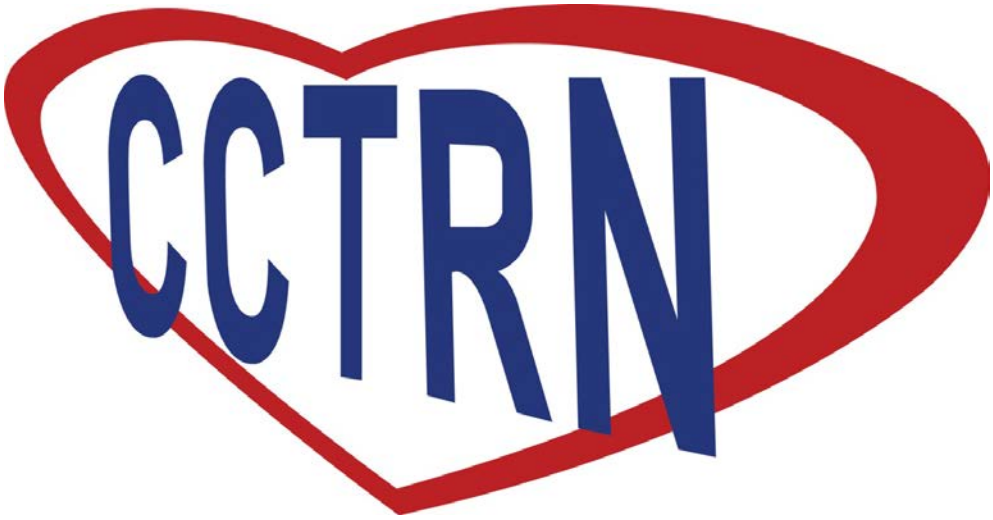
Cardiovascular Cell Therapy Research Network



Manual of Operating Procedures for the **SENECA** Protocol

A Phase I, First-in-Human, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study of the Safety and Efficacy of Allogeneic Mesenchymal Stem Cells in Cancer Survivors with Anthracycline-Induced Cardiomyopathy

Version 4 – August 1, 2017

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CCTRN SENECA PROTOCOL

I. Study Overview

Full Title: A Phase I, First-in-Human, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study of the Safety and Efficacy of Allogeneic Mesenchymal Stem Cells in Cancer Survivors with Anthracycline-Induced Cardiomyopathy

Short Title: SENECA

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 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: Allogeneic mesenchymal stem cells (allo-MSCs)

Population: Male and female cancer survivors with diagnosis of anthracycline-induced cardiomyopathy (AIC).

Sample Size: 36 subjects (six open-label lead-in subjects and thirty randomized subjects)

Treatment: Subjects enrolled in this study will be recruited from all of the sites participating in the National Heart, Lung, and Blood Institute (NHLBI) CCTRN.

Duration: Following cardiac catheterization and study product injections, subjects will be assessed at day 1, week 1, and months 1, 6, and 12.

Objective: The primary purpose of this study is to examine the safety and feasibility of delivering allogeneic human mesenchymal stem cells (allo-MSCs) by transendocardial injection to cancer survivors with left ventricular (LV) dysfunction secondary to anthracycline-induced cardiomyopathy (AIC).

The secondary purpose of this study is to obtain preliminary evidence for therapeutic efficacy of allo-MSCs delivered by transendocardial injection to cancer survivors with LV dysfunction secondary to AIC.

Safety: To demonstrate the relative safety of allo-MSCs when compared with placebo, the following safety data will be collected and analyzed by therapy group between baseline and a) 6 months and b) 12 months:

1. Major adverse cardiac events (MACE) including death, hospitalization for worsening heart failure (HF), and/or exacerbation of HF (non-hospitalization)
2. Other significant clinical events including non-fatal stroke, non-fatal myocardial infarction, coronary artery revascularization, ventricular fibrillation/tachycardia, pericardial tamponade, infectious myocarditis, hypersensitivity reaction, neoplasm, or any other potential deleterious late effects detected and corroborated by clinical presentation, laboratory investigations, image analysis, and when necessary with biopsy from suspected target sites in the body
3. All adverse events (AEs) at least grade 2 in severity

Feasibility: To assess whether the cells can be administered to cancer survivors with LV dysfunction secondary to AIC, and what methodological/logistic problems arise, the following measures will be reported. The number and percent of subjects who:

1. Have events between randomization and SPI that preclude the subject from receiving the SPI procedure
2. Receive less than 20 injections during the SPI procedure and reason
3. Do not receive the intended dose of cells (100 million), reason, and actual dose delivered
4. Have at least one cardiac MRI endpoint measure that is uninterpretable due to issues related to the device, including, but not limited to, inability to undergo the MRI procedure
5. Fail to complete follow-up and reason

Efficacy: To explore whether allo-MSCs produce a trend toward improved LV function and functional status when compared to placebo, the following domains and measures will be evaluated:

- Myocardial evaluations by cMRI over time:
  - Function:
    - Change in LVEF
    - Change in global and regional strain (HARP MRI)
  - Structure:
    - Change in LVEDVI
    - Change in LVESVI
    - Change in LV Sphericity Index
  - Morphology:
    - Change in area of injury (e.g., inflammation, edema, fibrosis)
- Functional capacity over time:
  - Change in exercise tolerance (6MWT)
  - Change in MLHF Questionnaire (subject reported)
- Clinical outcomes over time:
  - MACE

  - Cumulative days alive and out of hospital
- Biomarkers over time:
  - Change in NT-proBNP

II. Open Label Lead-In *(Enrollment Now Complete)*

This study will evaluate thirty-six subjects. The first six subjects received allo-MSC therapy (open label) and will be assessed for safety and feasibility of the study procedures. Following one-month data review of each of the six subjects by the NHLBI Gene and Cell Therapy Data Safety Monitoring Board, the study was approved to move forward with the randomized, double-blind portion of the trial, enrolling thirty subjects.

III. Randomized Clinical Trial

Thirty subjects will be randomized 1:1 to one of two treatment strategies:

1. Group A (15 subjects) – 100 x 10^6 (100 million) allo-MSCs delivered in twenty 0.4ml injections.
2. Group B (15 subjects) – 20 injections of 0.4 ml cell-free Buminate solution

For subjects randomized to Group A, the allo-MSCs will be derived from allogeneic bone marrow isolated from normal, healthy donors by standard iliac crest aspiration. The injections will be administered transendocardially during cardiac catheterization using the NOGA Myostar Injection System. Injections will be targeted throughout the left ventricle based on NOGA mapping and assessment of scar / fibrosis. All consented and eligible subjects will have study product injection within 45 days of signing informed consent. Following cardiac catheterization and allo-MSC or placebo injections, subjects will be followed at day 1, week 1, and months 1, 6, and 12 to complete all safety and efficacy assessments. Figure 1 below demonstrates subject activity from consent to follow-up.

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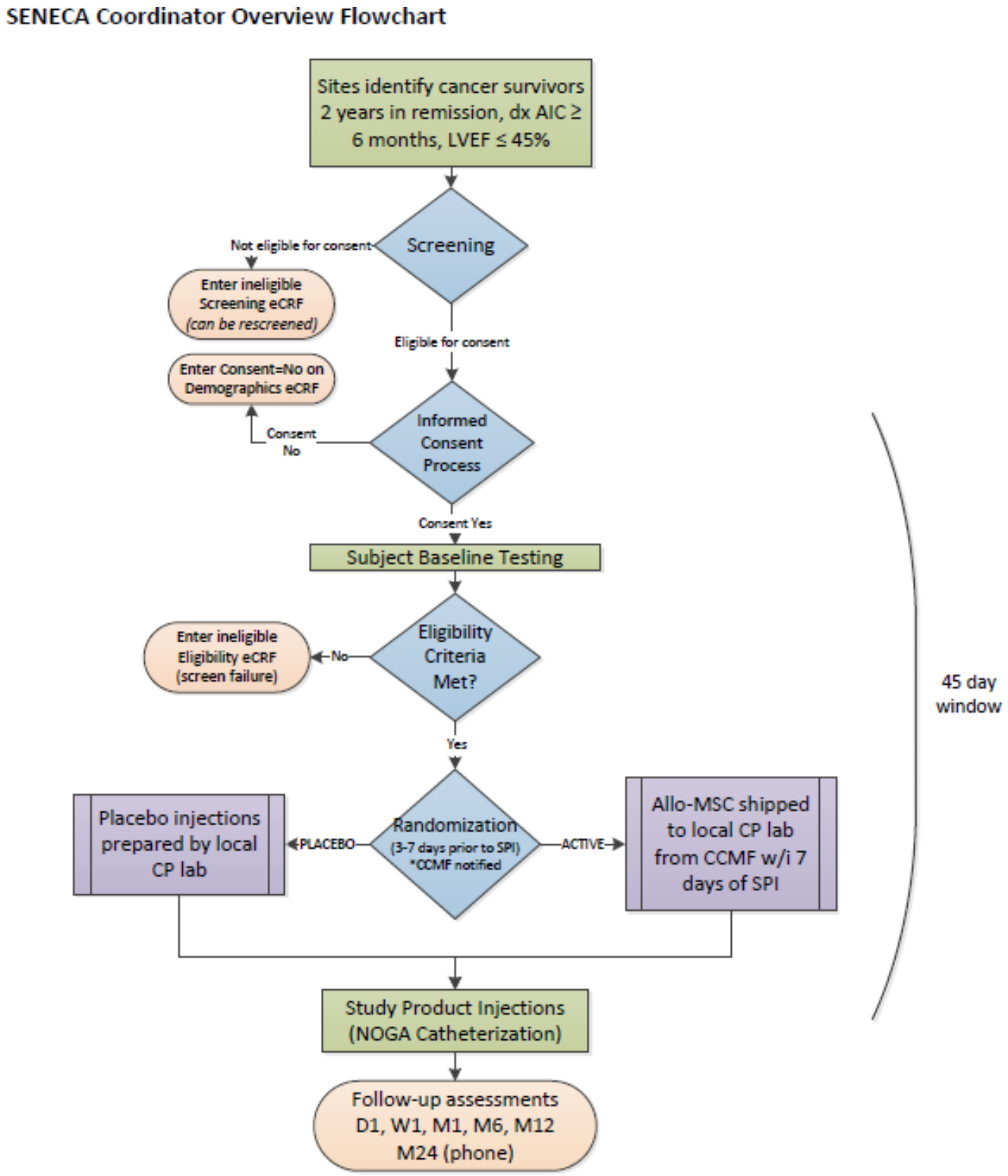
Figure 1. SENECA Study Activities



IV. Administrative Tools

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

A. Coordinator Checklists

The complete schedule of procedures and schedule of lab tests can be found in Sections 6.1 and 6.3 (respectively) of the protocol. To help you organize study related activities a procedures checklist template is available and can be modified by the site coordinator to meet the needs of the specific center. The Coordinator Checklist is located in:

- Member Resources/SENECA/MOP Documents/2-Procedures Checklist Template
- MOP Binder Section 2, Coordinator Checklist

B. Workbooks

SENECA case report forms (CRF) workbooks are located in:

- Member Resources/SENECA/MOP Documents/4-CRF Workbooks
- MOP Binder Section 4, CRF Workbooks

C. FAQs

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

- Member Resources/SENECA/MOP Documents/6-FAQs
- MOP Binder Section 6, FAQs

D. eCRF Users Guide

Refer to the SENECA 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 in:

- Member Resources/SENECA/eCRF Users Guide

E. Other Resources

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

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

V. Screening, Enrollment, and Study Procedures

A. Screening

The screening phase of the study pertains to the initial review of potential subject characteristics based on available data (i.e. medical records review). Limited demographic information and eligibility criteria based on available data are recorded on the Screening Form (see workbook in *MOP Binder Section 4, CRF Workbooks*) to capture the population approached for the study, how subjects first found out about the study and, when applicable, reason(s) for not consenting the screened population.

Screening of subjects includes reviewing medical records and imaging studies for inclusion/exclusions prior to consent. From the review of subjects' medical records and imaging studies on file, subjects who are determined to have a diagnosis of AIC, have NYHA class of II or higher, have LVEF ≤ 45%, are a candidate for cardiac catheterization, and do not have evidence in their medical record of study exclusions stated in Section 4.4, are eligible to be consented to the study.

LVEF ≤ 45% can be defined by gated blood pool scan (MUGA), cMRI, left ventriculogram, or EF ≤ 40% by two-dimensional echocardiogram.

In order to exclude those with ischemic heart disease, available imaging in the patient's chart will be reviewed. Acceptable imaging for the detection of obstructive CAD includes coronary arteriogram or any non-invasive test within five years prior to enrollment in the study provided that there have been no symptoms or evidence of CAD since the test. If the subject has not had one of these tests done in the corresponding timeframe, then the individual should have one of these tests as standard of care (institutional choice) to be reviewed for entry into the study. If a test is not otherwise authorized under a patient's insurance under standard of care, a stress echo will be included as part of the baseline testing and paid for by the study, to be reviewed for eligibility.

Screening Form and Study ID- A screening form should be completed for EVERY potential subject that is ≥ 18 and < 80 years of age (inclusion criterion #1 of the protocol and on the screening form) and is a cancer survivor with a diagnosis of AIC (inclusion criterion #2 of the protocol and on the screening form). All criteria do not need to be answered to submit the form for a subject who will be ineligible to consent to the trial. Screening forms should be entered on a weekly basis to keep screening numbers accurate for reporting to the Steering Committee. Potential subjects can be screened more than once with multiple screening forms entered for the same candidate before they are consented. A Study ID will be generated by submission of the first screening eCRF and the screening date will also appear to assist you with selecting the same candidate should you choose rescreen someone for the study. ***It is very important that you track the database-generated Study ID and screening date in a manner such that you can retrieve the individual's information should they be re-screened in the future (another***

Screening form would be entered at that time using the same Study ID). Tracking could be achieved for example, by either keeping an internal log or a separate binder to house the screening forms. In order to accurately count the number of people screened for the study, we must have only one Study ID for each candidate screened no matter how many times you screen them. You cannot screen a subject more than once per day.

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

B. Consent

Informed Consent Process-

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, as applicable. The information provided to the potential subject is included in the informed consent. The informed consent will provide information regarding standard alternative heart failure therapies and will include information regarding potential risks and benefits of participation. Potential subjects will be asked to consent to the Biorepository and the possibility of future genetic testing as separate consents within the main consent form.

Necessary elements of the informed consent process are included below:

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

For those not wishing to participate in the program:

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

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

Demographics Form and Acrostic-

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

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

Procedure for Generating Acrostic for VA Subjects-

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

C. Baseline Testing and Considerations

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 is 45 days (from consent to study product injection). The baseline evaluations cannot begin until after the informed consent has been signed.

Subjects may be excluded from the study if any of the baseline testing is not completed or meets an exclusion criterion during this period.

Oncology Assessment- Prior to study entry an oncology assessment form will be completed by the subject's post cancer follow up care provider to collect information to assess the risk of cancer recurrence. The patient's current medical records will be reviewed by the research team to verify the absence of any new metastatic disease, stage 4, or recurrence. A release of

information should be obtained from the subject in order to forward the Oncology Assessment (baseline) to their post cancer follow up care provider. Upon study consent, this assessment should be de-identified and forwarded to the DCC for Network oncologist review. You will receive Sponsor correspondence as to whether or not the patient meets eligibility criteria (inclusion criterion #6). Please keep the patient's assessment form, as well as the Sponsor correspondence, in the patient's chart as source documentation and evidence of eligibility review.

The Oncology Assessment (baseline) can be found on www.cctrn.org at Member Resources/SENECA/MOP Documents/1- MOP, and in MOP Binder Section 5.

Six Minute Walk Test (6MWT) Considerations-

1. Testing within an hour after a meal will be avoided.
2. Two tests will be done at each visit separated by at least 30 minutes. If the percent change between test 1 and test 2 for total distance walked is >10%, a third test will be done.
3. Follow-up 6MWTs should be performed at the same time of day as baseline (within 2hr window) and by the same tester (blinded to treatment arm) when possible.

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

MRI Testing and Device Considerations-

1. Dotarem is the required gadolinium-based contrast agent for the study.
2. Subjects with devices will be assessed carefully. Site staff will be trained by MR core to assess devices and work with the MR core to determine eligibility of subjects with devices.
3. MR core trained staff with pacemaker/ICD expertise will be directly involved to oversee device disabling and re-enabling, pre- and post-scan measures, subject monitoring, etc.
4. EP Training and Qualification will be done with the first subject with a device that consents to the study.
5. ICD interrogation will be done before and after every MRI as part of MRI protocol. *The interrogation report before the MRI will be assessed by local EP for VT / VF, RCs will enter event eCRFs if applicable, and a copy of the report should be keep in research record.*
6. Advanced Cardiovascular Life Support (ACLS) trained personnel and a "crash cart," including defibrillator, available throughout the procedure to address an adverse event.
7. Subjects should be advised to not eat or drink 4 hours before the MRI and to not take supplement medication (particularly those containing metals such as iron) 4 hours before the MRI. Participants should consult with the study team on whether or not to take regular medications or bring them to take after the test.
8. If MRI and 6MWT are done on the same day, care should be taken to ensure there are no lingering effects of sedative medications that may be administered in conjunction with MRI.

Please refer to the MRI Core Lab Manual. The manual can be found on www.cctrn.org at Member Resources/CONCERT/Core Labs/MRI
MRI Core Lab EP/Device contact information: Saman Nazarian, MD, Phone: 443-604-8399 Saman.Nazarian@uphs.upenn.edu. *Please copy Dr. Ostovaneh on all emails to Dr. Nazarian*

NOTE: MRI core lab and oncology assessment reviews can take up to 4 days for eligibility determination.
Once the baseline MRI is scheduled, RCs notify MRI core (and copy the DCC) of test schedule; indicate the date of the test and center ID. If the subject screen fails before a scheduled test, please send email update.

Contact information:

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

ACTIVITY SCHEDULE

Baseline Screening Visit *(45-day window from consent to SPI)*

Discuss and Review Consent Form
Review of medical and surgical history
Request pt. sign release of information for oncologist assessment (can be done prior to consent)
Concomitant medication assessment
Physical Exam/vitals (with NYHA classification)
ECG
Stress Echo (ONLY DONE for patients WITHOUT RECENT IMAGING not otherwise covered)
Labs (includes pregnancy test for applicable female subjects)
Cardiac MRI and ICD interrogation (if applicable, before and after cMRI)
Six minute walk—test 1 (T1) (Must be conducted at least 1 hour after last meal)
Six minute walk—test 2 (T2) (Must be conducted at least 30 mins after test 1)
Six minute walk—test 3 (done ONLY if variance b/t T1 and T2 >10%) (Must be conducted at least 30 mins after test 2)
MLHF questionnaire
Transmit images to MRI core
Chart on subject

Baseline Visit notes: *Prior to study entry an oncological assessment form will be completed by the subject's post cancer follow up care provider to collect information to be used to assess the risk of cancer recurrence. Site staff will review current medical records to verify the absence of any new metastatic disease, stage 4, or recurrence. If subject is on anticoagulation therapy see study protocol section 6.4 for management guidelines during SPI. Infectious disease testing results must be known at the time of completing the eligibility form. Stress echo only to be done for patients who have no recent (within 5 yrs) imaging that rules out CAD and for whom the test could not otherwise be conducted under standard of care.*

D. Form Completion and Scheduling Considerations

Completing the Eligibility Form-

Subjects may be excluded from the study if any of the baseline testing is not completed or meets an exclusion criterion during this period. Following completion of the baseline visits, if the subject is ineligible, there will only be four eCRFs for the individual submitted in the database. These four are the Screening eCRF, Demographics eCRF, Eligibility eCRF (with the reason for failure), and the End of Study eCRF.

If the subject is eligible, the RC would complete the Treatment Checklist eCRF.

Task	Action	Insure these eCRFs are entered
Eligibility (failed)	If determination ineligible Contact DCC if later you wish to re-screen a subject who failed after consent	Screening eCRF Demographics eCRF Eligibility eCRF (include reason for failure) End of Study eCRF
Eligibility (passed)	If determination eligible Coordinate SPI w/cath lab, interventionalist, BDS	Screening eCRF Demographics eCRF Eligibility eCRF Treatment Checklist eCRF (with SPI date)

Scheduling Study Product Injection-

The RC will need to contact Biologic Delivery Systems (BDS), **at least 2 weeks in advance**, to arrange for an onsite representative to be available for the SPI. Please check availability of the date with the subject, cath lab, interventionalist, and BDS team before completing the Treatment Checklist, as this date will be needed for the eCRF.

Completing the Treatment Checklist-

The Treatment Checklist is an eCRF which allows the web application to match eligibility criteria with data collected during baseline testing 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 Risk, the Six Minute Walk Test, the Baseline MLHFQ, and the Medication listing **MUST BE ENTERED BEFORE** the Treatment Checklist can be submitted which will confirm the subject is eligible for the study. Once the eligible subject 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 study product injection (SPI) procedure.

Randomization-

Randomization to treatment assignment (cells or placebo) will be conducted using a web access database created and maintained by the Data Coordinating Center (DCC). The research coordinator will randomize the subject via the CCTRN web-based database which will perform

the computer-generated randomization assignment and send automatic emails notifying the study team that the treatment assignment can be accessed by un-blinded study team members with appropriate security credentials The coordinator will not randomize the subject until the following criteria are met: i) the subject has provided written informed consent, ii) baseline evaluations are complete, iii) the inclusion and exclusion criteria for the study have been satisfied, and iv) MSC product is available at the cell manufacturing facility (CMF) should the subject be randomized to the cell group. **Randomization should occur no less than 3 days prior to the scheduled SPI procedure (to allow time for cell shipping and local product preparation) and no more than 7 days prior to the scheduled SPI procedure (to minimize the risk of randomizing subjects who do not receive treatment). Please note that 7 days prior to SPI is preferred.** Submitting the Randomization form will generate an automated email with the finalized SPI date to: DCC, CPQCL, local CP lab, CCMF, biorepository, MRI core, BDS, and site). **PLEASE confirm SPI date with your team and BDS before submitting the form.** Completion of the Randomization form will provide access to all remaining study forms in the navigation menu.

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 4, CRF Workbooks.*

E. Day 0 - Study Product Injection Visit

Pre-SPI:
PE and vitals (including temperature)
AE/SAE assessment and Medications updated
Labs (includes pregnancy test for applicable female subjects)
Peripheral blood (draw 20 ml **prior to sedation for the SPI**, if consented to biorepository; see snap freezing protocol MOP section 8)
Receive cooler with product from cell processors and sign chain of custody
Pre procedure vitals (including temperature)
ICD interrogation (if applicable)
SPI: *Mapping and delivery of 20 injections (each 0.4 ml and infused over 60 seconds)*
Post-SPI:
Post procedure vitals (including temperature)
ECG and 2D Echocardiogram (both within 6 hours of SPI)
Labs (Troponin I or T and CBC with Diff within 8 ± 2 hours post-SPI)
Subject monitored on telemetry up to 24 hrs post-SPI or until discharge, whichever is sooner
Chart on subject

SPI visit notes: *INR required prior to SPI if subject is on ACT; must be <1.6 to proceed (answer question on Physical Exam form). Pregnancy test must be completed within 36 hours prior to injection to proceed. Following SPI, please forward EF from post procedure echo and the NOGA map to the DCC.*

Information regarding the cell product can be found in the Investigator Brochure.
Color-coded syringe information is attached as Attachment G (also *MOP Binder Section 1*)

F. Events Affecting Study Product Delivery

Guidance for NOGA Catheter Usage

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

- Hypotensive episode defined as a sustained drop in blood pressure exceeding 20mm/Hg not responsive to fluid administration
- Hemodynamically significant arrhythmia requiring anti-arrhythmic therapy
- Two episodes of sustained ventricular tachycardia/ventricular fibrillation requiring cardioversion
- Hemodynamic instability
- Fever (Temperature increase to ≥100.4°F)
- Cardiac perforation
- Clinical signs and symptoms indicating a cerebrovascular accident

G. Day 1 and Discharge (Day 1 post-injection)

PE/vitals
ECG (before discharge)
Labs
AE/SAE assessment and Medications updated
Peripheral blood (20 ml for biorepository, if consented; see snap freezing protocol MOP section 8)
Provide temperature log to subject
Chart on subject

Day 1 Notes: *The subject is monitored overnight and provided with a log for monitoring temperature twice a day for the next seven days (see Attachment A for temperature log). This log may be returned at the 1 week visit. Day 1 labs collected 24 hours post-procedure or immediately prior to discharge, whichever is sooner.*

H. Follow-up Visits

Follow-up visits will take place at regularly scheduled intervals. Schedule below:

Week 1 Follow-Up *(Day 7 post-injection – window ±3 days)*

PE/vitals
AE/SAE assessment and Medications updated
ECG
Labs
Peripheral blood (20 ml for biorepository, if consented; see snap freezing protocol MOP section 8)
Collect temperature log from subject
Chart on subject

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

PE/vitals (with NYHA classification)
AE/SAE assessment and Medications updated
Labs
Peripheral blood (20 ml for biorepository, if consented; see snap freezing protocol MOP section 8)
Collect temperature log (if not already received)
Chart on subject

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

PE/vitals (with NYHA classification)
AE/SAE assessment and Medications updated
ECG
Labs (includes pregnancy test for applicable female subjects)
Peripheral blood (20 ml for biorepository, if consented; see snap freezing protocol MOP section 8)
Cardiac MRI
ICD interrogation (if applicable, before & after cMRI)
Six minute walk—test 1 (T1) (Must be conducted at least 1 hour after last meal)
Six minute walk—test 2 (T2) (Must be conducted at least 30 mins after test 1)
Six minute walk—test 3 (done ONLY if variance b/t T1 and T2 >10%) (Must be conducted at least 30 mins after test 2)
Transmit images to MRI cores
MLHF questionnaire
Chart on subject

Six Month Notes:

- *Follow-up 6MWTs should be performed at the same time of day as baseline (within 2hr window) and by the same tester (blinded to treatment arm) when possible.*
- *MRI technologists will need the baseline MRI completion form, QC form, and the link to the baseline images.*
- *The interrogation report before the MRI will be assessed by local EP for VT / VF, RCs will enter event eCRFs if applicable, and a copy of the report should be keep in research record.*
- *Subjects should be advised to not eat, drink, or take supplements (particularly those containing metals such as iron) 4 hours before the MRI. They should consult with the study team on whether or not to take other medications or bring them to take after the test.*
- *If MRI and SMWT are done on the same day, care should be taken to ensure there are no lingering effects of sedative medications that may be administered in conjunction with MRI.*

Twelve month Follow-Up ***(Day 365 post-injection – window ± 30 days)***

PE/vitals (with NYHA classification)
AE/SAE assessment and Medications updated
ECG
Labs (includes pregnancy test for applicable female subjects)
Cardiac MRI
ICD interrogation (if applicable, before & after cMRI)
Six minute walk—test 1 (T1) (Must be conducted at least 1 hour after last meal)
Six minute walk—test 2 (T2) (Must be conducted at least 30 mins after test 1)
Six minute walk—test 3 (done ONLY if variance b/t T1 and T2 >10%) (Must be conducted at least 30 mins after test 2)
Transmit images to MRI cores
MLHF questionnaire
Chart on subject

Twelve Month Notes:

- *A standard of care visit with subject post cancer follow up care provider within 3 months after study completion (to assess cancer recurrence during the study period). See Oncological Assessment (12 months) located in MOP binder section 5.*
- *Follow-up 6MWTs should be performed at the same time of day as baseline (within 2hr window) and by the same tester (blinded to treatment arm) when possible.*
- *MRI technologists will need the baseline MRI completion form, QC form, and the link to the baseline images.*
- *The interrogation report before the MRI will be assessed by local EP for VT / VF, RCs will enter event eCRFs if applicable, and a copy of the report should be keep in research record.*
- *Subjects should be advised to not eat, drink, or take supplements (particularly those containing metals such as iron) 4 hours before the MRI. They should consult with the study team on whether or not to take other medications or bring them to take after the test.*
- *If MRI and SMWT are done on the same day, care should be taken to ensure there are no lingering effects of sedative medications that may be administered in conjunction with MRI.*

Twenty-four month phone call ***(Day 730 post-injection – window ± 30 days)***

Assess morbidity and mortality
Enter End of Study Form

I. Missed and Interim Visits

Missed Visits and Lost to Follow-up

All subjects should be encouraged to complete all scheduled follow-up visits. Subjects should be contacted well in advance of their follow-up visit. In addition, if a subject misses a follow-up visit, contact the subject by phone to reschedule the visit in the window. After three failed telephone contacts, send the subject a letter by certified mail, asking them to contact the clinic. Subjects will be considered lost to follow-up after 3 consecutive failed telephone contacts AND one

certified letter returned to the site. Be sure to document all attempts to contact a subject and have these available for the Monitor for inspection (Attachment B – Subject Contact Log). Guidelines for submitting forms for missed visits, including missing form, protocol deviation for the missed visit, and end of study forms can be found in the **eCRF Users Guide**.

Interim Visits

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

VI. 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 SENECA protocol.

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

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

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

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

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

A. Adverse Event Reporting

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

B. Clinical Endpoint Reporting

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

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

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

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

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

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

Unanticipated problems

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

Protocol deviations/violations and exemption requests

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

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

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

VII. Data Clarifications and Data Change Requests

DCCRs will only be used for requests to eCRFs post-monitoring. Please see the **eCRFs Users Guide** for information on entry, verification, or modification to database forms. This document is located at: Member Resources, SENECA/eCRF Users Guide.

VIII. Transferring Subjects between Centers

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

IX. Site and Monitoring Visits

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

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

A. 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.

B. Interim Monitoring Visit (IMV)

Remote Monitoring

Upon enrollment of any of the 6 lead-in subjects or the first two subjects (if less than two subjects are enrolled during the lead-in), the site will send (via PDF/email or fax 713-486-0981) all the relevant source documents to the Clinical Monitor for 100% source data verification (SDV) by remote monitoring 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 E- SENECA Remote Monitoring Checklist Fax Coversheet. **BE SURE TO DE-IDENTIFY ALL DOCUMENTS.** All documents should be sent to the DCC within 5 business days of study product injection. The Clinical 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 Clinical 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

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

Interim Monitoring Visits (IMVs) will occur periodically depending on site enrollment. The Clinical Monitor, in consultation with the PM or designee, will determine the necessity and

frequency of additional IMVs based on site performance and adherence to SOPs. Visits are announced in a confirmation letter. **PI attendance is requested at least semiannually.** Action items are included in a follow-up letter. It is expected that the average duration of each IMV will be 1 to 3 days per protocol (depending on the number of subjects to be reviewed and any outstanding issues at that visit).

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

Final Monitoring / Close-out Visit (COV)

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

Biennial On-site Regulatory Document Review

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

X. Biorepository Sample Collection

This protocol includes peripheral blood 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 8, Biorepository Procedures*.

XI. Subject Care Reimbursement

A. Form Payments

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

B. Subject Travel Stipends (in-town residents)

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

For example, a center might use the following strategy:

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

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

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

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

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

Stipulations for travel reimbursements:

- Reimbursements may not be made for international travel.
- Sites should be diligent in reviewing patient records prior to inviting potential participants to the center. In other words, there must be reasonable evidence that the individual would be a likely candidate for the trial. For example, if there is no recent evidence of LV dysfunction in a patient's chart, one would want to see a standard-of-care imaging assessment, to confirm that the time/travel/expense is justified.

- Sites will be responsible for paying the travel reimbursements and keeping appropriate records in the participants file or CRF; this includes collection and tracking of the receipts and reimbursements to the patient, as well as for making pre-approval determinations as is outlined in the ICF language below.
- There is no retroactive reimbursement for travel. Please discuss with the potential participant prior to establishing an initial appointment.
- Sites are responsible for obtaining IRB approval for the consent wording associated with reimbursement (see template below). Sites that do not have sufficient funds for patient travel reimbursement are not required to add this language to their consent documents.
- Sites will be responsible for working with the study schedule to maximize the individual's participation while minimizing the time it takes to collect the data. In other words, if a visit can be collected on one day, a best effort should be made to collect the data in one day and not spread it out any further than is needed to accurately/safely collect the data.

Consent form wording:

"If you are an out-of-town resident (greater than 150 miles), travel and lodging expenses will be reimbursed on the basis of written receipts with a maximum amount of $700 per visit. Hotel accomodations are authorized for a standard room and should not exceed $200 per night without prior written approval. Prior written approval also is required for hotel accomodations exceeding more than 1 night. Air travel is authorized for economy class on a common carrier and should be booked at least 14 days in advance. You will receive reimbursement by check upon receipt of flight and hotel invoices. You will not receive reimbursement for any expenses after you are no longer in the study. While you are in the study, you should continue to get regular medical care. You (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not a part of this study."

Attachment A – Week 1 Subject Temperature Log

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

Study ID Number: _____ Acrostic: _____

Date of Study Product Injection: _____

Week 1

Date	AM	PM

Attachment B - Subject Contact Log

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 C – Grade 1 Event Log

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

ATTACHMENT D – SERIOUS ADVERSE EVENT/CLINICAL ENDPOINT FAX COVERSHEET

FAX NUMBER: 713-486-0981

ATTENTION: Dr. Lara Simpson or Project Management Team

TOTAL NUMBER OF PAGES (INCLUDING THIS PAGE): ____ TODAY'S DATE: ____

SITE: ____ EVENT REFERENCE NUMBER: ____

(↑IMPORTANT – FROM COMPLETED EVENT FORM IN EDC)

STUDY ID: ____ ACROSTIC: ____

EVENT NAME (DIAGNOSIS): ____

DATE OF EVENT: (ONSET) ____ DATE OF SAE REPORT IN DATABASE: ____

SITE REPRESENTATIVE NAME: ____

SIGNATURE: ____

☐ INITIAL SUBMISSION ☐ FOLLOW-UP SUBMISSION

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

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

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

ADDITIONAL COMMENTS:

Attachment E – Remote Monitoring Checklist-SENECA

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

SENECA Remote Monitoring Checklist Coversheet

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

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

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

Site: ☐

Study ID: ☐ **Subject 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
- ☐ Baseline MLHFQ
- ☐ Baseline 6 Minute Walk
- ☐ Baseline Labs
- ☐ Infectious Disease Lab Reports
- ☐ Treatment Checklist
- ☐ Study Product Injection
- ☐ Other: _____

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

Comments:

_____

_____

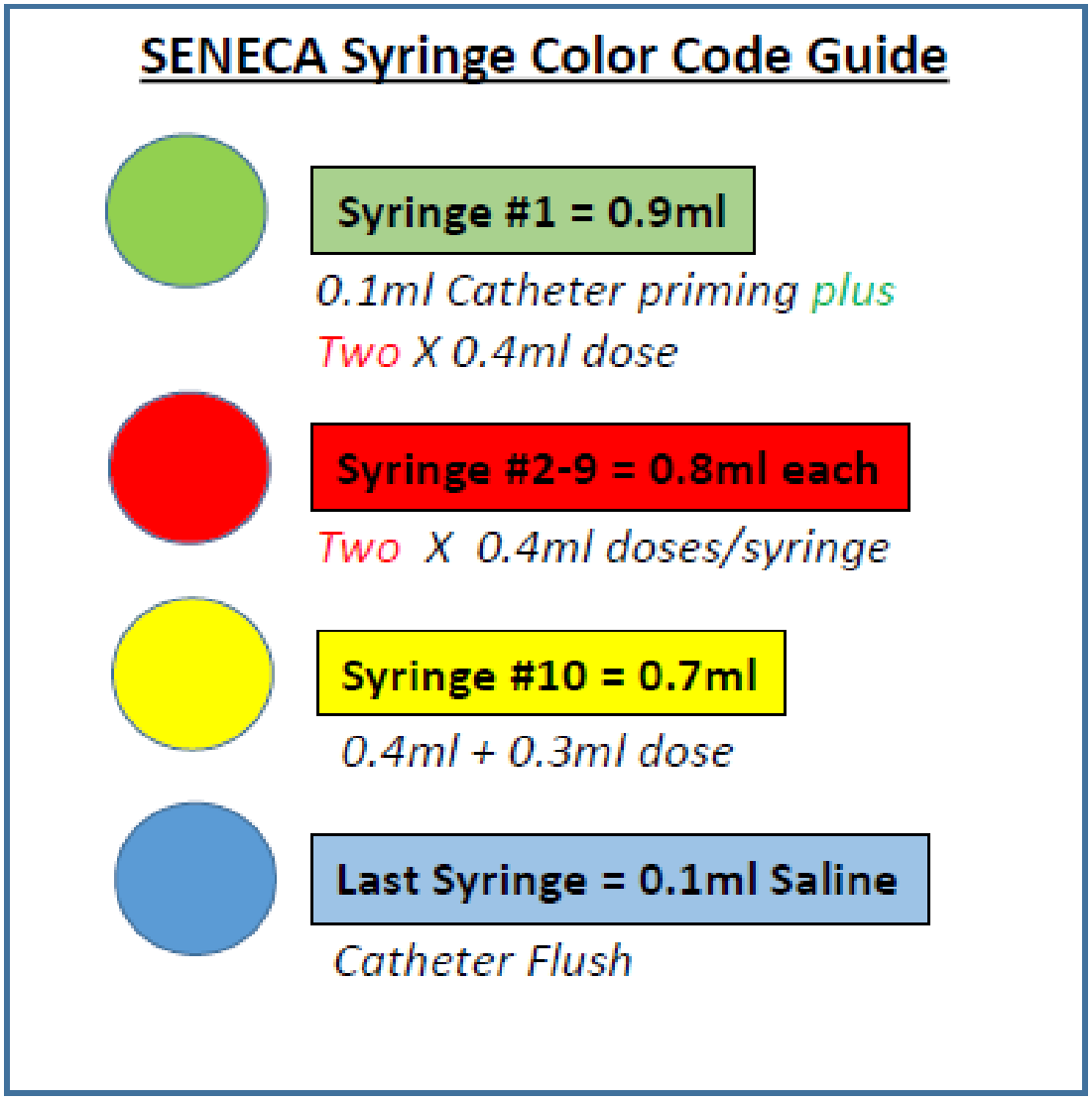
_____

_____

Attachment F – In Town Travel Stipend Reimbursement Log

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

Attachment G – SENECA Color Coded Syringe Chart



Each of the 11 total syringes are 1ml syringes to be administered in the order shown here.