UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	Matching Perfusion to Metabolic Activity in HFpEF
Principal Investigator:	Payman Zamani, MD, MTR Perelman Center for Advanced Medicine 3400 Civic Center Boulevard, South Tower, 11-176 267-496-5380
Emergency Contact:	Payman Zamani, MD, MTR 267-496-5380 24-Hour Emergency Number: 215-662-4000 (Ask for cardiology fellow on call)
Sponsor	National Institutes of Health

Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to test whether a dietary supplement called Potassium Nitrate (KNO_3), with and without 2 other supplements called Propionyl-L-Carnitine (PLC) and Nicotinamide Riboside (NR), improves exercise in participants with Heart Failure with Preserved Ejection Fraction (HFpEF). This study will also test inhaled oxygen can tell us who is most likely to benefit from which therapy.

If you agree to join the study, you will be asked to complete the following research procedures: take each of the following 3 study treatments in random order for 6 weeks each: (1) Potassium Nitrate (KNO_3); (2) Combination therapy with Potassium Nitrate + Nicotinamide Ribose + Propionyl-L-Carnitine, and (3) Potassium Chloride which will be used like a placebo (something with little impact on the body). You will also be asked to complete a muscle biopsy, exercise test, and MRI of your muscles after each study treatment. You will also be asked to perform one DEXA (bone density) scan at the beginning of the study. You will be compensated between $50-$100 (maximum $600), depending on the visits you complete, and your participation will last for approximately 7 months.

At this time, we do not have any medications that consistently help people with HFpEF. Even a small improvement in exercise is expected to help HFpEF participants do what they want to do with less limitation, increasing their quality of life and independence.

The most common risks of participation are:
Study drug related, including: nausea, vomiting, diarrhea, changes in stool, bloating, headache, muscle soreness/cramping.
Exercise related, including feeling tired and short of breath.
MRI scan related, including feeling uncomfortable in the MRI scanner, or getting minor leg discomfort from being asked to perform calf exercise.
Muscle biopsy related, including muscle soreness from the biopsy.
There is always a risk of breach of confidentiality from participating in a research study.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you have HFpEF. Your doctor may be an investigator in this research study. You do not have to participate in any research study offered by your doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or doctor. Being in a research study is different from being a patient. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form. You will be given a copy of the signed forms.

What is the purpose of this research study?

The purpose of this study is to compare whether Potassium Nitrate (KNO_3), with and without Propionyl-L-Carnitine (PLC) and Nicotinamide Riboside (NR), will improve exercise in people with HFpEF. This study also aims to assess whether a participant's response to the different therapies tested in this study can be predicted by how the muscles respond to extra oxygen during an MRI scan. This may help tell us who is most likely to benefit from our different interventions. The study drugs to be tested are not approved by the FDA and should be considered investigational.

How long will I be in the study?

You will be asked to participate for approximately 7 months (8 visits total). Each visit will last about half a day.

What am I being asked to do?

If you choose to participate in this study, you will be asked to take all 3 study drug therapies:

1. KNO_3 alone
2. Combination therapy with KNO_3 + PLC + NR
3. Potassium chloride, which will be used like a placebo. A placebo is something that we give which we do not think will have a significant effect on the body.

These treatments will be given in a random order that is unknown by you, the study team, and your doctors. The different therapies will each be taken for 6 weeks. At the end of each therapy, tests will be performed to assess the response of your muscles and body to the study drugs. There will be a 2-week 'washout' period in between each therapy during which you will not take any study medications. You will also be asked to undergo several research procedures that are described below.

Note: We want to inform you that there may be other risks in participating during the COVID pandemic. Please see the COVID information sheet for more details.

VISIT 1: Baseline Visit:

During the first visit, we will perform tests to make sure you fit the criteria for our study. **Prior to Visit 1 – a member of our research team may contact you to discuss foods that we would like you to avoid during the study and to provide additional information.** After you review and sign this informed consent form, the following procedures will be performed:

- Health and medication questions – You may be asked about your general health, your medical history, the medications you take, as well as other questions about your age, gender, race, and ethnicity.
- Vital signs and physical exam – We will check your blood pressure and heart rate, and a qualified member of our staff will perform a brief physical exam including height at weight.
- Questionnaire – a member of our research team will speak to you about foods that we would like you to avoid during this study. We will also give you a questionnaire that asks you questions about your symptoms and how you feel you are functioning in your day-to-day life (Kansas City Cardiomyopathy Questionnaire).
- Sample collection – We will draw blood from you. Blood will be drawn by inserting an intravenous catheter ("an IV") into a vein in your arm. We will measure various substances in the blood that tell us about the pressures in your heart, your nitrate levels, and your methemoglobin levels. We will discuss methemoglobin more below, but in brief, this is a compound that can accumulate in the blood and make it more difficult for your blood to carry oxygen to the body. Some drugs, and possibly potassium nitrate, may increase your methemoglobin levels, so we want to check

this. We will draw ~4 tablespoons of blood during the blood draw. We will also collect saliva (spit) and urine samples. Samples will also be set aside for research.

- Echocardiogram – This procedure is similar to previous echocardiograms that you may have had. In this procedure we put some gel on the skin on the left side of your chest and use a probe to take pictures of the heart and blood vessels. We may also take pictures of your lungs. This takes approximately 45 minutes.
- Electrocardiogram – During this procedure, we will place electrodes (stickers) on your chest to capture the electrical signals from the heart.
- Tonometry – This is a simple non-invasive test in which we will examine the pressure in your blood vessels. This test will allow us to determine how stiff your arteries are and to measure the pressure your heart is pumping against. This test will be done by a trained member of our team over approximately 30 minutes. Sticker-like electrodes will be placed over your skin on the chest to measure the electrical current generated by your heart. Next, the investigator will gently put the tonometer, which looks like a pencil, against your wrist, the side of your neck, and finally in your groin to measure the pulse.
- Body Composition – We will measure your body composition (for example, the amount and distribution of fat and muscle) using a method called dual energy x-ray absorptiometry (DEXA). This method uses a very low-powered x-ray beam to scan your muscles and your bones. The results are analyzed by a computer that estimates the make-up of your body. The test is done while lying on the soft tabletop of the DEXA machine. It does not involve being enclosed inside a tunnel. This test can take up to 30 minutes.
- Exercise Test -
    - Maximal effort exercise test: We will ask you to perform a bicycle exercise test to assess your maximum exercise ability. You will be lying on your back. The test will begin with a low level of resistance that will then increase every 3 minutes. The goal is to exercise as long as you can. We will be monitoring you throughout this period and will stop you if we see something unsafe. When you stop exercising, we will ask you to remain lying in the same position for about 6 minutes while we continue to collect information about your recovery. The total length of this bicycle exercise test will depend on you and how long you can exercise. During bicycle exercise testing, you will breathe through a mouthpiece that is connected to a machine that monitors the air that you breathe in and out. Specifically, the machine tells us about how much oxygen you are using, and how much carbon dioxide your body is making during exercise. We will also continuously monitor your heart rate and rhythm, and we will be checking your blood pressure frequently during the study. We will also monitor the oxygen levels in your blood using a finger or ear probe. This information will allow us to determine how much oxygen your body is using during exercise, the electrical conduction of your heart, how fast your heart is beating during exercise, and how much pressure there is in your arteries during exercise. During exercise and recovery, we may obtain additional data such as pictures of your heart, measures of the stiffness of your arteries, and blood samples. When/if available, we may also place a special device over your calf and forearm muscle. These

devices, called Near-Infrared Spectroscopy devices, or NIRS in short, use light to measure the amount of oxygen in your muscles. The device is smaller than an iPhone and rests on your skin. There is no pain or discomfort associated with this, and you do not feel the device measuring the levels.

- Submaximal effort exercise test: After a rest interval of at least 1 hour and eating a lunch that will be provided for you, you will undergo a submaximal exercise test. We will have you exercise as described above but only at 75% of the resistance achieved during the maximal effort test. The goal is to exercise for as long as you can at this workload.

If you meet all the criteria after all of the data from this visit has been reviewed, you will be given study drugs with instructions on when and how to take it. You will take the study drugs orally. Every participant will receive all of the different interventions; however, the order in which the participant gets the treatments will be different. This is called "randomization." Neither you, the study team, nor your doctor will know which study therapy you start with or are taking during the study. We can find out this information if needed due to an emergency.

There are a few lifestyle changes that we would like you to follow during the study:

(1) We would like you to avoid foods that are high in 'inorganic nitrate' during the study because inorganic nitrate is one of the study drugs that we are testing. You will be given an information sheet about the foods to avoid.
(2) We would like you to avoid using mouthwash during the study. Mouthwash kills the bacteria in your mouth, but the bacteria in your mouth are needed to activate the inorganic nitrate you will receive as a study medication.
(3) Please avoid strenuous exercise for 48 hours prior to your study visits.
(4) Please avoid caffeine for 24 hours prior to your study visits.
(5) Please arrive to your study visits following an overnight fast. You should have the dinner we provide the night before, but no other food. You may drink water, and you may take your regularly prescribed medications, but please do not take your study medications on the morning of a study visit.

INTERVENTION PERIOD 1 (Visits 2 & 3)

We may check up on you during the study in between visits. Please be sure to tell us about any side effects you may be experiencing and how you are doing.

Visit 2: (approximately ½ day)

After taking study drugs for 6 weeks, you will return to the exercise unit. Prior to this visit, you will receive an actigraphy monitor, which is similar to a 'FitBit' device. This device is worn like a watch and will collect activity information, including the number of steps you take per day. Please wear it as much as possible in the week prior to your visit. You will come to the exercise unit in the morning and in the fasted state. We ask that you avoid caffeine for 24hrs prior to this visit, and strenuous activity for 48hrs prior.

The following procedures will be performed as described above: Vitals and Physical exam, Questionnaire, Sample collection (IV placement with blood, urine, and saliva collection), a urine pregnancy test for females of childbearing potential, and the submaximal exercise test until exhaustion. We will also perform a skeletal muscle biopsy prior to the submaximal exercise test.

- Muscle biopsy – The muscle biopsy procedure involves sterilizing the biopsy area on your thigh, administering local anesthetic to numb the area, making a small incision through the skin and fat down to the muscle, and taking a few small pieces of the thigh muscle using a biopsy needle. We may need to insert the needle into the muscle several times in order to obtain enough tissue. The muscle biopsy is being done to tell us more information about how our study drugs affect your muscles, and if this is related to any changes in how you exercise. We will test many things about your muscle related to its function, its ability to make energy, and the different substances that are stored in it. The muscle biopsy is being done for research purposes only.

Following the muscle biopsy, you will perform a submaximal exercise test during which we will ask you to exercise for as long as possible. We may place an additional IV in your hand prior to exercise and place your hand in a heated box. The heated hand box allows us to get blood from your vein that resembles the blood in an artery, but without the risk of putting a needle in the artery. The hand box is maintained at a temperature less than most saunas and will not burn your hand. During exercise, we will give strong verbal encouragement to help you exercise until exhaustion.

You will continue on study medications for an additional 3-10 days prior to returning to UPenn for the MRI assessment.

Visit 3: (approximately 2 hours)

An MRI is a scan of the body using large magnets. You will not be asked to remain in the MRI for more than 1.5 hours. During the scan, you will be asked to perform a few (generally 2) bouts of calf exercise, consisting of pushing down on a pedal repetitively, similar to the gas pedal of your car or a piano foot pedal. After both the MRI and the bike test visit, you will then enter a 2-week washout period during which you will not take any study medication, before beginning Intervention Period 2. Depending on scheduling, the MRI visit may occur either before or after the bike exercise visit.

INTERVENTION PERIOD 2 (Visits 4 & 5)

Following the washout period of approximately 2 weeks, you will be given a different study therapy, to be taken for approximately 6 weeks. While staying on study medications, you will complete the same assessments as done during Visit 3 (muscle biopsy and bike test) and Visit 4 (MRI of the leg); you will also wear the actigraphy monitor to track your activity in the week before the study visits. You will then enter another 2-week washout period, before beginning Intervention Period 3.

INTERVENTION PERIOD 3 (Visits 6 & 7)

You will take the next and final 6 weeks of study drugs. While staying on study medications, you will complete the same assessments done at Visit 4 (muscle biopsy and bike test) and Visit 5 (MRI of the leg). You will also wear the actigraphy monitor to track your activity in the week before the study visits.

You will then enter washout period of at least a month.

Visit 8: (approximately ½ day)

At least 30 days from the last dose of study medications, you will again come to the MRI scanner for a final visit during which you will undergo **two** MRI scans. While the scanning protocol itself will be the same, the scans will be different because during one of the two scans, you will breath room air, and during the other you will be breathing 100% oxygen. These gases will be administered to you through a facemask, and neither you nor the person performing and interpreting the MRI scan will know which gas you are breathing at which time. During each MRI scan, you will be asked to perform brief episodes of calf exercise, consisting of pushing down on a pedal repetitively, similar to the gas pedal of your car or a piano foot pedal.

Visit	Procedures
Visit 1: Baseline Visit	• Eligibility/Informed Consent • Medical History, Medications Review, Vitals, Physical Exam • KCCQ • Sample Collection: blood, saliva, urine, pregnancy test (if applicable) • Testing: echo, tonometry, DEXA, maximal resistance exercise testing (max 100%) • 1-hour rest/lunch • Submaximal (75% resistance) exercise testing until exhaustion • Randomization (if meet criteria); education; study drug dispensed (may be mailed)
Intervention Period 1: 6 weeks of study drug A (Phone call after ~1 week of study drug)	
Visit 2:	• Actigraph (~1 week prior to visit) • Vitals, Physical Exam, KCCQ • Sample Collection: blood, saliva, urine, pregnancy (if applicable) • IV placement and use of Heated hand box • Testing: Muscle biopsy, submaximal (75% resistance) exercise testing until exhaustion, echo, tonometry
Visit 3: *(3-7d later)*	• Skeletal muscle calf MRI with exercise
2-week washout followed by Intervention Period 2: 6 weeks of study drug B (Phone call after ~1 week of study drug)	
Visit 4:	• Actigraph (~1 week prior to visit) • Vitals, Physical Exam, KCCQ • Sample Collection: blood, saliva, urine, pregnancy (if applicable) • IV placement and use of Heated hand box • Testing: Muscle biopsy, submaximal (75% resistance) exercise testing until exhaustion, echo, tonometry
Visit 5: *(3-7d later)*	• Skeletal muscle calf MRI with exercise
2-week washout followed by Intervention Period 3: 6 weeks of study drug C (Phone call after ~1 week of study drug)	
Visit 6:	• Actigraph (~1 week prior to visit) • Vitals, Physical Exam, KCCQ • Sample Collection: blood, saliva, urine, pregnancy (if applicable) • IV placement and use of Heated hand box • Testing: Muscle biopsy, submaximal (75% resistance) exercise testing until exhaustion, echo, tonometry
Visit 7: *(3-7d later)*	• Skeletal muscle MRI with calf exercise
One Month washout	

Visit 8: (at least 30 days from last study drug)	• Skeletal muscle calf MRI with calf exercise:
	  • Room air
	  • 100% Oxygen

What are the possible risks or discomforts?

Active Pharmacologic Therapy: This study includes 3 different pharmacologic interventions: (a) potassium nitrate (KNO_3); (b) potassium nitrate (KNO_3) + nicotinamide riboside (NR) + propionyl-L-carnitine (PLC); (c) potassium chloride. Risks are described below.

a. Potassium Nitrate (KNO_3)

- GI Upset (~33%): stomachache, diarrhea, nausea, or vomiting
- Slight headache (~20%)
- Fatigue (~10%)
- New onset or worsening lightheadedness, or lightheadedness with standing
- Low blood pressure
- Worsening shortness of breath
- Flushing
- Rash
- Dizziness

b. Propionyl-L-Carnitine (PLC) (~5%)

- Nausea
- GI upset/belly discomfort

c. Nicotinamide Riboside (NR)

- GI upset (~20%): nausea, vomiting, diarrhea, transient changes in stool, bloating
- Muscle soreness/cramping (~15%)
- Rash/flushing
- Headache

d. Potassium Chloride

- Stomach discomfort
- Nausea
- Vomiting
- GI upset: nausea, belly discomfort

These medications have not been given in combination before. It is possible that there may be additional/different side effects when the medications are using in combination. We will be in close contact with you throughout the study to identify any additional side effects.

Blood Potassium Level: The combinations of pills used in this study all contain a small amount of potassium. High levels of potassium can be dangerous in the blood. We do not think that the amount of potassium in our study medications will put you at risk for high potassium levels. As an extra safety precaution, we may check your blood potassium level after starting study medications if you have risk factors that may put you at higher risk for increased potassium. These risk factors include significant kidney disease, certain medications, and higher potassium levels at the start of the study.

Actigraphy and Step Counts: The actigraphy monitor is a watch-like device. There are no risks associated with actigraphy and acquisition of the step count data. It is possible that a subject might get mild irritation from the "watch strap" if the monitor is worn on the wrist.

Kansas City Cardiomyopathy Questionnaire: Participants may become uncomfortable with questions or feel sadness as a result of completing questionnaires.

Phlebotomy and blood draws: Risks from the peripheral venous catheterization include minor discomfort, minor bruising, bleeding, and/or fainting associated with the drawing of blood. There is also a very small chance (less than 1%) of infection at the blood draw site. An additional IV will also be placed in the hand prior to the submaximal exercise test, and the hand will be placed in a heated hand box during exercise. There are no additional risks associated with the heated hand box. The hand box stays cooler than a hot sauna and will not burn your hand.

Echocardiography: This is a non-invasive procedure and does not have any known significant risks. It is possible that you may experience mild, temporary discomfort or skin irritation from the echo probe, or from wearing the electrodes needed to monitor your heart rate during the examination.

Arterial Tonometry: Minor discomfort may occur when the tonometer is placed against your neck, wrist, and groin. This will feel like someone is taking your pulse in the neck, arm, or groin. We will use adhesive electrodes attached to your skin. These may occasionally cause itching and irritation in your skin.

Bone Density Scan (DEXA): You will be instructed to never look directly into laser of the scanning arm that passes over your body. In most instances, scans will occur one time.

Risks from Exposure to Radiation: This research study involves exposure to radiation from the DEXA scan. Therefore, you will receive a radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the doses you will receive, it is very likely that you will see no effects at all.

Muscle biopsy: The most significant risks occurring in adults include significant bleeding/bruising or a local infection. The rates of either of these events occurring is less than 1 in a thousand (<0.1%).

Exercise test: Exercise tests are used extensively for research purposes with minimal risk to participants. Common risks include feeling tired and short of breath. We ask that you push yourself during these tests, so you may begin to feel uncomfortable, nauseous, light-headed, or develop aches and pains during or after exercising. The risks of exercising as part of this study are no different than if you were to exercise on your own. The most significant risks of the test are abnormal heart rhythms or other cardiovascular complications, which are extremely rare. You will be monitored while you exercise in our exercise lab.

Lower Extremity MRI: The non-invasive nature, lack of radiation, and lack of MRI dye (gadolinium contrast) make the risks associated with our MRI studies small. MRI scans requires that you to be in a partially enclosed space inside the scanner, which some may find uncomfortable. The MRI scanner produces different noises during a scan. You will be given special earplugs to reduce the noise. Your legs may also get sore from lying in the MRI scanner, but this should resolve after you get up and walk around.

The greatest risk of MRI is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk, we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room. We will be able to communicate with you over a speaker system, even with the door closed.

There is also a potential risk of MRI for participants with medical implants or other metallic objects in their body. All subjects undergoing MRI scanning must complete a screening evaluation before the scan to identify the presence of medical implants or other foreign bodies that could cause an injury. Every effort will be made to ensure that disclosed implants or foreign bodies do not pose a risk to participants. If you do or may have metal in your body, we may need to investigate this further to make sure that the MRI will be safe for you to have. This may include performing an X-ray or obtaining old X-ray results. We may also discuss your situation with our radiologists and/or MRI technicians to make sure you will be safe. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be performed.

Some of the pulse sequences and/or RF coils are not FDA approved but are considered to pose no more than minimal risk. This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

Acute Oxygen Supplementation: Prolonged exposure to oxygen, such as for several days, can be harmful to your body. However, it is not expected that short-term 100% oxygen administration (not anticipated to exceed 1.5-2 hours) will have a negative

impact on your health. You may feel lightheaded. In people who have significant lung disease, and low oxygen levels at baseline, administration of oxygen can cause problems, but people with this degree of lung disease will not be enrolled in this study. If you experience any symptoms during the study, you should let us know immediately so that we can assess.

Reproductive risks
If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a urine pregnancy test before entry into the study. You are asked to use a medically accepted method of birth control while you participate in the study. You should not become pregnant while you are taking the study drugs. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist.

Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy-related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. We will ask you about pregnancy prior to the MRI scanning, and you will need to attest that you are not pregnant in order to undergo MRI scanning.

Confidentiality: There is a potential for a breach of confidentiality. We are committed to stringently protecting confidentiality as described in detail below.

There may be other risks that are currently unknown or unforeseeable. If you are injured as a result of your participation in this study, please inform your treating physician that you are participating in a research study. Please also let the study team know.

Commercial Products: Your samples/data may also be shared with for-profit entities for research purposes. Any for-profit companies receiving information/samples related to this study may ultimately discover products, drugs, tests, etc., as a result. This discovery may lead to commercial products and profit. You would not receive compensation for this.

Risks of Genetic Testing
We may also conduct genetic testing on your samples (in other words, determine your DNA sequences). Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely, health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long-term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
You are not expected to get any benefit from being in this research study. Your participation, however, may help us figure out new ways to treat participants with HFpEF, leading to an important societal benefit.

What other choices do I have if I do not participate?
You do not need to participate in this research study. Your personal physician can continue caring for your HFpEF according to the standard of care.

You can still participate in other research studies performed by our group, or others. If you decide not to take part or if you change your mind later, there will be no penalties or loss of any benefits to which you are otherwise entitled.

Will I be paid for being in this study?
You will receive compensation for your time and transportation according to the following schedule, for a possible total of $600.

Baseline Visit 1	**Visit 2 *(bike & biopsy)***	**Visit 3 *(leg MRI)***	**Visit 4 *(bike & biopsy)***	**Visit 5 *(leg MRI)***	**Visit 6 *(bike & biopsy)***	**Visit 7 *(leg MRI)***	**Visit 8 *(two leg MRI's)***
$50	$100	$50	$100	$50	$100	$50	$100

Participants will be paid via Greenphire ClinCard after completing each visit.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?
You will not have to pay for any research procedures. You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

Will I receive the results of research testing?
Most tests done in research studies are only for research and have no clear meaning for health care. Many of the research results will not be returned to you because they would not be relevant to your health care. Some results, such as the basic blood work and the echocardiograms of your heart, may be entered into your health record and can then be reviewed by your care providers.

What happens if I am injured from being in the study?
We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

An individual subject's participation will be over at the end of Study Visit 8. The overall study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by the study physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, study oversight group (for example, a Data Safety and Monitoring Board), or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

The research team will make every effort to keep all the information you tell us during the study strictly confidential, as required by law. If you decide to participate in the study, you will be assigned a unique identifier number (example: 023), and all your data will be handled in a way that cannot be easily linked to your name or other personal information. Only the investigator and study staff will have access to the list that connects your name to your data. Any documents you sign, where you can be identified by name, will be kept in a locked file cabinet within our research facilities. All of your electronic information will be kept in a password-protected secure server behind the health system firewall. Only the investigators will have access to the codes that link your health information with your personal data. These documents will be kept confidential.

There is no set time for destroying the information that will be collected for this study. Your permission to use and share the information and data from this study will continue until the research study ends and will not expire. Researchers continue to analyze data for many years, and it is not possible to know when they will be completely done. It is possible that your images, samples, and data may be shared with other researchers or companies, both within and outside of UPenn. These groups will not receive any identifying information about you. Neither you nor your heirs will gain financially from discoveries made using the information and/or specimens that you provide.

Will information about this study be available to the public?

Depending on the findings, the results of this study may be published in medical journals. No identifying information will be included in these publications. A description of this clinical trial will be available on http://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.

What may happen to my information and samples collected on this study?

Your data will be coded, meaning that identifying information (such as your name) will be removed from the data, samples, and specimens and replaced by your Study ID, a unique identifier that does not contain personal information. Only the study team will have access to the codes that link your study ID to your personal information. Due to the confidentiality safeguards we have in place, we think it is unlikely that your data could be identified, but this is always a risk.

Future Use of Data and/or Specimens

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information and samples could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you, as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (for example, laboratory tests and imaging studies) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

What information about me may be collected, used or shared with others?

- Name

- Address
- Telephone number
- Date of birth
- Social security number (for payment purposes)
- Personal and family medical history
- Results from physical examinations, tests or procedures performed either at our institution or another medical facility.
- Dates of tests or procedures
- Medical record numbers
- Data, samples, and images collected during the course of this study
- Medication history
- Email address

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of the School of Medicine, might receive my information?

We may share your data, samples, and scans with other investigators or companies within and outside of UPenn to help further the research. In this case, only coded information will be shared.

<u>Oversight organizations</u>

- The U. S. Office of Human Research Protections (OHRP)

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date
_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date

The study doctors believe that there may be opportunities in the future for other research studies. We would like your permission to contact you in the future.

Please initial below if you agree to being contacted in the future about additional studies.

_____: I agree to being contacted in the future about additional research studies. I understand that being contacted does not imply any agreement to participate.

_____: I do not agree to be contacted in the future about other studies

If you should change your mind about someone contacting you in the future, you will need to send a written letter to the study team at the address on the first page of this consent form.