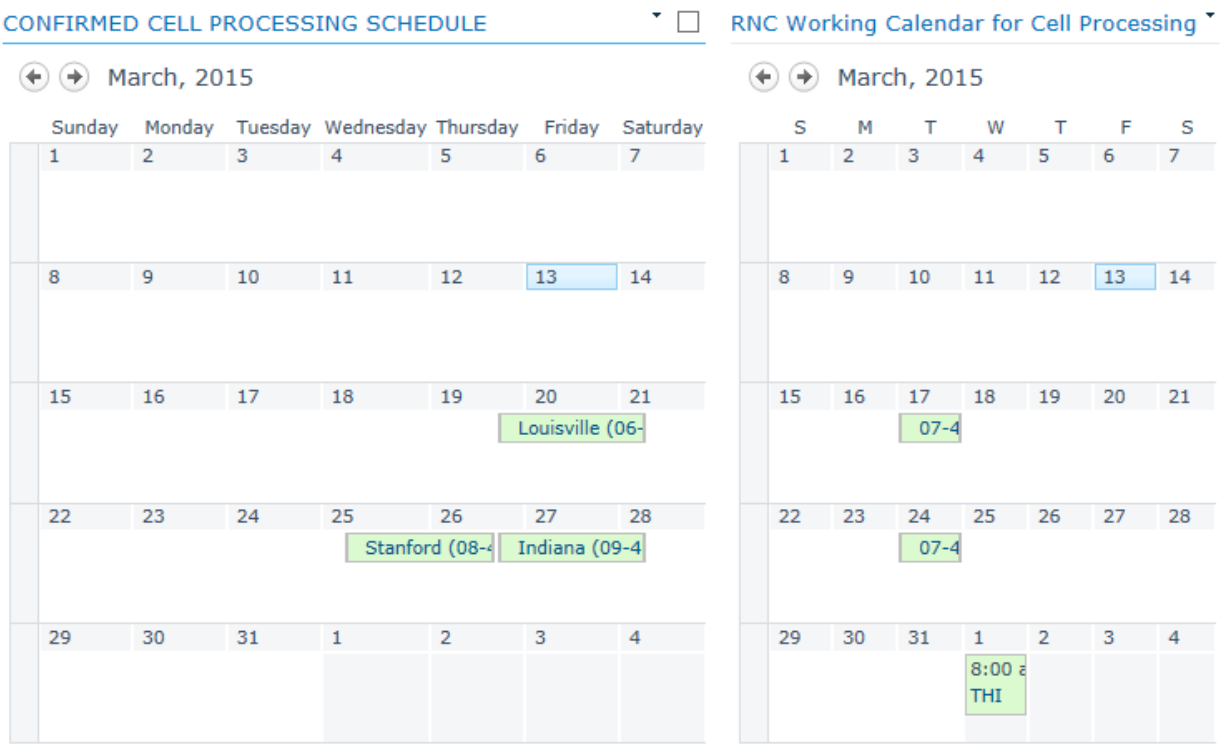
§ Treadmill core lab will assess the need for ABI/TBI assessment at the second visit.

2. Completing the Treatment Checklist

The Treatment Checklist is an eCRF which allows the web application to match eligibility criteria with data from the baseline physical exam, labs, ABI/TBI, treadmill test, and the baseline San Diego Claudication Questionnaire (SDCQ) thereby doing a systematic check to help ensure that only eligible participants are randomized. The following forms: the Demographics form, the Eligibility form, the Baseline Labs, the Baseline Physical Exam, the Baseline ABI/TBI, the Baseline Treadmill Exercise Test form, and the baseline SDCQ **MUST BE ENTERED BEFORE** the Treatment Checklist can be submitted which will confirm the patient is eligible for the study. Once the eligible patient has completed baseline testing and the baseline eCRFs have been successfully entered, the Coordinator will complete the Treatment Checklist form (see **eCRFs Users Guide**). Included on this form is the proposed date of the bone marrow aspiration (BMA) procedure. Detailed information for scheduling cell processing is included in the next section. **Be sure to confirm availability of the local cell processing lab before entering treatment checklist**

3. Cell Processing Scheduling

Although scheduling cell processing happens at the end of the baseline testing process, it is important to begin identifying possible BMA dates upon patient consent. This is due to the number of PACE sites and cell processing schedule, which allows for BMA on Tuesdays and Wednesdays ONLY. The PACE SharePoint site has two calendars: the RNC Working Calendar and the Confirmed Cell Processing Schedule (see screen shot below). RNCs should use both as tools to schedule their patients for cell processing. The first calendar is primarily a tool for facilitating communication between sites – potential dates for patients in baseline testing are entered here. Please do not enter more than 3 potential date options for each patient. Each entry should list the Site, Pt ID or Acrostic, and rank (1st choice, 2nd choice). RNCs are encouraged to contact each other (copying the DCC) if there is a conflict for a date. The Confirmed Cell Processing calendar is reserved for patients that have been deemed eligible and approved by CAGT for BMA. The DCC maintains this calendar and enters patients as requested by CAGT.



As mentioned above the proposed BMA date is included on the Treatment Checklist. Upon submission of this form, an automated email with the proposed BMA date is sent to the CAGT transport coordinator, local cell processing lab, DCC-Cell Processing Quality Control Lab, and the site research team. The CAGT transport coordinator will contact the research coordinator to confirm the proposed BMA date. If a date is not available, the BMA will have to be rescheduled and the new date confirmed with CAGT transport coordinator at that time. Once a BMA date has been approved, the CAGT transport coordinator then sends that date to the DCC for addition to

the Confirmed Cell Processing calendar. Cell processing scheduling procedures are listed in full in Attachment B. If cell processing is available, the research coordinator will randomize the patient by submitting the Randomization form (see **eCRFs Users Guide**) in the CCTRN database created and maintained by the DCC.

D. Randomization

Randomization will be performed in accordance with written standard operating procedures by personnel that are not involved in the selection, screening, or enrollment of subjects and blinded as to clinical documentation. Although research coordinators will be activating patient randomization, they will **NOT** be able to access the patient's treatment assignment – this will only be accessible by CAGT and the local cell processing lab personnel that is designated as the unblinded contact. **Randomization should occur 5 BUSINESS DAYS before BMA.**

See process outlined below:

1. Electronic procedure for generating Therapy Assignment (unblinded personnel)

1. Coordinator enters Treatment Checklist with proposed date of BMA.
2. Coordinator contacts transport coordinator to confirm BMA date or reschedule if necessary.
3. Coordinator will enter the Randomization form with finalized BMA date, which will generate an automatic email to CAGT, local cell processing lab, DCC/CPQCL, and the site research team.
4. Upon receipt of this email, the unblinded local cell processing lab contact and the transport coordinator will have access to see the treatment group and begin the appropriate plans.

2. Manual procedure for generating Therapy Assignment (or Study ID/Acrostic)

1. Call from Site personnel to DCC after BMA date/time is approved by CAGT.
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.

E. Bone Marrow Harvest – Visit 3

Bone marrow aspiration, cell processing, and study product injection follow in accordance with the protocol specified timeframe. **Bone marrow aspirations should be scheduled as early in the morning as possible to assure that bone marrow for active patients gets to CAGT the same day as the procedure.** See protocol Appendix C for Bone Marrow Aspiration procedures.

The 96 hour expiration date for study product is calculated from the end of the bone marrow aspiration – this time will need to be noted on the label on the bone marrow collection bag before it is sent to the local cell processing lab.

Visit 3 - Bone Marrow Harvest (Day -2)

TEST
Physical Exam
ECG
Blood Draw (for Biorepository, if consented)*
Bone Marrow Aspiration

**The research coordinator is also responsible for assuring the peripheral bloods collected for the biorepository are labeled and delivered to the cell processing lab to be included with the surplus bone marrow in the shipment to the biorepository (information regarding these procedures can be found in MOP Binder Section 5, Biorepository Procedures).*

If a subject has NOT given Biorepository consent, please confirm this with your local cell processing lab on the day of bone marrow harvest, so they will take appropriate actions and destroy any remaining bone marrow per local laboratory SOPs. No peripheral bloods should be drawn for any subject who has NOT given Biorepository consent.

F. Study Product Information (Transport Coordinator contact information)

Information regarding cell product can be found in the Investigator Brochure. Cell transport details can be found in *MOP Binder Section 6, Study Product Injection.*

CAGT Transport Coordinator Contact Information:
Sara Richman
sjrichma@texaschildrens.org
Mobile: 832-689-0142
Office: 832-824-3923

G. Events Precluding Delivery of Study Product

The events listed below are to be considered sufficient to halt the study procedure. **If subject develops any of the following conditions within 24 hours of planned injection, study product delivery will be halted:**

1. Hemodynamically unstable
2. Fever (Temperature increase to ≥100.4^{o}F)
3. Significant bleeding from bone marrow harvest site

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 DCC and notify them so they can contact CAGT and QC-CPL.**

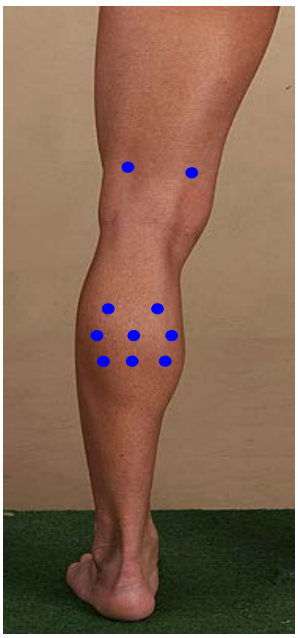
Should manufacturing or transportation failures involving the processed study product occur, there will be no repeat bone marrow aspiration, the patient will remain randomized to their original treatment condition, and they will be followed per protocol as part of the intention-to-treat analysis. The failure will be reported as an unanticipated problem.

H. Study Product Injection (SPI) – Visit 4

Visit 4 - Study Product Injection (Day 0)

TEST
Physical Exam
Study Product Preparation and Delivery (SPI)
Injection Site Assessment (post injection)¶

¶ Injection Site Assessment included on Physical Exam form at SPI and 1 week.



The total maximum out-of-body time (from bone marrow aspiration to study product injection) for the cells is 96 hours (4 days) which is calculated from the end of the bone marrow aspiration procedure.

Injection of ALDH^{br} cells or placebo will be performed in an outpatient clinic or procedure room as designated by the site. The SPI visit should be scheduled after 2:00pm local time to ensure that study product for active patients will be available. Coordination between the clinical site and local cell processing lab is critical on this day, in order to get the study product delivered in time for the SPI visit. The study product, either the placebo or cell product, cannot be kept at room temperature for more than 4 hours – if this occurs, the product cannot be used and the DCC and CAGT must be contacted immediately. Study product is administered in ten (10) injections (shots), eight injected into the calf muscle below the knee and the remaining two injections in the lower thigh muscle above the knee. The study product will be drawn up in the syringes at the clinical

site. See *MOP Binder Section 6* for guidelines on this procedure. When treatment has been delivered, the research coordinator will need to complete and enter the Study Product Injection eCRF. The source documentation will include a handwritten "map" of the location of study project injections on the inset picture. This information will only be in the patient record, it will not be collected in the database.

The protocol calls for application of anesthetic cream to help alleviate discomfort for the patients during SPI. For a description of suggested supplies and application process, see *MOP Binder Section 6, Study Product Injection.*

The participant is monitored for 1 hour post injection (at 30 minutes and 60 minutes) and provided with a log for monitoring temperature twice a day for the next seven days (see Attachment A for temperature log). Injection sites will be assessed again at the one week visit.

I. Follow-up Visits – Visits 5-8

Follow-up visits will take place at regularly scheduled intervals. Below is a schedule of activities for each follow-up visit:

Visit 5 - One week Follow-Up (Day 7 post injection – window 5-12 days)

TEST
Physical Exam
Injection Site Assessment (post injection)¶
ECG
Labs-Blood work
Blood Draw (for Biorepository, if consented)

¶ Injection Site Assessment included on Physical Exam form at SPI and 1 week.

(Note that participants will take twice daily measurements of temperature for 1 week following injection – this log will be returned at the 1 week visit. See Attachment C –One-week Patient Temperature Log)

Visit 6 - One month Follow-Up (Day 30 post injection – window ±7 days)

TEST
Physical Exam
ECG
Labs-Blood work
Blood Draw (for Biorepository, if consented)
Walking Impairment Questionnaire (WIQ)
Peripheral Artery Questionnaire (PAQ)

Visit 7 - Three month Follow-Up (Day 90 post injection – window ± 14 days)

TEST
Physical Exam
Walking Impairment Questionnaire (WIQ)
Peripheral Artery Questionnaire (PAQ)
TMET
ABI/TBI pre and post exercise

Visit 8 - Six month Follow-Up (Day 180 post injection – window ± 30 days)

TEST
Physical Exam
ECG
Labs-Blood work
Blood Draw (for Biorepository, if consented)
Walking Impairment Questionnaire (WIQ)
Peripheral Artery Questionnaire (PAQ)
Patient Expectation Questionnaire (PEQ)
TMET
ABI/TBI pre and post exercise
MRI

A brief telephone interview (including the PAQ) will be conducted at 12 months – window ± 30 days

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 attempts to contact a participant and have these available for the Monitor for inspection (Attachment D – Participant Contact Log). Guidelines for submitting forms for missed visits, including missing form, protocol deviation for the missed visit, and end of study forms can be found in the **eCRF Users Guide**.

J. Interim Visits

An interim physical exam 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 PACE protocol.

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

1) Dr. Linda Piller: 713-500-9507; Linda.B.Piller@uth.tmc.edu
2) Dr. Lara Simpson: 713-500-9503; Lara.M.Simpson@uth.tmc.edu
3) Dr. Lem Moyé: 713-500-9518; Lemmoye@msn.com

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

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

Serious Adverse Events (SAEs) or Serious Suspected Adverse Reaction (SSAR)
A *serious adverse event* (SAE) or *serious suspected adverse reaction* (SSAR) is defined as an AE/SAR which, in the view of the Investigator or Sponsor, results in: 1) Death; 2) a life-threatening event (i.e. an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); 3) inpatient hospitalization of > 24 hours or prolongation of existing hospitalization; 4) a significant disability/incapacity; or 5) a congenital anomaly/birth defect. Other important medical events may be considered SAEs/SSARs if, in the opinion of the Investigator or DCC, they jeopardize the subject or require intervention to prevent one of the other outcomes listed above.

A. Adverse Event Reporting

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

ii. Report **protocol deviation/violations** to the DCC via the database (see **eCRFs Users Guide**) within 7 days of the PI or staff's awareness of the event. If the departure from the protocol is required to protect the life or physical well-being of a 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 (see *MOP Binder Section 3*) or printable form from the CCTRN website (www.cctrn.org).
- Enter the information from the workbook into the CCTRN web application Protocol Deviation form (see **eCRFs Users Guide**) which describes the event.
  - If the protocol deviation is being completed to request an exemption, you should check the box labeled, "Event has not occurred (exemption request)"
  - If the protocol violation was submitted for an event that has already occurred, the receipt of information will be acknowledged.
- The DCC will complete the bottom portion of the form and enter if the exemption or waiver was granted.
- Copies of all protocol deviation/exemption correspondence should be placed in the corresponding 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 Clarifications/Data Change Requests (DCCRs)

The DCCR form (see *MOP Binder Section 4*) 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 either fax to the DCC with a DCC fax cover sheet or scan and e-mail it as PDF to Judy Bettencourt, Shelly Sayre, Rachel Vojvodic or Michelle Cohen.
- The DCC makes the change in the database, initials the DCCR form, scans and e-mails 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 either fax the form back to DCC with a DCC fax cover sheet or scan and e-mail it as PDF to Judy Bettencourt, Shelly Sayre, Rachel Vojvodic, or Michelle Cohen.
    - The site maintains a copy and the DCC maintains a copy.
3. The Clinical Monitor will verify all data change/data clarification requests with source documents during the monitoring visit.

VI. Transferring Participants between Centers

In the case that a patient needs to transfer between CCTRN centers, please contact a project manager at the DCC to inform them of the situation and they will facilitate this process. Please note: All outstanding data entry and data queries must be completed, reviewed, and 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.

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

- ***Site Initiation Visit (SIV)***

  CCTRN sites are selected by NHLBI, and thus Site Evaluation Visits (SEVs) will not be performed. A Site Initiation Visit (SIV*) may be performed* at the request of the Project Manager (PM) or designee. The SIV may be conducted by telephone or on-site.

- ***Interim Monitoring Visit (IMV)***

  - ***Remote Monitoring***

    CCTRN is incorporating remote monitoring into the monitoring plans for upcoming protocols. In PACE, remote monitoring will occur after treatment of the first two patients, then throughout the trial, as deemed necessary by the Monitor or PM.

    After treatment of each of the first 2 patients, the site will send (via PDF/email or fax 713-486-0981) all the relevant source documents to the Monitor for 100% source data verification (SDV) of baseline and treatment eCRFs to help ensure that the site is following the protocol and completing eCRFs and workbooks appropriately. The complete list of documents required for initial remote monitoring are listed in Attachment G – Remote Monitoring Checklist. **BE SURE TO DE-IDENTIFY ALL DOCUMENTS.** All documents should be sent to the DCC within 5 business days of study product injection. The Monitor or designee will review this documentation within 72 hours. The DCC may place a site on hold until the first 2 subjects have been monitored and any identified issues are resolved before continuing enrollment.

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

  - ***Onsite Monitoring***

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

days per protocol (depending on the number of subjects to be reviewed and any outstanding issues at that visit).
In regards to source document verification (SDV), 100% SDV will be conducted on eligibility, endpoints, and safety review. For the remaining data points, a percentage of the total is reviewed. During the first on-site monitoring visit, which will be scheduled within six weeks of the first patient randomization, the Monitor will review the original source documents for baseline and treatment to ensure they match the documents that were sent for remote monitoring.

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

- ***Final Monitoring / Close-out Visit (COV)***

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

- ***Biannual On-site Regulatory Document Review***
  Full regulatory document review (hard copy or electronic) will be conducted at the site biannually. Reviews may be conducted simultaneously with an IMV; in this case, separate reports will be filed.

VIII. 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 5, Biorepository Procedures*.

IX. Patient Care Payment

A. Form Payments

Payments are made on a per form basis. A payment schedule by form is included in *MOP Binder Section 8, Payment Information.* 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. 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 www.cctrn.org, select Data Resources
- Login with User ID and Password
- Select "Reports and Applications"
- Select "View Payment Vouchers"
- Select Invoice Date

B. Patient Travel Stipends

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

For example, a center might use the following strategy:

Miles from center	Reimbursement per visit
<25	$25
25-50	$50
51-100	$100
>100	$150

All travel reimbursement payments should be kept on a log with patient id, acrostic, study visit(s), distance traveled (miles) and amount paid. This spreadsheet will be submitted to the DCC on a quarterly basis, so these costs can be tracked across the Network. See Attachment H for Travel Reimbursement Log.

Attachment A – Cuff Inflation Test Procedure

Pressure cuff occlusion in the thigh, inducing skeletal muscle ischemia, is critical to the success of the MRI endpoints. However, there is concern that this pressure will cause significant discomfort in the index limb and cause the participant to move during the MR imaging sequences, distorting data acquisition. Therefore, during Visit 1-Baseline Testing, all participants will need to go through a five min test cuff inflation (as this same procedure will be done during the MRI in Visit 2-Baseline Testing) to:

- Confirm occlusion of the pedal vessel pressure at lowest possible cuff pressure to ease pain/discomfort
- Test participant's ability to handle pressure cuff for 5 mins during MRI procedure
- Establish a cuff inflation duration between 3-5 minutes, if the participant cannot tolerate 5 minutes

Visit 1 – Baseline Testing

Materials needed for test procedure: PACE MRI-compatible thigh cuff; Doppler probe for measuring blood flow

Please note: cuff inflation will be done on index (symptomatic) leg only by Research Coordinator(s) and/or Screening Physician

1. The participant will be told to expect a sensation of constriction around the thigh that may be uncomfortable and that will last for a period of five minutes; however, if intolerable, the examination will be immediately stopped and the cuff deflated. Please use standardized test intro below:

   As part of the measurements of leg blood flow in the PACE study, you will be having a blood flow test during the MRI imaging sequence. These tests have been performed for decades and are safe. They require a cuff to be inflated around your thigh for several minutes.

   In order to ensure you can tolerate this procedure, we will be inflating a cuff for up to five minutes around your thigh. During that time period we expect you to feel some pressure and tightness but no major discomfort.

   However, if you do become uncomfortable, please let us know, so we can adjust the cuff to obtain the best quality information.

2. The systolic arm pressure (SAP) measured during the baseline physical exam will be used as the target pressure for the thigh cuff inflation.

3. The thigh pressure cuff will be placed circumferentially around the participant's thigh as proximal as possible without pinching or creasing the skin.

4. A hand held Doppler probe will be used to identify the strongest arterial signal (posterior tibial or dorsalis pedal artery) at the ankle before the cuff is inflated. This will be the index artery for all cuff occlusion procedures.

5. The thigh cuff will be inflated to the systolic arm pressure by the screening coordinator, while the index artery is insonated with the Doppler probe by a second coordinator or screening physician. It is critical to keep the Doppler probe still and centered on the index artery, so it will be clear when the Doppler signal is gone.

6. If the Doppler signal completely ablates at this pressure, the cuff will remain inflated at that pressure for five minutes, or as long as can be tolerated, to assess the participant's comfort and ability to comply. The nominal (minimal) threshold for an evaluable test is 3 minutes of thigh cuff inflation.

7. If a signal persists in the index artery at the SAP, the cuff will be inflated further by 5mmHg increments until the Doppler signal is ablated. The Occlusion Pressure =SAP + mmHg above SAP needed for no pulse in index artery. The cuff will remain inflated at that pressure for five minutes, or as long as can be tolerated by the participant. At the end of the 3-5 minute occlusion period (before deflation), one should check the cuff inflation pressure, and using the Doppler, check to ensure that the arterial occlusion was maintained during the inflation.

8. If the participant cannot tolerate the occlusive cuff inflation for at least three minutes, they will be excluded from the study.

9. If the participant reports significant, but not intolerable discomfort that may be relieved with mild sedation, the participant will be offered this option for the day of the MRI procedure. Please note: the sedation offered must comply with what is currently in local consent form.

10. To be documented on MRI form: index artery (PT or DP), systolic arm pressure, occlusion pressure, amount of time pressure cuff was fully inflated (if less than 5 mins), and if the participant wishes to be mildly sedated during MRI exam.

Visit 2 – Baseline Testing (MRI)

Materials needed for MRI procedure: PACE MRI-compatible thigh cuff

Cuff inflation will be carried out in MRI suite by MRI technicians with assistance from Research Coordinator(s).

1. Systolic arm pressure will be measured on the day of the MRI by Research Coordinator within one hour of MRI exam. This will be the systolic arm pressure used for the initial estimate of the thigh cuff inflation pressure during the MRI session.

2. Once participant has been positioned in MRI machine per the MRI core lab protocol, the thigh cuff will be placed circumferentially around the participant's thigh as proximal as possible without pinching or creasing the skin.

3. Inflate thigh cuff to the Calculated OP (Systolic arm pressure from Visit 2 – Systolic arm pressure from Visit 1 + Occlusion pressure from Visit 1).

4. Cuff occlusion should be 5 minutes for best MRI results. Any MRI done with less than 3 minutes of cuff occlusion will be invalid and the participant will be excluded from the study. MRI with cuff inflation time between 3-5 minutes will be acceptable, however, if time is <5 mins, it will need to be noted on the MRI completion form, so the same time is used at the 6 month endpoint MRI. In general, all cuff inflation and deflation times should be noted on the MRI form.

Attachment B – Scheduling Instructions for PACE patients

1. Coordinators will add potential BMA date(s) for each patient they bring in for screening, including Pt ID / Acrostic on the RNC Working Calendar for Cell Processing located on the PACE SharePoint page. If more than one date is added for a patient, each date will be ranked as 1st choice, 2nd choice, etc.

2. At this time, they will be able to check to see if any other sites have potential pts for those days. Coordinators are encouraged to contact each other to negotiate dates that have more than one potential patient. Email communication between sites with corresponding schedules should include a copy to the DCC. The DCC will assist the sites with negotiations as needed.

3. By the time a patient is deemed eligible, a site should have a proposed BMA date for their patient only. This proposed date will be included on the treatment checklist.

4. Upon receipt of the eligibility notification, Sara Richman will email the site (within one business day) to confirm/deny proposed BMA date with copy to DCC.

5. Upon confirmation of BMA date, DCC will add confirmed BMA date to Confirmed Cell Processing calendar and delete other potential dates for patient from RNC Working Calendar, if necessary.

6. If date is denied, site will work with Sara Richman to schedule a different date using RNC working calendar to communicate with other sites, as needed.

Attachment C – One Week Patient Temperature Log

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

Study ID Number: _____ Acrostic: _____

Date of Product Injection: _____

Week 1

Date	AM	PM

Attachment D - Participant Contact Log

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

Attachment E – Grade 1 Event Log

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

Attachment F – SAE Checklist FAX Cover-PACE

SAE Documentation Checklist / Document Fax Cover Sheet

Attention: Dr. Lara Simpson or Dr. Linda Piller

Fax number: 713-486-0981

Total number of pages (including this page): ☐ **Today's Date:** ☐

Site: ☐ **Event Reference Number:** ☐

Study ID: ☐ **Patient Acrostic:** ☐

Event Name (Diagnosis): ☐

Date of Event: ☐ **Date of SAE Report in database:** ☐

Site Representative Name: ☐

Signature: ☐

☐ Initial Submission ☐ Follow-up Submission

Attached are the following documents for the Serious Adverse Event:

☐ Emergency Department Notes	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Admit Notes	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Progress Notes	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Consultant Notes	☐ Pending	☐ Not Available	☐ Not Applicable
☐ History and Physical	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Discharge Summary/Death Note	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Lab Reports (w/ref. ranges if OSH)	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Procedure Reports	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Diagnostic Test Reports	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Pathology Reports	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Death Certificate	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Autopsy Report	☐ Pending	☐ Not Available	☐ Not Applicable
☐ Other: _____	☐ Pending		

If you check "Pending", please note reason in Comments.

Comments:

Attachment G – Remote Monitoring Checklist FAX Cover

Attention: Uchechi Nwosu or Sibi Mathew

Fax number: 713-486-0981

Total number of pages (including this page): _____ **Today's Date:** _____

Site: _____

Study ID: _____ **Patient Acrostic:** _____

Site Representative Name: _____

Signature: _____

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

- ☐ Eligibility
- ☐ Baseline Risk
- ☐ Baseline Physical Exam
- ☐ Medication/Allergy List
- ☐ San Diego Claudication Questionnaire
- ☐ Baseline Labs
- ☐ Infectious Disease Lab Reports
- ☐ Treatment Checklist
- ☐ Bone Marrow Aspiration
- ☐ Study Product Injection
- ☐ Other: _____

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

Comments:

_____

_____

_____

_____

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

Attachment H – Travel Reimbursement Log

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