Cedars-Sinai Medical Center
And Johns Hopkins University School of Medicine
Heart Institute and Division of Cardiology
National Heart, Lung, and Blood Institute (NHLBI) Specialized Center for Cell-Based Therapy (SCCT)

Clinical Research Protocol

Title: A Phase I, Randomized, Dose Escalation Study of the Safety and Efficacy of Intracoronary Delivery of Cardiosphere-Derived Stem Cells in Patients With Ischemic Left Ventricular Dysfunction and a Recent Myocardial Infarction

Investigational Therapy Name: Autologous Human Cardiosphere-Derived Cells (CDCs)

FDA IND No.: 13930
Protocol No.: SCCT-CDC
Principal Investigator: Eduardo Marbán, M.D., Ph.D.
Telephone: 310-423-7557

Protocol Agreement Signature:

Eduardo Marbán, M.D., Ph.D.
Principal Investigator, SCCT

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**PROTOCOL SYNOPSIS**

**Sponsor:** National Heart, Lung, and Blood Institute (NHLBI) and Cedars-Sinai Medical Center Specialized Center for Cell-Based Therapy (SCCT)

**Name of Study Therapy:** Autologous Human Cardiosphere-Derived Cells (CDCs)

**Title of Study:** A Phase I, Randomized, Dose Escalation Study of the Safety and Efficacy of Intracoronary Delivery of Cardiosphere-Derived Stem Cells in Patients With Ischemic Left Ventricular Dysfunction and a Recent Myocardial Infarction

**Study Centers:** Cedars-Sinai Medical Center & The Johns Hopkins University School of Medicine

**Phase of Development:** Phase I

**Objectives:**

**Primary:** To demonstrate the safety of autologous CDCs administered by intra-coronary infusion in patients with ischemic left ventricular dysfunction and a recent myocardial infarction.

**Secondary:** To demonstrate the efficacy of autologous CDCs administered by intra-coronary infusion in patients with ischemic left ventricular dysfunction and a recent myocardial infarction.

**Design and Investigational Plan:** Twenty-four (24) with recent myocardial infarction with ischemic left ventricular dysfunction meeting all inclusion and no exclusion criteria will be evaluated at baseline. CDCs will be grown from cardiac biopsy specimens obtained between 14 days and 6 weeks of the myocardial infarction. The first group of 6 patients will be randomized after completion of the screening procedures to either 12.5 million CDCs administered via intra-coronary infusion or to a control group in a 2:1 CDC to control group ratio. The second group of 18 patients will be randomized after completion of the screening procedures to either 25 million CDCs administered via intra-coronary infusion or to a control group. Patients will be stratified by treatment center and left ventricular ejection fraction (0.25 – 0.35 or = 0.35-0.45) Patients will be randomized using permuted blocks in a 2:1 CDC to control group ratio, providing a projected distribution of 8:4:12 patients among the control, low dose and high dose groups, respectively. If the patient is randomized and 12.5 million CDCs are not achieved, then the patient will be analyzed separately and another patient enrolled. Intra-coronary infusion of CDCs will take place 4-8 weeks after the cardiac biopsy is obtained. All patients will be followed at week 2 and at 1, 2, 3, 6 and 12 months to complete the safety and efficacy assessments listed herein.

**Patient Population:** Twenty-four patients with recent myocardial infarction and ischemic left ventricular dysfunction.

**Diagnosis and Main Criteria for Inclusion/Enrollment:**

**Major Inclusion Criteria**

- Myocardial infarction due to coronary artery atherosclerotic disease and evidenced by typical ischemic symptoms, serial ST-T or Q wave ECG changes, and serum troponin I rise to > 99th percentile of the upper reference limit within 30 days of enrollment with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormalities.

- An area of regional dysfunction, i.e. hypokinetic, akinetic, or dyskinetic, as assessed by echocardiography, left ventriculography, or MRI.

- History of angioplasty and stent placement, with resultant TIMI flow ≥ 2, in the artery supplying the infarcted, dysfunctional territory and through which the CDCs or placebo will be infused.

- Left ventricular ejection fraction of ≥ 0.25 and ≤ 0.45 as determined by clinically-indicated assessment of cardiac function (echo, gated blood pool scan, x-ray contrast...
ventriculography, CT and/or MRI) one day or more following successful reperfusion.

- No further revascularization clinically indicated at the time the patient is assessed for participation in the clinical trial. This will be determined by a cardiologist who is not an investigator in the clinical trial. No further revascularization may be indicated by no arteries with significant stenosis, the location, and extent of any stenosis may not be suitable for angioplasty, the distal vessels may not be suitable for placement of bypass grafts, and/or the patient declines angioplasty or bypass surgery.
- Ability to provide informed consent.
- Age \( \geq 18 \) years.

### Major Exclusion Criteria

- Non-cardiovascular disease with expected life expectancy of \(< 3 \) years.
- Contraindications to MRI, including prior ICD placement, estimated glomerular filtration rate \(< 50 \) ml/min, known reaction to gadolinium, claustrophobia, pacemaker, ear implant, and cochlear implant. History of possible ferromagnetic material including programmable shunt, shrapnel, penile prosthesis, intra-uterine device, bullets, tattoos, artificial limb, blood vessel coil, and tissue expander may require special screening.
- Septal infarction involving the right ventricular endocardium as demonstrated by screening MRI, because its presence might increase the potential risks associated with the septal biopsy procedure and decrease treatment benefit due to decreased viability of injured septal-based stem cells.
- History of cardiac tumor, or cardiac tumor demonstrated on MRI.
- Requirement for chronic immunosuppressive therapy.
- Participation in an on-going protocol studying an experimental drug or device.
- Diagnosis of right ventricular arrhythmogenic dysplasia.
- Patients with occlusion of the infarct-related artery before administration of CDCs
- Current alcohol or drug abuse because of anticipated difficulty in complying with protocol-related procedures.
- Pregnant or child-bearing potential without use of effective contraception. Men intending to “father” children are also excluded.
- Human Immunodeficiency virus infection.
- Viral hepatitis.
- Uncontrolled diabetes and/or hemoglobin A1C \( > 8.5\% \)
- Abnormal liver function (SGPT \( > 3 \) times the upper reference range) and/or hematology (hematocrit \( < 25\% \), WBC \( < 3,000 \), platelets \( < 100,000 \)) studies without a reversible, identifiable cause.
- Ventricular tachycardia or fibrillation not associated with an acute ischemic episode.
- Symptomatic ventricular tachyarrhythmia complicating the index myocardial infarction.
- New York Heart Association Class 4 congestive heart failure.
- Canadian Cardiovascular Society Class of Angina Class 3 or 4.
- Evidence of tumor on screening chest/abdominal/pelvic (body) CT scan.
- Individuals who are not fluent in English.
Definition of Endpoints:

- **Safety (Primary):** The primary safety endpoint is the six-month post intra-coronary infusion proportion of patients experiencing death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, new cardiac tumor formation on MRI imaging, incidence of major adverse cardiac events (MACE), defined as the composite incidence of death, hospitalization for heart failure, or non-fatal recurrent MI and evidence of myocardial infarction as assessed by a rule-out MI cardiac enzyme protocol performed following administration of CDCs. Troponin and CKMB will be obtained every six hours for the first 24 hours. A troponin I rise to greater than the 99th percentile of the upper reference limit will define a new infarction.

- **Safety (Secondary):**
  (During the six-month follow-up period and final month 12 visit)
  - Any hospitalization due to a cardiovascular cause or to one related to CDC administration.
  - Any intercurrent cardiovascular illness, or one related to CDC administration, which prolongs hospitalization.
  - New TIMI-I flow following intra-coronary infusion of cells or placebo.
  - Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 20 beats or longer ascertained by periodic, protocol-mandated 48 hour ambulatory monitoring.
  - Abnormalities in laboratory studies that occur after infusion of CDCs and at 2 weeks and at 1, 3, 6, and 12 months after infusion.
  - Hospitalization for ischemic events. These include unstable angina and ST-elevation and non-ST-elevation myocardial infarctions.
  - Hospitalization for heart failure events defined as heart failure listed in the discharge diagnosis and with pulmonary vascular congestion on chest x-ray with response to diuretics while hospitalized.
  - Recurrent myocardial infarction, as defined above.

- **Efficacy (Secondary):**
  (During the six-month follow-up period and final month 12 visit)
  - Change in MRI-assessment of function in the region which received CDC therapy.
  - Change in MRI assessment of infarct size expressed in absolute value (grams) and as a percent of LV mass.
  - Change in MRI assessment of perfusion in the region which received CDC therapy.
  - Change in MRI assessment of global LV function.
  - Change in MRI assessment of LV end-diastolic and end-systolic volumes.
  - Serum pro-BNP as an objective measure of heart failure severity.

**Study Therapy:** Autologous human CDCs, grown from biopsies obtained from each patient within 6 weeks of myocardial infarction.

**Duration of Study Follow-Up:** Week 2 and months 1, 2, 3, 6 and 12 post baseline visit.
2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Introduction
The principal goal of this proposed phase one dose escalation study is to examine the safety of intracoronary administration of autologous cardiosphere-derived stem cells six to twelve weeks following a myocardial infarction. In addition, we plan to collect secondary outcomes which commonly occur in patients following a myocardial infarction so as to inform the design of future efficacy studies of cardiosphere-derived stem cell (CDCs).

2.2 Study Objectives

2.2.1 Primary Objective
To demonstrate the safety of autologous CDCs administered by intra-coronary infusion in patients with ischemic left ventricular dysfunction and a recent myocardial infarction.

2.2.2 Secondary Objectives
To demonstrate the efficacy of autologous CDCs administered by intra-coronary infusion in patients with ischemic left ventricular dysfunction and a recent myocardial infarction.

2.3 Study Endpoints

2.3.1 Primary Endpoint (Safety)
The primary safety endpoint is the six-month (post intra-coronary infusion) proportion of patients experiencing death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, myocardial infarction following cell infusion, new cardiac tumor formation on MRI imaging, and incidence of major adverse cardiac events (MACE), defined as the composite incidence of death, hospitalization for heart failure, or non-fatal recurrent MI.

Death due to ventricular tachycardia or ventricular fibrillation is defined as occurring with ECG documentation of these arrhythmias during ambulatory monitoring if outpatient or during routine ECG monitoring while an inpatient. Sudden death is defined as occurring within one hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause. Myocardial infarction will be defined by a rise in troponin I to greater than the 99th percentile of the upper reference limit with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
2.3.2 Secondary Endpoints (Efficacy)

The following additional efficacy endpoints will be evaluated in this trial during the six-month follow-up period and a final month 12 visit:

1. Change in MRI-assessment of function in the region which received CDCs.
2. Change in MRI assessment of infarct size expressed in absolute value (grams) and as a percent of LV mass.
3. Change in MRI assessment of perfusion in the region which received CDCs.
5. Change in MRI assessment of LV end-diastolic and end-systolic volumes.
6. Serum pro-BNP, as an objective measure of heart failure severity.

2.3.3 Secondary Endpoints (Safety)

The following additional safety endpoints will be evaluated in this trial (during the six-month follow-up period and a final month 12 visit):

1. Hospitalization for ischemic events. These include unstable angina and ST-elevation and non-ST-elevation myocardial infarctions.
2. Hospitalization for heart failure events defined as heart failure listed in the discharge diagnosis and with pulmonary vascular congestion on chest x-ray with response to diuretics while hospitalized.
3. Recurrent myocardial infarction as defined above (section 1.3.1)
4. Any hospitalization due to a cardiovascular cause or related to CDC administration.
5. Any intercurrent cardiovascular illness, or one related to CDC administration, which prolongs hospitalization.
6. Evidence of myocardial injury as assessed by a rule out MI cardiac enzyme protocol performed following administration of CDCs. Troponin I and CKMB will be obtained every six hours for the first 24 hours after cell infusion. A troponin I rise to greater than the 99th percentile of the upper reference limit will define a new infarction.
7. New TIMI-1 flow following intra-coronary infusion of CDCs.
8. Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 20 beats or longer as ascertained by periodic, protocol-mandated 48 hour ambulatory ECG recordings.
9. Abnormalities of the following laboratory studies that occur after infusion of CDCs and at 2 weeks and 1, 3, 6, and 12 months after CDC administration:

   a. complete blood count
   b. platelets
   c. comprehensive metabolic panel
   d. GGT
   e. urinalysis
   f. pro-BNP

3. STUDY DESIGN

Twenty-four patients with a recent myocardial infarction and ischemic left ventricular dysfunction and meeting all inclusion and no exclusion criteria will be evaluated at baseline. Following informed consent, and all screening studies, patients will be randomized to a control group or to undergo cardiac biopsy and receive CDCs via intra-coronary infusion. Those randomized to the cell infusion group will receive the infusion 4-8 weeks following the biopsy depending on the rate of cell expansion.

Both the control group and the group receiving CDCs will be followed at two weeks, and at one, two, three, six, and twelve months to obtain the safety and efficacy assessments.
3.1 Inclusion Criteria

a. Myocardial infarction due to coronary artery atherosclerotic disease. This is defined as a rise in serum troponin I to greater than the 99th percentile of the upper reference limit with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

b. An area of regional dysfunction, i.e. hypokinetic, akinetic, or dyskinetic, as assessed by echocardiography, left ventriculography, or MRI.

c. History of successful angioplasty and stent placement, with resultant TIMI flow ≥ 2, in the artery supplying the infarcted, dysfunctional territory and through which the CDCs will be infused.

d. Left ventricular ejection fraction of >.25 and < .45 as determined by clinically-indicated assessment of cardiac function (echocardiogram, gated blood pool scan, x-ray contrast ventriculography, CT and/or MRI one day or more following successful reperfusion.

e. No further revascularization clinically indicated at the time the patient is assessed for participation in the clinical trial. This will be determined by a cardiologist who is not an investigator in the clinical trial. No further revascularization may be indicated by no arteries with significant stenosis, the location, and extent of any stenosis may not be suitable for angioplasty, the distal vessels may not be suitable for placement of bypass grafts, and/or the patient declines angioplasty or bypass surgery.

f. Ability to provide informed consent and follow-up with protocol procedures.

g. Age ≥ 18 years

3.2 Exclusion Criteria


b. Contraindications to MRI, including prior ICD placement, estimated glomerular filtration rate < 50 ml/min, known reaction to gadolinium, claustrophobia, pacemaker, ear implant, and cochlear implant. History of possible presence of ferromagnetic material including programmable shunt, shrapnel, penile prosthesis, intra-uterine device, bullets, tattoos, artificial limb, blood vessel coil, and tissue expander may require special screening.

c. Septal infarction involving the right ventricular endocardium as demonstrated by screening MRI because its presence might increase the potential risks associated
with the septal biopsy procedure and decrease treatment benefit due to decreased viability of injured septal-based stem cells.

d. History of cardiac tumor, or cardiac tumor demonstrated on MRI.

e. Require chronic immunosuppressive therapy.

f. Participation in an on-going protocol studying an experimental drug or device.

g. Diagnosis of right ventricular arrhythmogenic dysplasia.

h. Patients with occlusion of the infarct-related artery before administration of CDCs.

i. Current alcohol or drug abuse because of anticipated difficulty in complying with protocol-related procedures.

j. Pregnancy or child-bearing potential without use of effective contraception. Men intending to “father” children are also excluded.

k. Human Immunodeficiency virus infection

l. Viral hepatitis

m. Uncontrolled diabetes and/or hemoglobin A1C > 8.5%.

n. Abnormal liver function (SGPT > 3 times the upper reference range) and/or hematology (hematocrit <25%, WBC < 3,000, platelets <100,000) studies without a reversible, identifiable cause

o. Ventricular tachycardia or fibrillation not associated with an acute ischemic episode.

p. Symptomatic ventricular tachyarrhythmias complicating the index infarction.

q. New York Heart Association Class 4 congestive heart failure

r. Canadian Cardiovascular Society Angina Class 3 or 4.

s. Evidence of tumor on screening chest/abdominal/pelvic (body) CT scan.

t. Individuals who are not fluent in English.

3.3 Justification for the Inclusion of a Control Group

Inclusion of a control group will improve the ability to assess both safety and efficacy. As adverse events are likely to occur over a 12 month period in patients with ischemic left ventricular dysfunction regardless of whether or not they receive cell therapy, inclusion of a concurrent control group affords an opportunity to assess whether these events are related to the natural history of the disease or to cell therapy. In addition, there is spontaneous recovery of LV function, decrease in relative infarct size and intrinsic re-modeling processes which occur during the first several months following an infarction without CDC administration. These are important outcomes and one design to distinguish those which occur spontaneously from those which can be related to the CDC intervention are with a
control group. The risks associated with cardiac biopsy and research catheterization preclude administration of a placebo and a double-blind design, according to FDA feedback in the IND evaluation process.

3.4 Risks of Cardiac Biopsy and CDC Administration

None of the 70 post-transplant or cardiomyopathy patients who underwent cardiac biopsy noted in this IND submission experienced adverse events. Data review from The Johns Hopkins Hospital for the seven years between 7/1/2000 and 7/1/2007 demonstrated 4114 cases and no deaths. There were a total of 30 complications. These consisted of 12 carotid punctures (0.29%) none with sequelae, 5 myocardial perforations with tamponade (0.12%) all of which were successfully treated, five unexplained transient hypotension episodes (0.12%), and 8 arrhythmias (0.22%) six of which were transient, one with subsequent ablation and one with subsequent pacemaker placement. There were no complications experienced by the patients whose samples were used in the pre-clinical studies. At Cedars Sinai Medical Center, 1366 biopsies were performed from January 2005 through December 2007. There were four complications; one hematoma, one tamponade, one contrast reaction, and one tamponade/perforation, all of which were treated successfully. Thus, the percutaneous biopsy procedure has a well-established safety record at our two institutions, consistent with published literature findings (Cooper, et al. 2007).

The risks of balloon inflation are largely related to the balloon inflation pressure. As opposed to the usual clinical setting wherein inflation is performed in the setting of a stenosis and inflation pressures are usually 10-16 atmospheres or higher, inflation in this study is performed solely to prevent reflux of the CDC infusion with a 1-3 atmosphere pressure. We estimate the risk of coronary dissection as less than 0.5 % in this setting and if dissection did occur, a stent would be placed.

4. TREATMENT OF PATIENTS

4.1 CDC and Dosages

4.1.1 CDC

CDCs will be grown from the cardiac biopsy specimens obtained within four weeks of the myocardial infarction. Specimens are shipped to the Cedars Sinai processing facility, cultured for 4-8 weeks, and returned to the clinical sites in a ready-to-use format.

Please refer to the CMC Section of the IND, available upon request, for additional details.
4.1.2 Dose Rationale

The 25 million cell dose was selected based on studies in the porcine model demonstrating that this dose is associated with measurable engraftment and is not associated with elevated troponin following administration. An initial review of the first six patients will be conducted by the DSMB. The CDC dose in this group will be 12.5 million cells to initially assess the safety of a significantly smaller dose.

4.1.3 Dosages and Dosing

Based upon the randomization assignment, the first group of four patients randomized to receive CDCs will receive:

- 12.5 million cells administered via intra-coronary infusion
- If fewer than 12.5 million cells are achieved in culture, patients will not receive CDCs and they will be replaced. We anticipate that this will occur in fewer than 3% of instances.

The second group of 12 patients randomized to receive CDCs will receive:

- 25.0 million cells administered via intra-coronary infusion. If fewer than 12.5 million cells are achieved in culture, patients will not receive CDCs and they will be replaced. If > 12.5 million, but ≤ 25 million cells are achieved in culture, patients will receive 12.5 million cells and they will be added to the first, low dose, group of patients. These will also be replaced so that the high dose group is complete.

4.2 Blinding and Unblinding

The patients, physicians, and investigators will not be blinded as to group assignment. However, the person interpreting the MRI scans, and laboratory studies will be blind to group assignment.

4.3 Study Investigational Agent Management

4.3.1 Storage and Handling of Study Investigational Agent

CDCs will only be dispensed once a patient has (1) provided written informed consent, (2) met all eligibility criteria for entry into the study, and (3) completed all baseline evaluations.

4.3.2 Study Investigational Agent Accountability Procedures

The Investigator is responsible for study investigational agent accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study center personnel must maintain accountability records.
throughout the study. Please refer to the CMC Section for additional details of accountability procedures.

4.4 Standard Treatment

All patients will receive standard post-infarction treatment including the following if there are no contraindications: antiplatelet, ACE-inhibitor, beta blocker, and statin therapy; cigarette cessation counseling if there is a history of current cigarette use; and referral to a cardiac rehabilitation program.

5. STUDY PROCEDURES

5.1 Time and Events Schedule

The Time and Events Schedule for the conduct of this study is shown in Table 1.

Patients will be screened within 30 days of a myocardial infarction. During the screening period, and after informed consent, patients will undergo history, physical examination, laboratory tests MRI, and a CT scan of the chest, abdomen, and pelvis to ascertain whether they meet all inclusion and no exclusion criteria.

After all screening information is obtained, if subjects continue to meet all of the inclusion criteria and none of the exclusion criteria, they will be randomized to either a control group or cell infusion group.

Those who are randomized to the cell infusion group will undergo right ventricular septal biopsy at least 14 days following the infarction and will then be discharged following observation.

Additionally, all study subjects will undergo baseline testing approximately 6-9 weeks following randomization. This will include a cardiac MRI, 48 hour ambulatory ECG monitoring, six minute walk test, pulmonary function test and laboratory tests. Optimally, for the cell infusion group, this should occur within one week prior to intra-coronary infusion of CDCs.

Study subjects randomized to receive cells will return for infusion of CDCs 4-8 weeks after biopsy depending on the rate of cell expansion. They will undergo catheterization and cell infusion on the day of admission and will be observed in the hospital for at least 24 hours afterwards. In the absence of serious adverse events, subjects will be discharged the day after catheterization.

All subjects will be monitored at two weeks and at one, two, three, six, and twelve months post-baseline visit. At all visits they will have a history, physical examination, laboratory
tests, and 48 hour ambulatory ECG monitoring. At six and twelve months they will undergo cardiac MRI as well. If patients receive a clinically-indicated ICD during the study protocol, a cardiac CT scan will be performed in follow-up instead of the cardiac MRI.
Schedule of Time and Events Table

<table>
<thead>
<tr>
<th>Table 1. Study Procedure</th>
<th>Screening &lt;4 weeks post MI</th>
<th>Biopsy 1-2 weeks post randomization</th>
<th>Baseline Visit 6-9 weeks post randomization</th>
<th>Cell Infusion &lt;1 wk post baseline visit</th>
<th>2-3 Weeks Post baseline visit</th>
<th>1 Month Post baseline visit</th>
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<td>Cardiac Biopsy</td>
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<td>Intra-coronary Infusion</td>
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*Cardiac CT scan will be performed instead of Cardiac MRI if a patient undergoes ICD placement during the study period.

** Serum Troponin will be measured using a 2-sided enzymatic immunoassay. **BLUE SHADED AREAS APPLY ONLY TO CELL INFUSION GROUP**
5.2 Study Phases and Visits

5.2.1 Screening Phase

All screening visit tests and procedures will occur within 4 weeks of the myocardial infarction. No screening exams will take place until the patient is fully informed of the research and signs the informed consent. Screening tests and procedures include history and physical examination, medication review, cardiac MRI, laboratory tests (hematology, chemistry, urinalysis, HIV, and hepatitis screens), and a CT of the chest, abdomen, and pelvis. Once all screening information is obtained, subjects will be randomized to either a control group or cell infusion group provided they meet all inclusion, and no exclusion, criteria.

5.2.2 Cardiac Biopsy

Patients randomized to receive CDCs will undergo cardiac biopsy at least 14 days from the infarction and 4-8 weeks prior to cell infusion. Prior to cardiac biopsy, patients will be stable as judged by no evidence of infection, stable blood pressure and pulse over the prior 12 hours, and no change in angina pattern, or in angina or heart failure medications over the prior four days.

They will undergo standard monitoring following the procedure including physical examination, electrocardiogram, and echocardiogram performed prior to discharge.

5.2.3 Baseline Phase

See Schedule of Time and Events Table for the procedures and assessments to be performed during this phase of the study. The baseline visit will occur approximately 6-9 weeks after randomization. Optimally, this visit will occur less than one week prior to CDC infusion for the group randomized to receive cells. During the baseline visit, a history and physical examination, medication review, 12 lead ECG, adverse events assessment, laboratory examinations, 48 hour ambulatory monitoring, peak O2 consumption, 6 minute walk test, cardiac MRI, and MLHF questionnaire will be performed.

5.2.4 Intra-Coronary Infusion

For those subjects randomized to receive cells, intra-coronary infusion of CDCs will occur approximately 4-8 weeks post-biopsy. Patients with clinical evidence of infarct-related artery occlusion between the time of biopsy and cell infusion will
be treated clinically, i.e. taken to the catheterization laboratory with attempted opening and restoration of TIMI-III flow if the artery is found to be occluded. If there is no clinically manifest infarct-related artery occlusion but the artery is found to be occluded when the patient is in the catheterization laboratory the decision of whether to attempt to restore TIMI-III flow will be based on clinical grounds. In any event, patients will not receive CDCs. Such patients will be replaced in the study. However, as the patient will have been randomized, we will continue to collect outcome variables for an intention to treat analysis.

Prior to intra-coronary infusion, patients will be stable as judged by no evidence of infection, stable blood pressure and pulse over the prior 12 hours, and no change in angina pattern, or in angina or heart failure medications over the prior four days. The balloon for cell infusion will be placed and inflated within the previously placed stent, i.e. distal to the treated lesion. Inflating the balloon within the stent is important because it protects the vessel wall from injury.

Laboratory studies including cardiac enzymes to rule out myocardial injury and adverse event assessment will occur over the following 24 hours, as well as ambulatory electrocardiogram recording for an additional 48 hours.

5.2.5 Week 2 Visit (Post-baseline)

At this time, a history, physical examination, medication review, 12 lead ECG, 48 hour ambulatory ECG recording, and laboratory and adverse event assessments will be performed.

5.2.6 Months 1,2,3 Visits (Post-baseline)

See Schedule of Time and Events Table for the safety and efficacy tests, procedures, and assessments to be performed during these visits. These include history, physical examination, medication review, 12 lead ECG, 48 hour ambulatory ECG recording, laboratory studies (hematology, renal, hepatic), and adverse event assessment. Outpatient visits will be completed as close to the scheduled visit dates as possible. The visit window is ± 6 clinic days from the intended date of the visit. If patients have difficulty visiting within this time window, we will extend it.

5.2.7 Month 6 Visit (Post-baseline)

In addition to the assessments performed during the first three months, cardiac MRI, peak oxygen consumption, 6-minute walk test, pulmonary function, and MLHF Questionnaire assessments will be performed. If patients undergo intercurrent ICD placement, a cardiac CT scan, instead of the cardiac MRI, will be performed. The visit window is ± 6 clinic days from the intended date of the visit. If patients have difficulty visiting within this time window, it will be extended.
5.2.8 Month 12 Visit (Post-baseline)

The studies performed during this visit will be identical to those performed at the Month 6 visit. They include history, physical examination, medication review, 12 lead ECG, 48 hour ambulatory ECG recording, laboratory studies (hematology, renal, hepatic), and adverse event assessment, cardiac MRI, peak VO\textsubscript{2} consumption, 6-minute walk test, pulmonary function, and MLHF Questionnaire assessments will be performed. If patients undergo intercurrent ICD placement, a cardiac CT scan, instead of the cardiac MRI, will be performed. The visit window is ± 6 clinic days from the intended date of the visit. If patients have difficulty visiting within this time window, it will be extended.

5.2.9 Enrollment Contingency Plans

The goal is to study four patients whose cells expand to 12.5 million, and 12 patients whose cells expand to 25.0 million, and whose cells meet release criteria by eight weeks, and who have an open artery at the time of catheterization for cell infusion 4-8 weeks following biopsy. The following list will be followed to take into account certain unexpected events that can disrupt the planned study schedule:

(1) Enrolled patients who unexpectedly die prior to cell infusion or otherwise withdraw from the study after the screening and/or baseline period but before intra-coronary infusion, may be replaced without limit.

(2) If the sterility test indicates evidence of contamination, then the patient will not undergo coronary artery catheterization and infusion and the patient will be replaced. The patient will, however, have been randomized and so will undergo the protocol-mandated follow-up evaluations and included in an intention-to-treat analysis.

(3) If the cytogenetics test indicates an abnormal number of chromosomes, then the patient will not undergo coronary artery catheterization and infusion and the patient will be replaced. The patient will, however, have been randomized and so will undergo the protocol-mandated follow-up evaluations and included in an intention-to-treat analysis.

(4) For the low dose group, if 12.5 million cells are not cultured in eight weeks’ time, the patient will be replaced and no cells will be administered. We anticipate that this will occur in < 3% of instances.
For the high dose group, if 12.5 million cells are not cultured in eight weeks’ time, the patient will be replaced and no cells will be administered. If >12.5 million, but < 25.0 million cells are cultured, 12.5 million cells will be administered and the patient will be analyzed with the low dose group. The patient will be replaced so that the high dose group is complete.

Regardless of cell administration, all patients will receive protocol-mandated follow-up and those who do not receive cells will be included in an intention-to-treat analysis.

(5) If at the time of catheterization the artery is found to be occluded the patient will not receive cells and will be replaced. The decision regarding attempted restoration of TIMI-3 flow will be based on clinical grounds.

Patients in those groups who do not receive cells will be analyzed separately in an intention-to-treat analysis.

5.3 Magnetic Resonance Imaging (MRI) Protocol

All patients will undergo contrast-enhanced MRI at screening, baseline and the months 6 and 12 post-baseline visits. Prior to the MRI examination, patients will be informed about the peculiarities of the MRI environment and coached on performing adequate breath-holds. Electrocardiographic leads and a blood pressure cuff will be positioned. A cardiac phased-array coil will be placed anteriorly and posteriorly on the patient’s chest. Participants will lie supine on the magnet table and enter feet-first into the center of the scanner. All cardiac images will be obtained during a 12-15 heartbeat breathhold at end-expiration, averaging 10-15 seconds with adequate rest periods between breathholds (about 10-15 seconds). The imaging protocol will first include sagittal, axial and oblique scout images to localize the heart. It is anticipated that the duration of each MRI session will be 45-60 minutes.

Acquisition parameters and techniques will be protocolized and visits between Cedars Sinai and Hopkins will occur to review these with a select, small group of technicians who will acquire the studies. The imaging data will be sent to, and read at, the SCCT Imaging Core which will be based at Hopkins. MRI will be performed on standard phantoms for quality assurance and to detect any changes in system sensitivity over time. MRIs will be interpreted by cardiovascular experts.
5.3.1 Cine Imaging Protocol

A cine imaging protocol will be utilized for global ejection fraction and LV volumes and mass determination. Cine images will be acquired with a steady-state free precession pulse sequence [sequence parameters: repetition time (TR) 3.8 ms, echo time (TE) 1.3 ms, average in-plane resolution 1.5x2.4 mm, flip angle $\alpha=45^\circ$, 8-mm slice thickness, and temporal resolution 40 msec] in long-axis planes and contiguous 8-mm short-axis slices from the mitral annulus to the LV apex.

5.3.2 Tissue Tagging Protocol

A tissue tagging protocol will be utilized for ejection fraction determination. This will be performed prior to contrast administration in order to minimize tag line fading post-gadolinium. The protocol is based upon an ECG triggered fast gradient echo pulse sequence. The tagging pulse consists of nonselective radiofrequency pulses separated by spatial modulation of magnetization encoding gradients to achieve a tag separation of 6 mm. Tagging pulses are applied immediately before the imaging pulse and triggered by the upslope of the electrocardiographic QRS complex. After scout images, 6-8 contiguous stacks of short-axis images in a grid matrix in orthogonal orientations are acquired. Six long-axis views will also be prescribed in a radial fashion every 30°. Imaging parameters are: 36-40 cm field of view, 8 mm slice thickness, matrix size 256x128, TR=5.1 msec, TE=1.4 msec, flip angle=12°, and 8 phase-encoded views per frame.

First pass perfusion sequence for regional perfusion: Saturation recovery TrueFISP perfusion sequence parameters are: TR/TE 2.5/1.1, in-plane resolution 1.9x2.3, slice thickness 8mm, flip angle 40°, inversion time 180 msec, GRAPPA=2, 4 slices/2 R-R over 60 heartbeats. We will use a dual bolus gadolinium injection method: first dose is 0.005 mmol/kg (to maintain linearity of the LV signal intensity) followed by a 0.05 mmol/kg dose (for the myocardial signal analysis). The low dose concentration is administered during a first breath-hold and the 2nd dose during a 2nd breath-hold between scans.

5.3.3 Delayed Contrast-Enhancement Protocol

This is the most accurate assessment of infarct scar size. Following MRI tissue tagging, patients will receive a total bolus intravenous injection of 0.2 mmol/kg of gadolinium contrast as long as GFR is > 60 ml/min (for GFR 30-60 ml/min, 0.15 mmol/kg will be given; patients whose GFR declines to <30 during the study period will be excluded from subsequent MRI studies). High-resolution delayed enhancement images will be obtained using an inversion-recovery prepared gated fast gradient echo pulse sequence. Ten to twelve short-axis cross sections of the left ventricle to ensure entire cardiac coverage will then be acquired. Beginning with the peripheral bolus of gadolinium, the entire heart will
be imaged in short-axis every 4-5 minutes, visually adjusting the inversion time (TI) for optimal suppression of the normal myocardium. This will continue for 25-30 minutes post-contrast bolus. Pulse sequence parameters are as follows: TR 8.3 msec, TE 3.9 msec, flip angle 25º, 1 R-R, in-plane spatial resolution 2.2x1.4 mm, 8-mm slice thickness, TI 175-300 msec (adjusted as needed in the delayed enhancement image acquisitions to optimally null the signal of normal myocardium).

5.4 CT Protocol

In patients who receive a clinically-indicated ICD or pacemaker after the initial baseline MRI examination, follow-up studies of left ventricular (LV) systolic function, global and regional wall motion, LV volumetric parameters, and infarct scar size measurements will be measured using first-pass and delayed enhanced X-ray computed tomography (CT). Imaging will be performed on two scanning systems: 1) Dynamic Volume 320 Row Detector CT scanning system (Aquilion One™, Toshiba Medical Systems) at Johns Hopkins and 2) Dual source CT scanning system (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany). The scanning protocols that follow will take advantage of radiation dose reduction techniques when appropriate, including dose modulation and prospective ECG gating.

5.4.1 Patient Preparation

Following informed consent, patients will have an 18G or 20 G intravenous line placed preferably in the right antecubital fossa. Patients will lie supine on the scanner table and be attached to a 12 lead electrocardiographic monitor and an automated blood pressure monitor. Beta-blockers, in addition to patient’s normally prescribed dose, will not be given. Scout images will be obtained for determining scan range.

5.4.2 CT Function and Rest Perfusion Imaging

5.4.2.1 320-Dynamic Volume CT - CT functional and rest perfusion imaging will be performed using dose modulation and image acquisition over 3 heart beats to allow for segmented reconstruction and a temporal resolution of about 83 msec using a 320 row detector scanner. Rest perfusion imaging will be acquired at peak tube current (400mA) for 10% of R-R interval in mid diastole. Trough tube current will be 300 mA. Dose modulation and low tube voltage (100 kV) will be used to minimize the radiation dose. Detector collimation will be 128 x 1 mm. Intravenous iodinated contrast (Isovue 370, Bracco Diagnostics) will be injected at a rate of 5 cc/sec with the following 3-phase protocol: 1) 100% contrast for 70 cc, 2) 30:70% mixture of contrast: saline for 50cc, 3) 100% saline for 40 cc.
Immediately following CT imaging and additional 35 cc of contrast will be infused. This will ensure that 120 cc of contrast are available for delayed enhanced CT imaging. Total contrast dose will be 120 cc. The estimated radiation dose for function and rest perfusion imaging is estimated to not exceed 15.5 mSv.

5.4.2.2 Dual Source CT - CT functional and rest perfusion imaging will be performed using dose modulation and a temporal resolution of approximately 83 msec using a dual source CT scanner. Rest perfusion imaging will be acquired at peak tube current (600 mA) for 10% of R-R interval in mid diastole. Trough tube current will be 450 mA. Dose modulation and low tube voltage (100 kV) will be used to minimize the radiation dose. Detector collimation will be 2 x 16 x 1.2 mm with a slice acquisition 2 x 32 x 1.2 mm my means of a z-flying focal spot. The gantry rotation time will be 330 msec with a pitch of 0.2 – 0.5 automatically adapted to heart rate. Intravenous iodinated contrast (Isovure 370, Bracco Diagnostics) will be injected at a rate of 5 cc/sec with the following 3-phase protocol: 1) 100% contrast for 70 cc, 2) 30:70% mixture of contrast:saline for 50cc, 3) 100% saline for 40 cc. Immediately following CT imaging and additional 35 cc of contrast will be infused. This will ensure that 120 cc of contrast are available for delayed enhanced CT imaging. Total contrast dose will be 120 cc. The estimated radiation dose for function and rest perfusion imaging is estimated to not exceed 15 mSv.

5.4.3 CT Delayed-enhanced Imaging for Infarct Scar Size

Five minutes following the completion of contrast administration, delayed enhanced imaging will be performed with the following protocols.

5.4.3.1 320 Dynamic Volume CT – Scanning will be performed over one, two, or three heart beats depending on heart rate and optimization of temporal resolution using prospective ECG-gating half scan or segmented reconstruction as appropriate. Ten percent of the R-R interval will be imaged in mid-diastole. The following scan parameters will be used: tube voltage = 100 kV, tube current 500 mA, detector collimation 128 x 1.0 mm. No additional contrast will be administered. The estimated radiation dose for delayed-enhanced imaging is estimated not to exceed 8.5 mSv.

5.4.3.2 Dual Source CT – Scanning will be performed using ECG-pulsing (step and shoot mode) with imaging performed over 10% of the R-R interval in mid-diastole. The following scan parameters will be used: tube voltage = 100 kV, tube current 600 mA, Detector collimation will be 2 x 16 x 1.2 mm with a slice acquisition 2 x 32 x 1.2 mm my means of a z-flying focal spot. No additional contrast will be administered. The estimated radiation dose for delayed-enhanced imaging is estimated not to exceed 3.0 mSv.
5.4.4 Image Reconstruction and Analysis

Functional images will be reconstructed every 5% of the R-R interval. Global left ventricular systolic function, regional wall motion and wall thickening, end-systolic and end-diastolic volumes will be measured using commercially available software (Q-mass, Medis Medical Imaging Systems, Inc).

Rest perfusion images and delayed enhanced images will be reconstructed at the phase with least cardiac motion in mid-diastole using myocardial perfusion convolution kernels and beam hardening correction. Custom myocardial perfusion software (Toshiba Medical Systems, Otawara, Japan) will be used to measure infarct size during first-pass CT imaging.

5.5 Intra-Coronary Infusion Protocol

As noted above, prior to the intra-coronary infusion protocol, patients will be stable as judged by no evidence of infection, stable blood pressure and pulse over the prior 12 hours; and no change in angina pattern, or in angina or heart failure medications over the prior four days.

Two doses of CDCs will be evaluated sequentially: 1) 12.5 million cells and 2) 25 million cells. These doses are based on the porcine pre-clinical studies which demonstrated that the 15 million cell dose (in 35-50 kg animals) was not associated with elevated troponin over the 24 hours following administration and in a separate placebo-controlled study improved hemodynamics (maximum rate of pressure development) and decreased the infarcted portion of the left ventricle. The cells will be administered approximately 4-8 weeks following the biopsy to allow sufficient time for expansion to the requisite number.

Selective angiography will be performed to ensure patency of the infarct-related artery. If it is not patent, attempts to re-angioplasty the lesion will be performed, but the patient will not be eligible to receive cells. The intracoronary cell infusion will be performed using an "over the wire" (OTW) balloon angioplasty catheter. A balloon catheter up to 0.5 mm larger in diameter than the stent diameter and shorter in length (preferably 8-12 mm) will be positioned in the stented segment and inflated at low pressures (1-4 atm) to attain occlusion of the infarct related artery. The cells will then be injected through the wire lumen of the balloon catheter after the guide wire is removed. The balloon is kept inflated and deflated in 3 minute cycles for 3 times. One third of the cell dose is injected as a bolus during each balloon inflation cycle.

The CDCs will be in 10 mL of solution containing heparin, 100 units/mL and nitroglycerine, 50 mcg/mL diluted in calcium and magnesium-free PBS. Two mL of the infusion solution without cells are infused before the cells and 1 mL of the
infusion solution without cells are infused after the cells, so as to wash any remaining cells from the catheter.

Hemodynamics, symptoms, and electrocardiogram are continuously monitored while patients are in the catheterization laboratory. If there is any evidence of infarction, the infusion protocol will be halted. Patients will be monitored for 24 hours following the infusion including history and detailed physical examination for evidence of neurologic dysfunction and bleeding as well as for arrhythmias and cardiac damage by ECG and cardiac enzymes.

5.6 Cardiac Biopsy Protocol and Monitoring

As noted above, prior to cardiac biopsy, patients will be stable as judged by no evidence of infection, stable blood pressure and pulse over the prior 12 hours, and no change in angina pattern, or in angina or heart failure medications over the prior four days.

A highly skilled cardiologist will perform the fluoroscopically-guided percutaneous biopsy of the right ventricular side of the interventricular septum using a disposable bioptome. Local anesthesia with 2% lidocaine is applied over the right internal jugular vein with a 25 gauge needle. A 5 F micropuncture needle is inserted with a 7 F sheath through which the bioptome is placed. Following 5-10 biopsies and measurement of right sided pressures the catheter and sheath are removed, local pressure is applied and sterile bandage applied.

Patients will be monitored in the hospital for arrhythmias for 24 hours following the biopsy and for 48 hours with ambulatory ECG recording after discharge. Right sided pressures are measured immediately following the procedure and vital signs and oxygen saturation measured for 24 hours thereafter. Perforation would be evidenced by an increase in right atrial pressure and pulse concomitant with a decrease in systolic pressure and oxygen saturation. Any further biopsy procedures would be halted. If there was a change in blood pressure or oxygen saturation after the patient leaves the catheterization laboratory, an echocardiogram will be performed. If there is evidence of tamponade, a pericardiocentesis will be performed with the drain in place until stable. Infection risk is low as all foreign material is removed after the procedure. However, the site will be examined for evidence of infection daily before discharge and at the first two week visit. In addition, the patient will be asked to notify the study investigators if they experience pain, observe redness or discharge at the site, or if their temperature is elevated. We do not anticipate neurologic complications as the patient will only have local anesthesia and there is no left sided catheterization. However, detailed physical examination will be performed following the procedure and daily prior to discharge.
5.7 Stopping Criteria for Cardiac Biopsy and Cardiac Infusion Protocols

Stopping criteria that would trigger halting of the septal biopsy or CDC infusion are:

a. Sustained hypotension unresponsive to fluids
b. Evidence of acute coronary syndrome
c. Evidence of cerebrovascular accident
d. Evidence of cardiac tamponade
e. Hemopericardium requiring pericardiocentesis
f. Sustained ventricular tachycardia/ventricular fibrillation that requires cardioversion or administration of an antiarrhythmic
g. Evidence of thrombus in the aorta that was not previously seen on imaging studies.
h. Suspected or confirmed aortic dissection
i. Fever > 99.4 degrees

5.8 Cardiac Arrhythmia Monitoring

The electrocardiogram will be continuously monitored and recorded while patients are in the hospital for the intra-coronary infusion portion of the protocol. They will also have 48-hour ambulatory ECG recordings performed after discharge from the hospital and at the two week, one-month, two-month, three-month, six-month, and twelve-month visits.

6. ADVERSE EVENT MANAGEMENT

6.1 Definition of an Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of an AE include:
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- A new condition detected or diagnosed after study therapy administration even though it may have been present prior to the start of the study.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a patient’s previous treatment regimen).

An AE does not include:
- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure is an AE.
- Social or convenience hospital admissions where an untoward medical occurrence did not occur.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the patient’s condition.

6.2 Definition of a Serious Adverse Event
A Serious Adverse Event (SAE) is any adverse experience occurring at any dose that:
1. results in death
2. is life-threatening (at risk of death at the time of the event)
3. requires inpatient hospitalization or prolongation of existing hospitalization
   NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.
4. results in disability/incapacity
   NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
5. is a congenital anomaly/birth defect.
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

6.3 Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 5.1 (“Definition of an Adverse Event”) or SAE, as defined in Section 5.2 (“Definition of a Serious Adverse Event”). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient’s condition, or that are present or detected at the start of the study but do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant.

6.4 Recording of Adverse Events and Serious Adverse Events

The Investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The Investigator will then record all relevant information regarding an AE/SAE into the electronic data system. It is not acceptable for the Investigator to send photocopies of the patients’ medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when the medical monitor (an independent physician who is not participating in the clinical study), requests copies of medical records for certain cases. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the medical monitor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs and symptoms.
6.5 Intensity of Adverse Events and Serious Adverse Events

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator’s clinical judgment. The intensity of each AE and SAE will be assigned to one of the following categories:

**Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is described as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 5.2, “Definition of an SAE.”

6.6 Relationship of Adverse Events and Serious Adverse Events to Study Therapy

The Investigator is obligated to assess the relationship between study therapy and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the study therapy was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study therapy will be considered and investigated. The Investigator will also consult the Clinical Investigator’s Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

All AE/SAE that occur during the course of the clinical study will be evaluated and a determination of relatedness to the investigational product will be defined according to one of the following categories:

- **Definite** - The AE/SAE is clearly related to the investigational product.
- **Probable** - The AE/SAE is likely related to the investigational product.
- **Possible** - The AE/SAE may be related to the investigational product. All AEs and SAEs that occur within 30 days of intervention will, because of the temporal relationship, be considered as at least possibly related to the procedure and will be reported to the DSMB.
- **Unlikely** - The AE/SAE is doubtfully related to the investigational product.
- **Unrelated** - The AE/SAE is clearly NOT related to the investigational product.
There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality.

6.7 Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information to the medical monitor on the patient’s condition. All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

Adverse events and SAEs will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a patient experiencing a critical adverse event is treated successfully and stabilized even though they may continue to experience lingering sequelae that may never resolve), until the patient is lost to follow-up, or until it is agreed that further follow-up of the event is not warranted (e.g. non-serious, study therapy unrelated, mild or moderate adverse events ongoing at a patient’s final study visit). If a patient dies during participation in the study or during a recognized follow-up period, the medical monitor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded by modifying the AE forms in the electronic data system.

6.8 Timeframes for Submitting SAE Reports to the SCCT DSMB

Once an Investigator becomes aware that an SAE has occurred in a study patient, he/she will record the information in the electronic data record within 48 hours. Any fatal or life-threatening event must be reported within 24 hours. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before recording the event in the data system and completing as much information known at the time of the submission. The reporting timeframes for any SAE occurring during the study are summarized in Table 2.

Furthermore, the DSMB will be notified within 72 hours of the occurrence of SAEs temporally related to study procedures such as biopsy or product administration or related to product, such as tumor in the heart.

The DSMB will receive regular safety updates. The DSMB will be notified in real-time (within 72 hours of knowledge of the event) of any SAE that is at least possibly related to the procedures or CDCs during the entire study period. AEs and SAEs that occur within 30 days of intervention will, because of the temporal
relationship, be considered as at least possibly related to the procedure and will be reported to the DSMB.

The DSMB will also be notified in real-time if a stopping guideline is met. The medical monitor will review the information and contact the Investigator for additional information, as necessary. The principal investigator, or his designee, is responsible for notifying the NHLBI DSMB of all SAEs. The FDA will be notified by telephone or FAX of any unexpected fatal or life-threatening adverse event associated with the use of the CDCs as soon as is possible, but in no event later than 7 calendar days after the sponsor’s initial receipt of the information. Follow-up information will be provided as required.

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<th>Table 2. Serious Adverse Event Reporting Requirements to the DSMB</th>
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</thead>
<tbody>
<tr>
<td><strong>Type of SAE</strong></td>
</tr>
<tr>
<td>Fatal or Life-Threatening</td>
</tr>
<tr>
<td>Reporting Timeframes</td>
</tr>
<tr>
<td>Documents Required</td>
</tr>
</tbody>
</table>

6.9 SCCT Post-Study Adverse Events and Serious Adverse Events
The Investigator should notify the medical monitor of any death or SAE occurring at any time after a patient has completed or terminated a clinical trial, when such death or SAE may reasonably be related to the study therapy used in this SCCT investigational trial. Investigators are not obligated to actively seek AEs from former study participants.

6.10 Regulatory Aspects of Adverse Event Reporting
The Investigator will promptly report all SAEs within the timeframes specified in Section 5.8. Prompt notification of SAEs by the Investigator is essential so that SCCT can meet legal obligations and fulfill ethical responsibilities towards the safety of all patients participating in SCCT-sponsored investigational trials.
The Investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to his or her Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

This protocol is being filed under an Investigational New Drug (IND) application with the FDA. A given SAE may qualify for an Expedited Safety Report (ESR) if the SAE is both attributable to study therapy and unexpected. In this case, all Investigators participating in an IND study will receive the ESR.

The ESRs are prepared according to SCCT policy and are forwarded to the Investigator as necessary. The purpose of the ESR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

6.11 SCCT Monitoring of Adverse Events

The following list summarizes the SCCT’s role in monitoring AE/SAEs:

- All SAEs will be reviewed by the Medical Monitor at the Data Coordinating Center, within 1 business day of receiving the adverse event form (or MedWatch form) from the clinical center.
- If the Medical Monitor requires additional information to make his/her assessment, the clinical centers will have 2 business days to respond to the request for additional information.
- The DCC is responsible for notifying the NHLBI Project Officer immediately of all SAEs, regardless of attribution, and of any concerns regarding the frequency or type of SAE(s) on a study or treatment arm.
- The attribution, as assessed by the clinical center and the DCC Medical Monitor, will be provided to the NHLBI Project Officer within 2 business days of receiving the report.
- All SAEs, at least possibly related, will also be sent to the DSMB chair.
- The DSMB will monitor SAEs in “real time.” We anticipate (1) phone conversation with DSMB chair within 72 hours of every death, and (2) regular communication regarding SAEs. We will also request that the DSMB chair acknowledge receipt of SAEs within 72 hours of notification.
- In addition, the DSMB will be provided with a summary of ALL AEs and SAEs, regardless of attribution, and additional safety and outcomes data every six months as part of their scheduled interim review. In addition to AE and SAE review, specific safety and outcomes data that will be reviewed include enzyme evidence of any infarction within 24 hours of the infusion and the ambulatory ECG monitoring results.

The NHLBI Project Officer (or designee) is responsible for reviewing the SAE materials to determine if the documents are complete. If there are any concerns regarding the type or frequency of the event, the NHLBI Project Officer will request that the DSMB Executive Secretary notify the DSMB Chair. The DSMB
Chair will review the SAE materials, determine if the information is complete, determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study.

The DCC will prepare semi-annual summary reports of all AEs/SAEs for the NHLBI Project Officer and DSMB Chair. Semi-annual reports will be made available on a secure website and the NHLBI Project Officer and DSMB Chair will be notified by e-mail when the materials are posted.

7. DATA COLLECTION AND STATISTICAL ISSUES

This section describes methods for randomization, data collection, sample size determination, analysis populations, and planned analyses for safety and efficacy endpoints.

7.1 Enrollment

Patients will be registered using the SCCT Advantage Electronic Data Capture (EDC). The following procedures shall be followed:

1. An authorized user at the clinical center completes the initial screening by entering patient demographics and Segment A information (inclusion/exclusion criteria) of the Eligibility Form within two weeks of the myocardial infarction.

2. If the patient is eligible and undergoes cardiac biopsy, a blinded study treatment number is generated at that time.

If a connection is interrupted during a randomization session, the process is completely canceled and logged. A backup manual registration and randomization system will also be available to provide for short-term system failure or unavailability.

7.2 Randomization

Patients will be randomized following the screening procedures using permuted blocks, initially to the 12.5 million cells dose or the control group in a 2:1 ratio; and then after 6 patients have been enrolled and approval by the DSMB, to 25 million cells or the control group in a 2:1 ratio, providing a projected distribution of 4:8:12 (lower dose, control group, higher dose, respectively). The NHLBI DSMB will also review the results of the first nine patients in the higher dose group (i.e. patients 7-15) before the remaining nine patients in the higher dose group are enrolled. Randomization will be stratified by treatment center and left ventricular ejection fraction (0.25 - < 0.35 or 0.35-0.45). The study treatment number is sent via email to the Cedars Sinai Laboratory, which will have the table to identify the
treatment assignment associated with the study treatment number. A visit schedule based on treatment start date is displayed for printing.

7.3 Data Collection
Data will be entered using the SCCT Advantage EDC. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User’s Guide. The Investigator or designee must record all required patient data, and an explanation must be documented for any missing data.

7.3.1 Follow-up Assessments
The timing of follow-up visits is based on the date of study therapy administration. Following intra-coronary infusion, a Patient Visit Schedule listing target dates for assessments can be printed from the EDC system.

7.3.2 Criteria for Forms Submission
Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User’s Guide. Forms that are not received at the Data Coordinating Center (DCC) within the specified time will be considered delinquent. Past due forms can be viewed via the Web-based data entry system. A missing form will continue to appear until the form is entered into the DCC’s master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook and User’s Guide.

7.3.3 Site Center Personnel Training
A site visit will be conducted at the two participating centers prior to accrual. At this visit, there will be a thorough review of the study protocol, study procedures, the case report forms, the data collection and submission process, and the site’s regulatory obligations as well as any special procedures with the center personnel. A representative from the Data Coordinating Center will lead the site initiation visits. The training will be documented.
7.4 Statistical Considerations

7.4.1 Study Design

The study is a Phase I, randomized, multi-center trial. It is designed to assess the safety and efficacy of intra-coronary infusion of autologous human cardiosphere derived cells (CDCs) in patients with ischemic left ventricular dysfunction following a recent myocardial infarction. The sample size is 24 patients.

7.4.2 Accrual

It is estimated that one year of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age. No children will be enrolled. We expect that the gender and minority distribution will reflect that of our infarct patient population. At Johns Hopkins, the MI population is 32% female, 25% African-American, 3% Hispanic, 5% Asian-Pacific Islander, 67% Caucasian, and less than 1% Native-American. The Cedars-Sinai population is also highly multicultural.

There are no particular recruitment strategies for women. However, we note prior success in enrolling only women with acute coronary syndromes in our estrogen/placebo study (Schulman SP et al: Effects of acute hormone therapy on recurrent ischemia in post-menopausal women. JACC 2002;39:231-237).

7.4.3 Study Duration

Patients will be followed for 12 months, at two weeks and at one, two, three, six, and twelve months post-baseline visit.

7.4.4 Primary Objective

The primary objective is to evaluate the safety of autologous CDCs administered by intra-coronary infusion in patients with ischemic left ventricular dysfunction following a recent MI. The primary endpoint is the six-month proportion of patients who experience death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, myocardial infarction following cell infusion, new cardiac tumor formation on MRI imaging or a major adverse cardiac event (MACE), defined as the composite of death, hospitalization for heart failure or non-fatal recurrent MI. The six-month serious adverse event rates in the treatment two groups will also be a primary focus.
7.4.5 Sample Size and Power Calculations

The total sample size is 24 patients for this trial. However the sample size and power considerations will be based on the 16 subjects infused with CDCs. Exact binomial ninety-five percent confidence intervals were calculated for varying number of events based on the sample size. Table 3 provides confidence intervals for a variety of true underlying number of events. Of particular interest is the anticipated six-month proportion of patients who experience death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, myocardial infarction following cell infusion, new cardiac tumor formation on MRI imaging or a major adverse cardiac event (MACE), which is 15% which translates into between 2 and 3 patients with events out of 16 patients. For the setting of 3 patients, the confidence interval is 0.04 to 0.46. The probabilities above and below 3 represent other plausible scenarios.

The precision of the estimates alternatively could be viewed as a lower bound on the rate of events. The probability to rule out the proportion experiencing the primary objective of a certain size can be interpreted as “power.” Table 4 provides the probability (or power) that the lower bound of a 95% two-sided confidence interval for the primary endpoint will be greater than thresholds of 1, 2, 3, 4, 5, 6, and 7 events. When the true number of events is 2, there is 68% power to rule out a number of patients experiencing the primary endpoint of 7 or higher.

Table 3. Exact Binomial 95% Confidence Intervals for Various Sample Sizes and Proportion of Patients Experiencing the Primary Endpoint
**Table 4. Probability of Ruling Out a Threshold of Size T or larger for Various Sample Sizes and True Underlying SAE Proportion of Patients Experiencing the Primary Endpoint**

<table>
<thead>
<tr>
<th>Patients randomized to the first and second dose group</th>
<th>Number of patients experiencing the primary endpoint</th>
<th>Exact 95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>1</td>
<td>0.002, 0.30</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.02, 0.38</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.04, 0.46</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.07, 0.52</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.11, 0.59</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.15, 0.65</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.20, 0.70</td>
</tr>
</tbody>
</table>
7.4.6 Justification for the Inclusion of a Control Group

Inclusion of a control group will allow improved assessment of both safety and efficacy. As adverse events are likely to occur over a 12 month period in patients with ischemic left ventricular dysfunction regardless of whether or not they receive cell therapy, inclusion of a concurrent control group affords an opportunity to assess whether these events are related to the natural history of the disease or to cell therapy. In addition, spontaneous recovery of LV function, decrease in relative infarct size, and intrinsic re-modeling processes occur during the first several months following an infarction even without cell therapy (Gerber, Garot et al. 2002). These are important outcomes and inclusion of the control group will provide some insight into distinguishing those which occur spontaneously from those which can be related to the cell intervention. Interpretation of the MRI scans will be performed by someone who is blinded to group assignment.

7.4.7 “Stopping” Guidelines

The proportion of patients experiencing procedure-related outcomes including death, serious arrhythmias with ventricular tachycardia or ventricular fibrillation requiring cardioversion or MI with angiographically documented occlusion with ST elevation and TIMI grade 1 flow will be monitored within 24 hours of infusion. This guideline is to be used to indicate boundaries requiring discussion by the DSMB and is designed to assist the independent NHLBI-appointed Data and Safety Monitoring Board (DSMB) in overseeing the study. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study.

Monitoring of key safety endpoints will be conducted. If rates significantly exceed the pre-set threshold, then the NHLBI will be notified in order that the DSMB can be advised.

The proportion of patients experiencing procedure-related outcomes will be monitored using a stopping guideline that compares the rates in both arms that
are receiving CDC doses to an external standard for safety in patients undergoing angioplasty and stent placement.

A Bayesian motivated safety stopping guideline will be used for this trial (Dekker 2004). The expected underlying procedure-related outcome probability is assumed to be 5% and that a probability of greater than 20% is unacceptable.

A Beta distribution can be used as the prior distribution of ?; ? is the proportion of patients who experience a SAE. The stopping rule is based on the beta-binomial methodology and assumes a prior expected failure rate. This leads to prior Beta parameters where a=0.4 and b=7.6 and approximately 8 patients worth of experience in the prior distribution. The Beta distribution will have a prior mean of 0.05 and a prior probability <0.05 of exceeding 0.20. The guideline is derived such that if there is strong evidence (posterior probability > 0.95) that the probability of the event is greater than 20%, the trial will be stopped. The resulting boundaries tabulated in Table 5 were generated by rounded to be conservative with the stopping guideline and is considered after 4 patients are enrolled on study.

<table>
<thead>
<tr>
<th># Events</th>
<th># Patients in Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4-8</td>
</tr>
<tr>
<td>3</td>
<td>9-16</td>
</tr>
</tbody>
</table>

* The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not formal “stopping rules” that would mandate automatic closure of study enrollment.

A simulation study was conducted to evaluate the operating characteristics of this stopping rule. Data were generated from the binomial distribution with varying probabilities of failure (?) and assuming a sample size of 16 patients. Table 6 shows the probability of stopping the trial early and the average sample size of the trials that stopped (N), conditional on stopping early, at which the boundary is crossed for each value of ?.
Table 6. Operating Characteristics for Bayesian Motivated Stopping Guideline

<table>
<thead>
<tr>
<th>Mean of Prior Distribution</th>
<th>θ</th>
<th>Probability of stopping</th>
<th>Average Sample Size of Trials Stopped (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>0.50</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.70</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.83</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.35</td>
<td>0.96</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Although the motivation for the boundary is Bayesian, the operating characteristics can be evaluated from a frequentist perspective of Type I error and power. The stopping rule for a 5% event rate has a 8% chance (“Type I error”) of suggesting early termination when the true rate is 0.05, and an 70% chance (“power”) when the true rate is 0.20, rising to 83% when the true rate is 0.25.

Patients in the control group will also be monitored. The DSMB will be consulted for additional review in the event 2 patients experience procedure-related outcomes including death, serious arrhythmias with ventricular tachycardia or ventricular fibrillation requiring cardioversion or MI with angiographically documented occlusion or with serum troponin I elevation to greater than the 99th percentile of the upper range limit within 24 hours of infusion.

7.4.8 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined include age, gender, race/ethnicity, ejection fraction, Six-Minute Walk Test Performance, Peak V0\textsubscript{2}, etc.

7.4.9 Analysis of the Primary Endpoint

Descriptive analyses of the primary endpoint will be performed. Point estimates and confidence intervals of the proportion of patients that experience death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, myocardial infarction following cell infusion, new cardiac tumor formation on MRI imaging or a major adverse cardiac event (MACE), defined as the composite incidence of death, hospitalization for heart failure or non-fatal recurrent MI will be computed by treatment arm at 6-months post infusion. Event rates will be compared across treatment arms and against historical data, recognizing that in
this limited sample size only very large differences can be detected. The frequency, severity, timing and the potential relationship to the intervention will be assessed in order to characterize the safety of the intervention. A chi-square test will be performed by pooling the two dose groups (N=16) to compare to the control group (N=8) for the proportion of patients experiencing the primary endpoint at 6 months and is restricted due to the limited sample size.

7.4.10 Analysis of the Primary Endpoint between Pooled Dose Groups and the Control Group

An analysis of the primary endpoint between the pooled dose groups and the control group will be conducted when all patients have reached 6-months post infusion. The 6-month probability of reaching the primary endpoint in the pooled treatment arms ($\theta_T$) will be compared to the 6-month probability of reaching the primary endpoint in the control group ($\theta_P$). A one-sided, $a=0.1$, Barnard's test for superiority will be used to test if the event rates are higher in the pooled treatment group as compared to the control group. Table 7 shows the power of the test given various underlying probabilities. Of note, if the true underlying probability is 0.05, there is 89% power to detect an increase in the probability to 0.50. Note that due to the small sample size, there is only sufficient power to detect large disparities in event rates.

| Table 7. Operating Characteristics for Barnard’s test for Superiority |
|-----------------|-----------------|-----------------|
| $\theta_T$ | $\theta_P$ | Power |
| 0.05 | 0.05 | <0.01 |
| 0.25 | 0.05 | 0.42 |
0.50 | 0.05 | 0.89
0.75 | 0.05 | 0.99
0.15 | 0.15 | 0.06
0.25 | 0.15 | 0.19
0.50 | 0.15 | 0.67
0.75 | 0.15 | 0.96
0.25 | 0.25 | 0.08
0.50 | 0.25 | 0.45
0.75 | 0.25 | 0.87

**7.4.11 Analysis of Secondary Endpoints**

Descriptive analyses of all secondary endpoints will be performed using point and confidence interval estimation. Treatment effects will be assessed using appropriate methods for continuous, dichotomous, or ordinal categorical data, such as the Wilcoxon, Fisher’s exact, and linear rank tests. Plots will be constructed to display secondary endpoints over time. Statistical methods for analyzing repeated measurements will be conducted to compare treatments at specific times and averaged over time. An analysis will be performed by pooling the two dose groups (N=16) and comparing their data with that of the pooled control groups (N=8).

**7.4.12 Data and Safety Monitoring Board (DSMB)**

Interim analyses will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately six-month intervals. The DSMB Chair will be notified each time an SAE occurs. The DSMB will evaluate unblinded AE data (including SAEs) when the first six patients have been enrolled and those receiving cells discharged after all have been discharged after receiving cells. They will review enzyme evidence of any infarction within 24 hours of the infusion and 72 hours of ECG monitoring (24 hours inpatient and 48 hours of ambulatory monitoring). This review will occur prior to proceeding with the 25 million cell dose patient group. Other safety data, including the laboratory values will also be evaluated by the DSMB as appropriate. Monitoring of key safety endpoints will be conducted as described above, and if rates significantly exceed pre-set thresholds, NHLBI will be notified and information will be supplied to the DSMB. Policies of the DSMB are described in the SCCT Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not
formal “stopping rules” that would mandate automatic closure of study enrollment. Stopping will be at the discretion of the DSMB.

8. Study Administration

8.1 REGULATORY AND ETHICAL CONSIDERATIONS

8.1.1 Regulatory Authority Approval

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

8.1.2 Ethics Approval

It is the Investigators’ responsibility to ensure that, prior to initiating this study, this protocol is reviewed and approved by the appropriate local IRB. The composition and conduct of this committee must conform to the United States CFR.

The IRB/IEC must also review and approve the site’s informed consent form (ICF), other written information provided to the patient, and all advertisements that may be used for patient recruitment. If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new patients are consented to participate in the study using the amended version of the ICF.
8.1.3 Patient Informed Consent

Before being admitted to the clinical study, all patients must consent in writing to participate. An ICF will be given to each patient, which will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the patient.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator will review the study with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review will be in a form understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or his/her designee will emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The site must use the amended consent form for all new patients and repeat the consent process with the amended ICF for any ongoing patients.

8.2 Confidentiality of Information

Patients' names will remain confidential and will not be included in the database. Only patient number, patient initials, and birth date will be recorded in the data system. If the patient name appears on any other document collected (e.g., hospital discharge summary), the name will be obliterated before the document is transmitted. All study findings will be stored in electronic databases. The patients will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect their medical records to verify the information collected.

Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA.
All participants in the will provide written authorization to disclose private health information either as a part of the written ICF or as a separate authorization form. The authorization will contain all required elements specified by 45 CFR 164, and will contain a waiver of patient access to study-related private health information until the conclusion of the clinical study. The authorization will remain valid and in full force and effect until the first to occur of (1) the expiration of 2 years after the study therapy is approved for the indication being studied, or (2) the expiration of 2 years after the research program is discontinued. Individual patient medical information obtained during this study is confidential and its disclosure to third parties (other than those mentioned in this Section) is strictly prohibited. In addition, medical information obtained during this study may be provided to the patient's personal physician or to other appropriate medical personnel when required in connection with the patient's continued health and welfare.

The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

8.3 Payments to Patients

Patients will be reimbursed $100 for all visits except for the baseline visit, cardiac biopsy visit, intracoronary infusion visit, and months 6 and 12, when $200 will be provided. These disbursements are meant to cover the time required to complete these study visits. In addition, all necessary travel and parking expenses will be reimbursed.

9. REFERENCES


Kamihata, H., H. Matsubara, et al. (2001). "Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral
perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines." Circulation 104(9): 1046-52.


10. DSMB CHARTER
Charter, Data and Safety Monitoring Board for Gene and Cell-Based Therapy
August 2007

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for Gene and Cell-Based Therapy Clinical Trials.

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the studies.

The DSMB is an independent group advisory to the Director, NHLBI, and is required to provide recommendations about starting, continuing, and stopping the studies. In addition, the DSMB is asked to make recommendations, as appropriate, to the NHLBI about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
  - Amendments to the study protocol and consent forms
  - Performance of individual centers and core labs
  - Participant safety
  - Notification of and referral for abnormal findings

3. Organization and Interactions

Communication with DSMB members will be primarily through the NHLBI Program Office and the Data Coordinating Center (DCC) for each Program. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members and NHLBI Program Staff

DSMB members and the NHLBI Staff involved in the oversight and the management of Gene Therapy, the Specialized Centers for Cell-Based Therapy and the Cardiovascular Cell Therapy Research Network are listed in Appendix A. Consistent with NHLBI policy, each DSMB is assigned an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

5. Scheduling, Timing, and Organization of Meetings

DSMB meetings are usually held in the Washington, DC area. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study activities, to review and
make recommendations about the protocol(s), and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups.

Enrollment in a study cannot begin until the DSMB’s recommendation for approval has been accepted by the Director, NHLBI, IRB, and other required approvals has been obtained at each site.

Meetings are usually held approximately twice a year, with additional meetings or conference calls scheduled as needed. Meetings and conference calls will be scheduled by the DCC in collaboration with the NHLBI Program Office.

- For this DSMB meetings will be held a minimum of twice per year, and calls will be held no more than three times per year.

- Review of interim data analyses will occur per the protocol.

The agenda for DSMB meetings and calls may be drafted by the DCC in consultation with NHLBI staff. The ES will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the DCC two- three weeks before each meeting or call.

Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last formal annual report to NHLBI. If a new conflict is reported, the Chair and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point.

KHS expressed that all DSMB members sensed overengineering and week. However, this is not unexpected. Therefore, the DSMB may wish to establish a norm for budgeting variables. Additionally, IHC and DCC members were pleased. The project team would submit data and develop a written plan for validation.

2. Consequences of the Final Analysis

DSMB received all submitted data and examined them.

- During the open manuscript, the DSMB was provided with thegetClientOriginalName().
- Additional data were submitted to the DSMB on an hourly bases, as well as a written plan for validation.

You should make sure the data are accurate prior to sending it to the DSMB members and NHLBI Executive. Sending raw data prevents them from核实 data independently. Validating...

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB’s recommendations. This provides an opportunity for study investigators, the DCC, and NHLBI to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

Initial summary: The NHLBI ES is responsible for assuring the accuracy and transmission of a brief summary of the DSMB’s discussion and recommendations for the Director, NHLBI, within 48 hours of the meeting or call. The Director or designee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the DCC, and the clinical investigators.

- Action plan: If the DSMB’s recommendations require significant changes or follow-up, NHLBI staff in collaboration with the DCC will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The NHLBI ES is responsible for the accuracy and transmission of the formal DSMB minutes for the Director, NHLBI, within 14 days of the meeting or call. These minutes are subject to FOIA requests and are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. These minutes will be reviewed by NHLBI staff, key study personnel and the DCC before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to Office of the Director, NHLBI, for OD approval. Subsequently, the minutes are sent back to the DCC and the relevant investigators, and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.

8. Reports to the DSMB

For each meeting, the DCC, with input from NHLBI staff, will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss the at the first or subsequent meetings what data they wish to review and how it should be presented.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination
or continuation of the trial. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons.