Official Study Title: A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, and Efficacy of Autologous Mesenchymal Stem Cells and c-kit+ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects with Ischemic Heart Failure

Short Title: *C*ombination *O*f mese*N*chymal and c-kit^{+} *C*ardiac st*E*m cells as *R*egenerative *T*herapy for *H*eart *F*ailure (**CONCERT-HF**)

NCT Number: NCT02501811

Informed Consent Template (IRB approval date): Version 1.8_110518 Approval date:12/14/2018

Protocol Title: **A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, and Efficacy of Autologous Mesenchymal Stem Cells and c-kit$^+$ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects with Ischemic Heart Failure**

(<INSERT IRB APPROVAL NUMBER HERE>)

Study Identifier: **CONCERT-HF**

Study Sponsor: **The Cardiovascular Cell Therapy Research Network (CCTRN)**

Principal Investigator: **<Insert INVESTIGATOR NAME HERE>**
<INSERT INVESTIGATOR INSTITUTION HERE>

INVITATION TO TAKE PART

You are being invited to take part in a research study (title above) conducted by <INVESTIGATOR NAME> and his/her staff at <INSTITUTION NAME>. This is a national study with six other centers located across the country. The study will enroll approximately 144 people nationally. This location will enroll approximately 30-40 people.

This study has funding from The National Heart, Lung, and Blood Institute (NHLBI), which is part of the National Institutes of Health. This research study has been reviewed by the <INSERT NAME OF IRB and IRB APPROVAL NUMBER>. The study is also regularly reviewed by NHLBI's Gene and Cell Therapy Data Safety Monitoring Board, which is an independent (separate from the study) group of individuals with expertise in research studies, cardiovascular medicine, ethics (morals or beliefs), and cell biology.

Your decision to take part is voluntary and you may refuse to take part, or choose to stop taking part, at any time during the study. A decision not to take part or to stop being a part of this research study will not change the healthcare services that are available to you by the doctor, hospital, or other clinics.

You may refuse to answer any questions asked or written on any forms.

The nature of the study, benefits, risks, discomforts, and other information about the study are discussed below. You will be told of any findings discovered during the study, which may affect your willingness to take part. You are urged to discuss any questions you have about the study with the research staff.

<INSERT INVESTIGATOR CONFLICT OF INTEREST INFORMATION HERE IF APPLICABLE>
One or more of the investigators conducting this study serve as paid speakers, consultants or advisory committee members for a company that makes or promotes products used in this study. These financial interests are within permissible limits established by the <Institution Name> Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask your study doctor or call the Institutional Review Board at <INSERT PHONE>

PURPOSE AND BACKGROUND INFORMATION

Heart failure is a serious and common condition. It is a condition in which the heart muscle does not pump blood throughout the body as well as it should. Over a period of years, the heart's pumping ability

continues to get worse and a heart transplant may become necessary. Treatment options are extremely limited. Also, because of the small number of donor organs, very few people receive heart transplants when they need one.

The purpose of this research study is to determine if c-kit+ cells produced from a sample of your heart muscle, mesenchymal stem cells (MSCs) produced from a sample of your bone marrow, either alone or in combination with each other, will safely help your heart to work better. Experiments performed in small and large animals suggest that giving either c-kit+ cells or MSCs alone, or the combination of c-kit+ cells and MSCs together, improves the ability of diseased hearts to pump blood throughout the body.

You are being asked to be in this research study because in the past you had a heart attack and currently you are not an ideal candidate for other forms of standard therapy such as surgery or techniques used to widen or unclog an artery. You also have left ventricular dysfunction (your heart does not pump blood as well as it should) and because of this you are experiencing heart failure. Your doctor has determined your arteries are not suitable for coronary artery bypass surgery or stenting (opening arteries by the placement of stents).

Randomization

If you agree to take part in this study, you will be randomized (similar to flipping a coin) to receive one of four study products: MSCs alone, c-kit+ cells alone, a combination of MSCs *and* c-kit+ cells or a placebo (which is a solution that contains no cells, only salt and proteins). It is not known whether the cells will be of benefit. For this reason, some study participants must receive a placebo. This will allow a careful comparison to study the benefits and side effects of the study products containing cells. One fourth of the patients will receive MSCs alone, one fourth will receive c-kit+ cells alone, one fourth will receive the combination of MSCs *and* c-kit+ cells, and one fourth of the patients will receive placebo. Neither you nor your doctors treating you will know what study product you will receive. Regardless of which group you are in, you will otherwise receive the same standard treatment for your coronary artery disease and heart failure.

If you are randomized to one of the groups receiving MSCs, the MSCs given to you in the study product will be taken from your bone marrow. If you are randomized to one of the groups receiving c-kit+ cells, the c-kit+ cells given to you in the study product will be taken from your heart. The procedures for getting the cells are explained below. Giving patients their own MSCs or c-kit+ cells, either alone or in combination, is an investigational procedure that has been authorized by the Food and Drug Administration (FDA) for this study.

All patients will have bone marrow collected and will undergo a right heart catheterization. Only those patients assigned to the c-kit+ cells or combination groups however, will have heart tissue collected as part of their right heart catheterization (see right heart catheterization description below). Depending on which group you are randomized to, your bone marrow may or may not be used to create cell product to give back to you. For example, if you are assigned to the placebo group or c-kit+ cells alone group, your bone marrow will still be collected but it will not be processed to make any cell product. You will have the option of allowing us to send any remaining bone marrow to a research storage laboratory facility called a biorepository. There is a separate section in this consent form that describes the biorepository in more detail.

If you agree to allow us to save your remaining bone marrow, and if you are assigned to the placebo or c-kit+ cell alone group, then the entire amount of bone marrow that we collect from you will be shipped to

the biorepository. If you are assigned to one of the MSC groups (MSC alone or the combination), any bone marrow collected that was in excess of that needed to create the cell product will be shipped to the biorepository. If you do not allow us to save your remaining bone marrow, then all samples we collect will be destroyed and if you are assigned to one of the three groups receiving study products containing cells, any remaining samples not used to produce the study product will be destroyed. All heart tissue collected from participants in the c-kit+ cells or combination groups will be used to make the study product.

STUDY PROCEDURES AND ASSOCIATED RISKS

Importantly, your taking part in this research study will not affect the usual treatment of medical therapy that all patients with heart failure receive. If you agree to take part in this study you will undergo several tests and procedures during outpatient visits and during the follow-up visits which are in addition to those normally performed for patients being treated for heart failure. To take part in this study, you must return for all scheduled follow-up visits, as instructed by your doctor, until follow-up is no longer necessary. As a participant in this study, you agree to keep your doctor informed of all future changes in your address and phone number.

After you sign the informed consent form, you will be asked to have several tests and exams to see if you are eligible for the study. You will have up to 60 days to complete these tests, depending on the schedule you work out with your study doctor. It is possible that after you have completed these tests, the results may show that you do not qualify for the study. This means you would not be eligible to receive the study product. If this happens, you will be informed of the reason(s) you are not eligible and will be referred back to your regular doctor for care. **A schedule and brief descriptions of the research activities are provided below.**

Schedule of Study Visits

Baseline Visit (approximately 7.5-9 hours) §

TEST	TIME for TEST (approximate)
Discuss and Sign Consent Form	1-2 hours
History and Physical Exam	45 minutes
ECG	30 minutes
Labs-Blood work	15 minutes
Pregnancy test (females)	10 minutes
MRI (with ICD evaluation)	1 – 1.5 hours
Exercise Testing (treadmill)	45 minutes
Questionnaires	45 minutes
Exercise Testing (six-minute walk)- two tests*	45 minutes each

§ Activities may be split into two separate visits as needed

***A third test may be required depending on results from the first two tests.**

Harvest Visit (approximately 7.5-8 hours)

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
Bone Marrow Aspiration	5 hours*
Right heart catheterization(with or without biopsy)	1 hour
Echocardiograms (before and after right heart cath)	30 minutes each

***Includes preparation for the procedure, the harvest, and the recovery time**

MRI Visit (*within 30 days of Study Product Injection*)- (approximately 1-1.5 hours)

TEST	TIME for TEST (approximate)
Labs-Blood work	15 minutes
MRI (with ICD evaluation)*	1 – 1.5 hours

***MRI will be completed within 30 days of receiving study product and will be compared to previous MRI**

Study Product Injection Visit (approximately 3 hours)

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
ECG	30 minutes
Labs- Blood work	15 minutes
Pregnancy test (females)	10 minutes
Blood draw-biorepository only	15 minutes
ICD evaluation (if applicable)	10 minutes
Cardiac Catheterization/NOGA procedure*	1 hour
Echocardiogram	30 minutes

* **Monitored overnight on telemetry (ECG monitored) unit.**

Day after Injection Visit (approximately 1.5 hours)

TEST	TIME for TEST (approximate)
Physical Exam*	30 minutes
ECG	30 minutes
Labs- Blood work	15 minutes
Blood draw-biorepository only	15 minutes

***Receive temperature log to monitor for infection.**

One week Follow -up (approximately 1.5 hours)

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
ECG	30 minutes
Labs-Blood work	15 minutes
Blood draw-biorepository only	15 minutes

One month Follow-up (approximately 1-1.5 hours)

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
Labs-Blood work	15 minutes
Blood draw-biorepository only	15 minutes
Pregnancy test (females)	10 minutes

Three month Follow-up (approximately 1.5 hours)

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
Questionnaire	30 minutes
Labs- Blood work	15 minutes

Six month Follow-up (approximately 5-6 hours)§

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
Questionnaires	45 minutes
ECG	30 minutes
Labs- Blood work	15 minutes
Pregnancy test (females)	10 minutes
Blood draw-biorepository only	15 minutes
Exercise Testing (six-minute walk)- two tests*	45 minutes each
Exercise Testing (treadmill)	45 minutes
MRI (with ICD evaluation)	1 – 1.5 hours

§ Activities may be split into two separate visits as needed
***A third test may be required depending on results from the first two tests.**

Twelve month Follow-up (approximately 5-6 hours) §

TEST	TIME for TEST (approximate)
Physical Exam	30 minutes
Questionnaires	45 minutes
ECG	30 minutes
Labs- Blood work	15 minutes
Pregnancy test (females)	10 minutes
Exercise Testing (six-minute walk)-two tests*	45 minutes each
Exercise Testing (treadmill)	45 minutes
MRI (with ICD evaluation)	1 – 1.5 hours

§ Activities may be split into two separate visits as needed
***A third test may be required depending on results from the first two tests.**

Telephone Contact- Twenty-four month Follow-up (approximately 20 minutes)

ACTIVITY	TIME for ACTIVITY (approximate)
Telephone Interview	20 minutes

Descriptions of Research Activities

History and Physical Exam
Your medical history and current use of medicines will be reviewed. You will also undergo a physical exam which will include temperature, blood pressure, heart rate, and breathing rate, as well as height and weight measurement.

ECG
An electrocardiogram (ECG) is a tracing of your heart rhythm and is used to record the electrical activity of your heart. These will take place during six of your visits.

Labs
A needle will be inserted into the vein of your arm and blood will be withdrawn (about 2-3 tablespoons on nine different occasions or about 18-27 tablespoons total for the entire trial). If you agree to the optional biorepository (described later in this consent form) there will be additional blood draws on five occasions.

Questionnaires
You will be asked to complete questionnaires at different times during the study.

The Minnesota Living with Heart Failure Questionnaire- this questionnaire asks how your daily activities (such as job, family life, and food habits) are affected by your condition. This questionnaire will take about 15 minutes to fill out. You will be asked these questions during the baseline period and follow-up appointments at months 3, 6, and 12.

International Index for Erectile Function (male participants only)- this questionnaire asks about how your sexual function is affected by your condition. This questionnaire will take about 15 minutes to fill out. You will be asked these questions during the baseline period and follow-up appointments at months 6 and 12.

The Female Sexual Function Index (female participants only)- this questionnaire asks about how your sexual function is affected by your condition. This questionnaire will take about 15 minutes to fill out. You will be asked these questions during the baseline period and follow-up appointments at months 6 and 12.

Exercise Testing

Treadmill- During this exercise test, you will walk on a treadmill while your heart rate and blood pressure are monitored. You will wear a mouthpiece (similar to a snorkel) or a mask, and you will breathe in and out through it while you exercise. You will have small adhesive (sticky) electrodes put on your chest and sides. The wires attached to these electrodes will connect you to a heart monitor. You will be asked to exercise for about 10 minutes or until you become tired. This test measures how much oxygen your body is using during exercise. This is an important indicator of how well your heart is working. The time it takes to complete this test varies. It is usually about an hour from start to finish. This testing will be completed at the beginning of the study and also at months 6 and 12.

Six-Minute Walk Test- You will be asked to walk in a corridor (without elevation). You will be asked to walk at your own pace, while trying to cover as much ground as possible in six minutes. You can stop and rest during the test, but you will be asked to resume walking as soon as you feel you are able to do so. After six minutes, you will be asked to stop walking. The total distance walked and symptoms experienced during the walk (e.g., chest pain, trouble breathing, a feeling of tiredness, dizziness) will be recorded. This testing will be completed at the beginning of the study and also at months 6 and 12. At each of these visits you will complete this test twice, with time in between the tests for you to rest. In rare circumstances, you may be asked to complete the test a third time, depending on the results of the first two tests.

MRI and ICD Evaluation

You will have a **Magnetic Resonance Imaging (MRI)** exam at the beginning of the study, within one month before your study product injection, and again at the 6- and 12-month visits. A MRI is used to determine how healthy your heart is and how well it works. MRI uses large magnets and radio frequency waves to make pictures of the inside of the body; no radiation exposure is involved. This test gathers information about the heart by creating moving images of the heart while it is beating. The MRI is used to look at the presence of disease in the heart.

Before this test, you will be asked if you have certain metals in your body. Additionally, **if you have a pacemaker/internal cardiac defibrillator (ICD)**, the study doctor will check your device by using a wand placed on the skin over your ICD. The study team will be checking you during the test by using a blood pressure cuff, heart monitor, and oxygen monitor throughout the scan. The MRI scans take 60-90 minutes on average, but may take a little longer (20-30 additional minutes) if you have one of these devices.

During your MRI exam, you will lie on a padded table. You will have an intravenous (IV) line placed in your arm. A soft padded coil will be placed at the area where the pictures will be taken. The coil is necessary to help the MRI machine take pictures. The table will be moved into the center of a long narrow tube. If you have a history of claustrophobia (being uncomfortable in an enclosed space), tell the study nurse in advance. A small dose of medicine <INSERT NAME OF MED HERE> can be given to help you feel less anxious. A large magnet inside the tube will begin taking pictures. When the pictures are taken, it is normal for the MRI machine to make loud banging and clicking noises. You may be asked to wear earplugs or headphones for your comfort during the exam. During the exam, the MRI staff is able to see and hear you and you can hear the MRI staff. The MRI staff will be talking to you throughout your MRI exam and may give you simple instructions, such as to hold your breath. You will be asked to lie perfectly still throughout the exam. At some point during the exam the MRI staff will stop the scanning procedure in order to put a contrast dye into a vein in the IV line in your arm. The contrast dye makes the heart more visible in the pictures.

Harvest Visit Procedures

Sedation and Bone Marrow Aspiration

You will undergo a procedure called bone marrow aspiration to collect the MSCs (cells). Prior to this procedure, you will be offered a sedative medicine <INSERT NAME OF MEDICATION HERE> to help you relax. Conscious sedation is safe and effective for patients who need minor surgery or a procedure such as a bone marrow aspiration. You may receive the medicine through an intravenous line (IV, in a vein) or a shot into a muscle. You will begin to feel drowsy and relaxed very quickly. You may fall asleep, but you will wake up easily to respond to people in the room. Your breathing will slow down, and your blood pressure may drop a little. Your nurse or doctor will monitor you frequently during your procedure to make sure you are okay. This person will stay with you at all times during the procedure.

During the bone marrow aspiration, a doctor will anesthetize (numb) a small area in the back of your hip and insert a needle into your hip bone and withdraw bone marrow. The total amount to be withdrawn is about 6 tablespoons (3 oz.) of bone marrow. This will then be sent to a laboratory at the University of Miami Interdisciplinary Stem Cell Institute that uses a special process to select the MSCs from the marrow and grow more of these cells to produce the study dose.

As required by the cell processing facility and the Food and Drug Administration (FDA), your blood will be tested for certain viruses such as hepatitis and HIV. If you test positive for active Hepatitis B, Hepatitis C, or HIV you will not be able to take part in this study. In addition, the lab is required by law to report positive results to <INSERT ALL RELEVANT STATE REPORTING AGENCIES>. Reportable data may include: patient name, birth date, ethnicity, race, residence, date of specimen collection, treatment prescribed or dispensed, treatment date, doctor name, address, phone number, and other information related to the case. You will also be told of a positive HIV or Hepatitis B or C test.

Right Heart Catheterization (with or without heart biopsy)

This test, also called a "right-heart cath", allows your doctor to test the pressures of the inside of the heart's right chambers, where blood returning from the body is pumped into the lungs to receive a fresh oxygen supply. During the test, the tip of a catheter (a long, thin, bendable tube) is inserted into a vein in the neck or upper thigh. Using a TV screen and x-rays, a specially-trained cardiologist threads the catheter along the vein, through the heart, and into the blood vessels leading to the lungs. During the procedure, cardiologists can examine function of the heart, check blood pressure in heart chambers, and measure blood-oxygen levels in different parts of the heart.

Depending on the treatment group to which you are assigned, during the right heart cath procedure, you may or may not have tissue samples collected. The collection of tissue (also called a heart biopsy) is needed to collect the tissue that will be used to produce c-kit+ cells. If you are not assigned to a group that will receive c-kit+ cells, no tissue will be biopsied but pressures are still collected; the procedure will simulate a biopsy however so that you will not know whether heart tissue is collected or not (this is also called a sham procedure). Sham procedures are used in research in order to reduce risk to participants but also prevent them from knowing their true treatment assignment.

During a biopsy (not sham) a tiny portion of heart tissue (the size of a pin head) is removed. If you undergo the biopsy, you will have up to six such portions removed during this procedure. For this test, your skin is scrubbed and numbed. Then, a catheter (a small tube thinner than a piece of spaghetti) is inserted either into a vein in your neck (jugular) or into the femoral artery of your leg. A type of moving x-ray image (called fluoroscopy) is used to guide the insertion. A catheter that has jaws in its tip, called a bioptome, is then introduced and threaded into your heart. Once the bioptome is in place, small pieces of heart muscle tissue are removed from the inner wall of the heart. This tissue will then be sent to a laboratory, at the University of Miami Interdisciplinary Stem Cell Institute, that uses a special process to grow c-kit+ cells to produce the study product dose. For those undergoing a sham procedure, a catheter will be inserted as described in the right heart cath procedure; however tissue samples will not be collected. The procedure (biopsy or sham) takes about 30 to 45 minutes. You will be observed for approximately another hour after the test.

Echocardiogram (Echo)

An echocardiogram (echo) is an ultrasound image of your heart. It is used to see how well your heart is working. First a gel is put on your chest. A device called a transducer is moved over the surface of your chest. The transducer picks up the sound waves from your heart and sends them to a monitor to show a picture. This test checks the heart size, how well it pumps, and how well the heart valves look and work. There is no exposure to radiation with this test. As part of this procedure, a dye may be injected into one of your veins to make the image clearer. You will have three echoes during the study. There will be an echo before and after the right heart catheterization procedure and another after the study product injection, during the hospitalization period of the study.

Study Product Delivery Procedures
The study team will schedule this procedure to take place about 14 weeks after your bone marrow aspiration and right heart catheterization procedure. This timeframe is needed to grow the amount of cells in the study product (MSCs, c-kit+ cells, and the combination of the two).

Cardiac Catheterization/Left Ventricular Angiocardiography and NOGA Mapping
During this procedure for the study, the doctor will insert a long, narrow tube, called a catheter, into a blood vessel, usually in your leg, and then guide the catheter to your heart with the help of a special X-ray machine. X-ray dye is then injected through the catheter so that the X-ray machine can take pictures/movies of the left ventricle (left lower chamber) of your heart. The doctor uses a special device, called NOGA, which monitors the electrical and mechanical function of your heart. This procedure, referred to as NOGA mapping, will help your doctor find out which part of your heart muscle is still healthy but is not receiving enough blood and oxygen because this is the part that is most likely to respond to the study product injections. This helps the doctor decide where to inject the study product.

Study Product Injection
Your doctor will use a special catheter with a retractable needle (called a NOGA Myostar catheter) to inject the study product into the damaged area of your heart muscle. This catheter is investigational and not approved by the FDA. There will be about 15 injections of a very small amount (a drop) of fluid containing millions of cells, or placebo, into your heart muscle. Following the procedure, you will be watched carefully, overnight, in a telemetry (ECG monitored) unit. You will have an echocardiogram after the study product injection, during the hospitalization period of the study (see description of the procedure on the previous page).

Temperature Log
You will be asked to take and record your temperature two times a day for one week following your injection procedure. The purpose of this is to monitor for infection. You will be given a "Temperature Log" before you are discharged to keep track of your temperatures twice a day for 1 week. Instructions for reporting an increase in temperature are on the log. You will be asked to turn in your log at your one-week visit. Should signs of infection be present, your study doctor will ask you to return for a physical examination, and if necessary you may be started on an antibiotic treatment.

FOLLOW-UP EVALUATIONS

Follow-up Visits
You will be asked to return for follow-up visits at 1 week and 1, 3, 6 and 12 months after your injection procedure. A brief telephone interview will be conducted at 24 months. Please refer to the schedule of activities for specific tests and assessments to be performed at each visit.

Time Commitment
The study elements and time are: (1) <u>baseline, harvest, MRI, and injection visit procedures</u>- includes baseline testing, bone marrow harvest, right heart catheterization, MRI, and injection procedure (about 18-21 hours over several days); (2) <u>overnight stay following injection and day of discharge activities</u> (about 24 hours); (3) <u>follow up visit procedures</u>- includes five follow up appointments at 1 week and 1, 3, 6, and 12 months after the injection procedure (range from 1.5-5 hours each, 12-16 hours total); and (4) <u>follow up telephone interview at 24 months</u> (about 20-30 minutes). **The total *maximum* number of hours is approximately 62 hours**.

ALTERNATIVES

You may choose not to participate in this study. Alternative forms of therapy exist for patients who have chronic heart problems. If you choose not to take part, you can receive the standard therapy for people who have previously had a heart attack. Optimal medication management would be the most common alternative therapy for you.

RISKS AND/OR DISCOMFORTS

Your doctor will explain all the possible risks of the procedures associated with this study. The specific risks and discomforts for each test are described below. As with any procedure, whether it is investigational or approved, there may be risks which are unanticipated or unknown at this time.

ECG

It may be necessary to shave small areas of your chest to apply the adhesive patches. You may experience slight discomfort when the adhesive patches are removed.

Labs

Risks associated with drawing blood from your arm include pain, bruising, site swelling, light-headedness and, on rare occasions, infection.

Special note to women: Being part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman able to become pregnant, a pregnancy test will be done and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures while taking part in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as tubal ligation or hysterectomy), 2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) intrauterine device (IUD). If you become pregnant while taking part in this study or if you have unprotected sex, you must inform the study doctor immediately.

Questionnaires

Some of the questions on the questionnaires ask you to consider areas of your life that you may not commonly think about. There are no physical risks from completing the survey, but the questions could cause you concern or possibly emotional distress.

Exercise Testing (Treadmill and Six-minute walk test)

The most common discomfort after exercising is muscle soreness and feeling tired. You may also feel some joint pain. If you feel any soreness or pain while you are exercising on the treadmill, you may stop at any time. Very rarely, during exercising, it is possible that you may experience an increase or decrease in your blood pressure, or heart rate, or you may feel dizzy. There is a very small risk that you could develop a heart attack or stroke while you are walking on the treadmill or shortly thereafter. There is a small risk that you could experience worsened heart failure. The potential risks of the six-minute walk test are episodes of temporary lightheadedness, fainting, chest discomfort, leg cramps, and very rarely, heart attack.

Magnetic Resonance Imaging (MRI) procedure
There may be mild to moderate risks and discomforts with placement of an IV line, administration of medications, or the blood draw. The risks of starting an IV and drawing blood include pain, redness, minor bleeding, swelling, and bruising at the injection site. Rarely, lightheadedness, fainting, and infection might happen. The nurse will monitor you and appropriate treatments will be given if you develop any complications.

You may feel uncomfortable or tired from lying down in the MRI machine. You will be asked to hold your breath. Each breath hold lasts about 10-15 seconds. If you are anxious or have a history of claustrophobia (feeling uncomfortable in small enclosed spaces), you may experience this during the MRI; as noted above, medication can be made available to help you relax. Administration of contrast dye may cause nausea, vomiting, or headache. Allergic reactions to contrast dye are rare, but there are extremely rare instances of reactions causing death.

The contrast dye used in the cMRI procedure is referred to as a gadolinium based contrast agent (GBCAs). After it is given, GBCAs leave the body mostly through the kidneys. Recent medical papers report some deposits from GBCAs remain in the brains of some patients who have four or more contrast MRI scans, long after the last dose is received. Recent studies conducted in humans and animals have confirmed that these deposits can remain in the brain, even in people with normal kidney function. It is unknown whether these deposits are harmful or can lead to adverse health effects. Available information does not identify any adverse health effects. However, this issue continues to be studied by the FDA and you will be informed should any new specific danger or threat to your health emerge.

The contrast dye may also induce kidney damage or nephrogenic systemic fibrosis (NSF), a serious and potentially fatal disease that involves the skin, muscle, and internal organs. The risk of this is increased with patients who already had some evidence of kidney disease or diabetes, or are dehydrated. In general, if a patient has normal kidney function, then the risks of kidney failure caused by contrast dye are small. Your kidneys will be tested prior to any dye that would be given. You should contact your doctor if you develop signs or symptoms of NSF, which include: Skin burning or itching, reddened or darkened patches and/or skin swelling, hardening and/or tightening; yellow raised spots on the whites of the eyes; joint stiffness, limited range of motion in the arms, hands, legs or feet; pain deep in the hip bone or ribs; and/or muscle weakness.

There is no radiation (x-ray) exposure from MRIs. There is a risk of heat injury from radiofrequency coils and the cables to the coil and monitoring equipment (heart monitor, oxygen monitor, etc.). Please report any heating or burning sensation immediately and the scan will be stopped.

For those with pacemakers and ICDs: Magnetic resonance imaging works by generating a strong magnetic field. Both pacemakers and ICDs are devices that contain wires with electrodes that are connected to one or more of your heart's chambers. These are designed to restore normal rhythm to the heart by sending electrical pulses through the wires. It is important that you know that some, but not all, of these devices are approved by the FDA to be used in a MRI scanning environment. Researchers have imaged hundreds of patients with such devices under careful monitoring without incident. The investigators of this study have undergone training in these imaging techniques and will follow the best safety practices from these researchers. The powerful magnetic fields and radio waves that are part of MRI scans could cause the ICD wires to overheat, potentially damaging heart tissue. MRIs can induce unwanted currents that would either make the heart beat wildly, or in the case of ICDs, cause an unnecessary shock.

Pacemakers and ICDs can be temporarily reprogrammed so they don't react to an MRI's magnetic field. Reprogramming a pacemaker or ICD can be done noninvasively, through the skin with a wand like device. Pacemakers can be put into the "inhibited pacing mode," which means the heartbeat has to get very slow before the device activates and starts helping the heart beat regularly. The part of the ICD that senses a racing, irregular heartbeat (tachycardia) is temporarily disabled.

If you have a pacemaker/ICD, it will be monitored during the MRI scan. Theoretically, the MRI scan could interfere with, or possibly damage, your pacemaker/ICD, but its functioning will be verified immediately after the procedure. During the scan you are at an increased risk of experiencing an arrhythmia, which could be life threatening or fatal (result in death). A cardiologist with pacemaker/ICD expertise will check your device before, during, and after the scan to ensure your safety. Trained life support staff will be present and a crash cart (defibrillator) will be available during the procedure should you experience a life threatening arrhythmia. The staff will keep in contact with you visually and vocally throughout the procedure. You will be monitored continuously during the scan.

Harvest Procedures

Anticoagulation Medications

If you are taking anticoagulation medications (i.e. blood thinners) at the time of the harvest procedures (bone marrow aspiration and right heart catheterization), some of these medications (e.g. Coumadin) may be stopped for a short period before the procedures; during which time you may be at an increased risk of a stroke. It is very important that you inform the research team immediately of any symptoms of headache, dizziness, light-headedness, blurred vision, slurred speech, facial drooping, decreased sensations anywhere on your body, or weakness or a decrease in strength of your arms or legs. You will be closely monitored, during any interruption in anticoagulation therapy, for the events listed above.

Sedation

Possible risks of conscious sedation can include: problems with your breathing (if you are given too much medicine). A doctor or nurse will be watching you during the whole procedure and will have special equipment to help you with your breathing, if needed. Because of the sedation, your physician may request that you have someone available that can drive you home.

Bone Marrow Aspiration

Possible risks of bone marrow aspiration include bruising, bleeding, infection, hematoma (a swelling filled with blood) at site of biopsy, brief discomfort in your hip area and faintness from the procedure. It is possible you could experience worsening of your heart failure symptoms. There is a possibility of a fat embolism (fat tissue passing into the bloodstream and blocking a blood vessel) leading to shortness of breath, confusion, drowsiness, rash, fever, or seizure.

Right Heart Catheterization with or without Heart Biopsy

During the right heart catheterization you will receive some radiation (see the Radiation Risks Section below). You may experience stinging from the numbing medicine, bruising, and discomfort from lying flat on the exam table for 20-30 minutes. Possible risks include decreases in blood pressure and ICD firing due to abnormal heart rhythms that last only a few seconds and go away. Less likely risks include bleeding, infection, serious and long-lasting heart rhythm problems, injury to the pulmonary artery, blood clots in the lungs, damage to the walls of the heart, and puncture of the heart wall with a risk of death. One patient in this study has died from a puncture of the heart wall following biopsy.

Study Product Delivery Procedures

Cardiac Catheterization and NOGA Mapping

Your study doctor will fully explain the catheterization procedure and associated risks to you. Some problems that might happen include (but others could occur) oozing of blood around where the catheter (small hollow tube) goes into your skin, a swelling filled with blood (hematoma) under the skin, allergic reaction to the dye that is injected when the doctor looks at the heart vessels (angiography) either during or following the study product injection procedure, abdominal pain, or formation of a blood clot (a blockage) at the place where the catheter goes into your skin. A blood clot could stop the flow of blood or hurt the blood vessel. If blood flow is stopped or slowed a lot, the body parts that rely on that blood could also be damaged, which could lead to loss of function or surgical removal of the body part, or could worsen your heart condition and its symptoms. Other problems that could happen because of this test are: local nerve damage (loss of feeling), infection, changes in the how your heart beats, stroke, and heart attack. Some temporary problems that might happen are: temporary movements (spasm) of a muscle, vein, or artery; pulling apart of blood vessel walls (separation of the layers of the walls of a blood vessel); or sudden blockage (closure) of a blood vessel. A very rare complication could result in death or a need for an urgent coronary artery bypass graft (open-heart surgery). Serious complications, including death, happen in less than 1 in every 1,000 tests that are performed.

The risks of the use of the iodine that is in the contrast media for the heart angiography procedure are rare. Some problems that might occur are hypersensitivity or even severe allergic reactions, or decreased kidney function, particularly if you have underlying kidney problems. Your doctor will measure your kidney function before this procedure to find out if your kidneys are working properly.

The possible risks of NOGA mapping include, but are not limited to: damage to blood vessels, bleeding, infection, inflammation of the sac surrounding the heart, damage to kidneys, a small risk of heart attack, stroke, damage to the heart valves, perforation (a small hole) in the heart causing blood to accumulate around the heart, irregular heartbeats (including ventricular tachycardia and ventricular fibrillation), possible ICD firing, decreased blood pressure, dislodgement of material into other arteries leading to possible blockage, radiation exposure and a very small risk of death. You will receive some radiation as part of the NOGA study (see the Radiation Risks Section below).

Study Product Injection

The catheter used to inject the study product is investigational (not yet approved for this use by the FDA). Some problems that might happen include (but others could occur): decreased blood pressure, irregular heartbeats, chest pain or discomfort, possible firing of ICD, damage to the heart muscle, perforation of the heart causing blood to accumulate around the heart, bleeding, heart attack, stroke, dislodgement of material into other arteries (possibly causing blockage), need for emergency surgery such as coronary re-vascularization, and death. It is possible that a small amount of cells will enter the bloodstream of the heart rather than the heart muscle. If the injection catheter penetrates through the heart (from inside to outside) and cells appear in the fluid filled area surrounding your heart, which cushions the heart as it moves (pericardial space) there is a possibility of potentially harmful effects which could cause an inflammatory response. Injection directly into the heart muscle also may cause inflammation or irritability. Your medical team will closely monitor you to minimize the chance of any problems occurring during the procedure.

Cell Processing Procedure
Processing the cells is done under strict sterile conditions; however, there is a rare chance that the cells could get contaminated while being processed. Testing will be done on the cells; however, it takes about 2 weeks to get the results. If the tests show your cells were contaminated, you will be notified and instructed on whether or not you should be treated with antibiotics. You will be taking your temperature twice a day for one week, which may help determine if you are developing an infection before the test results are known.

Samples will travel from this location to a laboratory at the University of Miami Interdisciplinary Stem Cell Institute for processing and will be returned back to this location. There may be some circumstances where we are unable to give you the processed cells; such as a processing failure or poor quality of the cells. If events such as these occur, the failed product will not be released back to your doctor and you will not receive it; instead you will receive the placebo. If you are randomized to the combination product, and only one of the products fails processing but the other product passes, you will be given the product that passes (e.g. c-kit+ cell fails but MSC passes, you will receive MSCs only). There are steps in place to prevent these failures from happening include continuous temperature monitoring of the product during travel and the use of standard operating procedures for processing, which will identify any problems with the study product before it is released.

Radiation Risks
This research study involves exposure to radiation during the catheterization/NOGA mapping procedure and the right heart catheterization procedure. This radiation exposure is not necessary for your routine medical care and is for the purposes of this research study. These exposures are, however, similar to the exposures many non-research patients encounter in the course of their medical evaluations for heart problems. The Radiation Safety Committee has reviewed this use of radiation and has approved this use as involving minimal risk.

Although each organ will receive a different dose, the expected total amount of radiation exposure you will receive in this study is approximately 2.4 rem. This calculated value is known as the effective dose and is approximately half of the 5 rem (or 5000 millirem) annual radiation dose that is allowed in the United States for medical and other workers who are employed in radiation areas such as Nuclear Medicine and Radiology departments.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources such as the sun, outer space, and radioactive materials that are found naturally in the earth's air and soil. The dose you will receive from this research study is about the same amount you would normally receive in 8 years from these natural sources. The investigator can provide you with a contact person if you would like more information about radiation exposure.

The effects of radiation exposure on humans have been studied for over 60 years. No harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been clearly demonstrated, some scientists believe that radiation can be harmful at any dose – even low doses such as those received during this research. Risks might include a small increase in the risk of cancer from this radiation. This change in risk is small and cannot be measured directly. Compared to other everyday risks, such as flying in an airplane or driving in a car, this increase is considered slight.

Risks That Are Not Known
Because cell therapy treatment is investigational, that is, not FDA approved, there may be risks that we do not know about at this time. There are no long-term safety data available. If we discover new risk information during the study, we will share this information with you.

Participation in more than one research study or project may further increase the risk to you. If you are already enrolled in a research study, please tell the person reviewing this consent with you before enrolling in this or any other research study or project.

BENEFITS

It is not known whether this procedure is beneficial. It may improve your heart's ability to pump blood through your body, and the information gained from the research study will help answer these questions, not only for you but, for the general population. It is possible that you may not receive any direct benefit from this research study. The information learned in this research study may help researchers better understand how safe it is to use these cells in the heart and may help advance medical knowledge in general.

WITHDRAWAL

You may withdraw your consent to take part in this study at any time. If you choose to withdraw from the study, you will receive the usual standard of care without any loss of healthcare services. Also, your doctor may end your participation if continuing in the study does not appear to be in your best medical interest. <INSERT INVESTIGATOR NAME HERE>may end your participation in the study at any time. If you decide to withdraw from the study, your data collected prior to withdrawal may still be used, up to the point of withdrawal.

Your doctor or the sponsor can stop the study at any time, for any of the following reasons: if you have an adverse effect from the study product or procedures, if you need a treatment not allowed in this study, if you are unable to keep your appointments with your doctor, if you do not later consent to future changes that are made in the study plan, if the study is stopped by the FDA or the sponsor ahead of schedule, or for any other reason. Should the study be stopped, your study doctor will discuss other options with you.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration (FDA), the <INSERT IRB NAME HERE>, the sponsor of this research (NHLBI), and the Data Coordinating Center for the study may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of the date of birth, subject initials, and treatment/service dates. You will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign, which details the use and disclosure of your protected health information.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PERMISSION TO RELEASE PERSONAL HEALTH INFORMATION

Authorization for Use and Disclosure of Health Information for Research Purposes

We understand that information about you and your health is personal, and we are committed to protecting the privacy of that information. Federal law requires us to get your permission to use your protected health information for this study.

Protected health information includes all information about you collected during the research study for research purposes and the information about you in medical records that is related to the research study. The information collected may include your name, date of birth, address, social security number, and results of all the tests and procedures done during the study.

If health information about you is required, the reviewers may need your entire medical record.

USE AND DISCLOSURE COVERED BY THIS AUTHORIZATION

Who will disclose, receive, and/or use the information? The following people and organizations may disclose, use, and receive the information, but they may only use and disclose the information to the other parties on the list, to you or your legally responsible person, or as otherwise permitted or required by law.

- Investigator (study doctor), research coordinator, members of the research staff, and the Study Sponsor.
- Your study records and your entire medical record, including your personal health information may be inspected by regulatory authorities in the United States, such as the Food and Drug Administration (FDA), clinical monitor or auditor, any people or companies contracted by the sponsor (NHLBI), the Data Coordinating Center, or by <INSTITUTION> or the <INSERT IRB>. These reviews are done to check on the quality of the study.
- Members of the hospital's administrative staff who are responsible for administering clinical trials and other research activities

The results of the study may be published in a medical book or journal, or presented at meetings for educational purposes. Neither your name, nor any other personal health information that specifically identifies you, will be used in those materials or presentations.

You may ask the study doctor to see and copy your personal health information related to the study. You may ask the study doctor to correct any study related information about you that is wrong. This permission to share your personal health information will expire ten years after the end of the study. If you no longer want to share your personal health information, you may cancel your permission at any time by writing to the study staff and/or the study doctor at the address below:

<Insert Investigator Name, Address, Telephone number>

If you cancel your permission after you have started in the study, the study staff and the study doctor will stop collecting your personal health information. Although they will stop collecting new information about you, they will need to use the information they have already collected to evaluate the study results. If you start the study and then cancel your permission, you may not be able to continue to take part in the study. This is because the study staff and/or study doctor would not be able to collect the information needed to evaluate the study procedure.

The study doctor and study staff will make every effort to keep your personal health information private. But after the study staff or the study doctor share your personal health information from the study, federal privacy laws may not keep it private. There might be laws in your state or other federal laws that would protect the privacy of this information.

IN CASE OF INJURY

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment for the injury. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You or your insurance provider will have to pay for those services just like any other medical care. You should report any injury to Dr. _____ at <INSERT principal investigator's name and phone number here> and to <INSERT IRB name and phone number here>. You will not give up any of your legal rights by signing this consent form.

STUDY COST

All testing and services done, that would not have been done but for your taking part in the study, will be provided at no cost. You (or your insurance) are responsible for all other costs that are part of your usual medical care and that would have been done regardless of your enrollment in the study. If your health insurance or Medicare requires any co-payment, co-insurance or deductible associated with your usual medical care, you will be responsible for making the payment.

You will not be paid for taking part in this study <IF SITE HAS ABILITY TO PROVIDE REIMBURSEMENT FOR PARKING FROM THE SITE BUDGET THIS CAN BE INCLUDED HERE>. If you received a bill that you believe is related to your taking part in this research study, please contact <INSERT SITE CONTACT INFO HERE> with questions.

QUESTIONS

If you have questions about this clinical study or would like more specific information, you may contact the principal investigator <INSERT INVESTIGATOR NAME and 24-HOUR CONTACT NUMBER>. If you have any questions about your rights as a research study participant, you may contact the<INSERT IRB NAME AND CONTACT INFO HERE>.

SIGNATURES

Sign below only if you understand the information given to you about this research study and choose to take part. Please make sure that any questions have been answered and that you understand what is being asked of you in this research study. If you have any questions or concerns about your rights as a research subject, call the <INSERT IRB NAME AND CONTACT NUMBER HERE>. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____

Printed Name of Subject or Legally Authorized Representative

_____ _____ _____

Signature of Subject or Legally Authorized Representative Date Time (am/pm or 24 hr)

I have fully explained the procedures, identifying those, which are investigational, and have explained their purpose. I have asked whether or not any questions have arisen regarding the procedures and answered these questions to the best of my ability.

_____

Printed Name of Person Obtaining Informed Consent

_____ _____ _____

Signature of Person Obtaining Informed Consent Date Time (am/pm or 24 hr)

OPTIONAL BLOOD AND TISSUE DONATION

In addition to the main part of the research study, there is an optional part of the research. You can participate in the main research without agreeing to take part in this optional research.

You have the choice of allowing us to save bone marrow, blood, and explanted heart tissue samples, from research analysis described in the consent, at a research storage laboratory facility (Biorepository Core-BRC), to be used to help further understand how cells function. If you agree to participate, your samples will be shipped to Dr. Doris Taylor at the BRC, located at the Texas Heart Institute in Houston, Texas.

Dr. Taylor and her colleagues will use standardized processes and procedures to study which types of cells and related proteins might best help in the treatment of cardiovascular diseases. The remainder of the samples will be stored for future research. It is important that you know these samples: 1) will be used for research purposes only (not for profit); 2) will be stored by the BRC for up to ten years without personal identifying information, meaning it would not include any information such as your name, address, or other data that could be easily used to identify you; and 3) will be shared with researchers who will conduct studies to improve our understanding of the effects of cell therapies. Only qualified researchers will have access to the samples and data at a later date. No future studies will happen unless the investigators requesting your samples receive approval from the Institutional Review Board (IRB) that oversees their work. The purpose of the IRB is to protect the rights of participants in research studies. If, for any reason, you withdraw or are excluded from the study, and you have consented to donate your samples, the research team will discuss with you your options; including the possible withdrawal of consent to donate the samples. Samples will be destroyed after 10 years.

It is unlikely that these studies will have a direct benefit to you, your heirs or devisees. The results of these tests will not have an effect on your care and will not be provided to you. To avoid potential discrimination from your employer or your medical insurance, neither your doctor nor you will receive results of these future studies, nor will the results be put in your health record.

Although we have systems in place to protect your identity, there is always a potential risk of loss of confidentiality. Sometimes blood and tissue samples are used for genetic research about diseases that are passed on in families. Even if your samples are used for this kind of research, the results will not be put in your health records and every effort will be made to keep your identity confidential. The study investigator <INSERT INVESTIGATOR NAME HERE> does not have ownership or proprietary interest in (rights to) these samples. There are no plans to provide financial compensation to you, your heirs or devisees (those listed in your will).

If you do not wish to donate any samples to the BRC, it will not affect your eligibility for taking part in this study.

Please review the sample requests below and indicate your preferences regarding the optional collection and storage of samples for future research studies.

COLLECTION OF SAMPLES

Bone marrow samples- In an effort to get the number of cells needed for the injection procedure, it is possible that we may collect more cells during the bone marrow harvest than are required for the study dose.

☐ I do voluntarily consent to donate my excess processed bone marrow to the biorepository.

☐ I do not consent to donate my excess processed bone marrow to the biorepository.

Explanted Heart- In the event of death or your heart transplant, the researcher requests your permission to do an examination of your old heart so that researchers can gain a better understanding of the consequences of cell transfer.

☐ I do voluntarily consent to donate my old heart, in the event of my death or following my heart transplant, to the biorepository.

☐ I do not consent to donate my old heart, upon my death or transplant, to the biorepository.

Blood samples – (each draw is about 1.5 tablespoons) will be collected at:

- Study product delivery visit
- During four follow up visits (day 1, week 1, month 1, and month 6)- these samples will be collected during the blood draws already scheduled for the main study.

☐ I do voluntarily consent to donate additional blood samples to the biorepository.

☐ I do not consent to donate additional blood samples to the biorepository.

USE AND STORAGE OF SAMPLES FOR FUTURE RESEARCH

Future research studies (e.g. study of proteins) about cardiovascular diseases.

☐ Yes, I agree for my samples to be used and stored for *cardiovascular research*.

☐ No, I do not agree for my samples to be used and stored for *cardiovascular research*.

☐ Did not consent to any sample collection (in previous section)

Genetic research studies (e.g. using DNA and RNA) about cardiovascular diseases.

☐ Yes, I agree for my samples to be used and stored for *genetic* studies of cardiovascular disease.

☐ No, I do not agree for my samples to be used and stored for genetic studies of cardiovascular disease.

☐ Did not consent to any sample collection (in previous section)

De-identified information about me (e.g. age, smoking history, etc.) may be included in a data set that is available to qualified researchers outside the study.

☐ Yes, I agree for de-identified information about me to be included in a data set.

☐ No, I do not agree for de-identified information about me to be included in a data set.

☐ Did not consent to any sample collection (in previous section)

By signing this consent form, you indicate that you have reviewed the options and indicated your preferences for the collection of your specimens as well as their use and storage for future research.

_____

Printed Name of Subject or Legally Authorized Representative

_____ _____ _____

Signature of Subject or Legally Authorized Representative Date Time (am/pm or 24 hr)

I have fully explained the procedures, identifying those, which are investigational, and have explained their purpose. I have asked whether or not any questions have arisen regarding the procedures and answered these questions to the best of my ability.

_____

Printed Name of Person Obtaining Informed Consent

_____ _____ _____

Signature of Person Obtaining Informed Consent Date Time (am/pm or 24 hr)

This study <INSERT IRB APPROVAL NUMBER HERE> has been reviewed by the <INSERT NAME OF IRB HERE> of <INSERT INSTITUTION NAME HERE>. For any questions about research subject's rights, or to report a research-related injury, call the IRB at <INSERT IRB PHONE NUMBER HERE>.