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Official Title

A single-center, randomized, double-blind, placebo-controlled study to evaluate microvascular disease after 12 weeks of therapy with SGLT2i compared to placebo in symptomatic women with non-obstructive CAD (SMILE)

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Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____ Medical Record #_____

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

This study is funded by grants from the National Institutes of Health (NIH).

Key Information About This Research Study

Principal Investigator:	Patricia Rodriguez-Lozano, MD Department of Cardiology University of Virginia School of Medicine Box 800158 Charlottesville, VA 22908 Telephone: (434)982-0853
Sponsor:	National Center for Advancing Translational Sciences (NIH)

You are being asked to take part in a research study. You do not have to take part in this study.
You should only agree to take part in this study after reading this consent form and discussing it with the study team. You may also discuss this with your family, friends, health care providers or others before you decide.

What problem is this study trying to solve?

Cardiovascular disease occurs when the heart and blood vessels become unable to function well. Cardiovascular disease is the leading cause of death for women in the United States. Most deaths due to cardiovascular disease are caused by a type of cardiovascular disease called ischemic heart disease. Ischemic heart disease in women differs from ischemic heart disease in men. Women with ischemia are more likely to have non-obstructive coronary artery disease (INOCA), for which no specific treatment exists. Most women with INOCA have dysfunction in the small blood vessels of the heart, called the microvasculature. Microvascular dysfunction causes reduced blood flow in the heart muscle, which is thought to cause symptoms of ischemia in the absence of obstructive disease. Recently, a class of drugs that were originally approved to treat Type 2 diabetes have been shown to improve outcomes in patients with cardiovascular disease.

The purpose of this study is to test whether these drugs improve blood flow and reduce symptoms in women with INOCA.

Drugs that inhibit the sodium-glucose cotransporter (SGLT2 inhibitors or SGLT2i) are a class of prescription medicines that are approved by the Food and Drug Administration (FDA) for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors have been shown to decrease deaths and hospitalizations due to cardiovascular disease in patients with Type 2 diabetes. Recently, SGLT2 inhibitors were found to reduce hospitalizations in non-diabetic patients who had heart failure. The FDA has approved SGLT2 inhibitors to treat heart failure, and these drugs, although investigational and not approved by the FDA for the treatment of cardiovascular disease, are increasingly prescribed "off label" to patients who have other types of heart disease.

The SGLT2 inhibitor used in this study is dapagliflozin and is not approved by the FDA for the treatment of ischemic heart disease in the absence of obstructive coronary artery disease (INOCA). For the purpose of this study, dapagliflozin is considered investigational. This study is trying to find out whether SGLT2i drugs improve blood flow to the heart muscle (the myocardium) in women with INOCA.

If you agree to participate, you will take a SGLT2i medication (dapagliflozin) or placebo for 12 weeks. A placebo does not contain any active study drug. Neither the researchers nor the study participants will know whether they have been assigned dapagliflozin or placebo, so we refer to both as "study drug". During this study, we will measure myocardial blood flow before study participants start taking study drug, and again after they have been taking study drug for 12 weeks.

In this study, we will use magnetic resonance imaging of the heart (cardiac MRI) to measure myocardial blood flow. We will take MRI pictures of the heart while giving a "stress" drug. This drug makes the arteries of the heart open, causing more blood flow to the myocardium. This is similar to what happens when you exercise. A person undergoing cardiac MRI must lie very still so that we can take clear pictures. We use a drug to stress the heart during MRI because exercise is not possible. We give the drug through an IV in your arm. We will take MRI pictures while the stress drug is given through the IV. We will take MRI pictures during stress and at rest. We will compare the two sets of pictures to measure myocardial blood flow.

You will be given a "stress" drug (adenosine or regadenoson) during the MRI stress test part of your study. Both adenosine and regadenoson are approved by the US Food and Drug Administration (FDA) for cardiac stress tests. However, they have not specifically been approved for use during cardiac magnetic resonance (CMR), and are therefore considered investigational for this study.

The research study also involves the use of gadolinium-based contrast agents. These gadolinium-containing drugs are FDA approved for use in MRI examinations. However, their use is considered investigational for this study.



You are being asked to take part in this study because you are a woman with signs and symptoms of ischemic heart disease in the absence of obstructive coronary artery disease (INOCA), as determined by testing within the last 2 years.

Why would you want to take part in this study?
Participation in this study is not designed to benefit individual participants. Our goal is to help other people in the future, by finding out how SGLT2i affects myocardial blood flow in women with INOCA. You might like to take part in this study because the MRI pictures will give us a highly detailed look at your heart function. MRI is the best technique to look at scar tissue in the heart muscle from known or unknown heart attack(s) you may have had in the past.

Why would you NOT want to take part in this study?
You might not want to take part in this study because there are risks involved. The risks are discussed in detail later in this consent form. The major risks of this study include:

Risks of dapagliflozin (study drug) include infections of the urinary tract and genitals, changes in blood lipids, and volume depletion. You will be screened for risk factors, such as recurrent urinary tract infections and impaired kidney function that can make these risks more likely.

Risks of MRI:
The MRI uses a powerful magnet to take pictures. If you have any metallic or magnetic objects in your body, these could move or become hot. Additionally, some people may become anxious inside the confined space of the MRI ("claustrophobia"). You will be screened to minimize these risks.

Risks of Gadolinium:
This study uses a contrast agent to take better pictures with the MRI. The contrast agent contains the metallic element, Gadolinium (Gad). Some people who have impaired kidney function have been seriously injured by Gad. You will be screened for kidney disease to minimize this risk. In addition, a small amount of Gad may remain in the body.

Risks of Pharmacological Stress:
This study will use a “stress” drug (either regadenoson or adenosine) to stress the heart while we take pictures with the MRI. The stress drug may cause you to feel uncomfortable during the test. There is a very small risk of developing difficulty breathing, serious heart problems, or death when using these drugs. We will screen for these risks by asking about your medical history and checking the electrical activity of your heart.

Risks of coronary CTA:
This study may involve radiation exposure from a computed tomography (CT) scan of your heart. In addition, you will receive intravenous (IV) contrast and the drugs nitroglycerine and metoprolol with this exam. The risks of these drugs include flushing, slow heart rate, headache, allergic reaction and contrast-induced kidney injury. You will be screened for contrast allergy, pregnancy, and kidney function to minimize the risks of the coronary CTA.



What will I have to do if I take part in this study?
Full details of all the procedures are found later in this form. If you take part in this study, you will:

- Complete up to 4 study visits to the UVA Hospital over 3 months (12 weeks).
- Take study drug (either dapagliflozin or placebo) for 12 weeks
    - If you have Type 2 diabetes and are taking certain medications, we will ask you to monitor your glucose closely for the first 4 weeks of the study.
- At the Baseline & Week 12 visits, undergo stress cardiac MRI. These visits will take up to 4 hours.
    - You must fast from food and nicotine for 4 hours and abstain from caffeine- coffee, tea, cola and chocolate for 24 hours before each of these visits.
    - You must stop taking cardiac medicines (beta-blockers, alpha-blockers, CCB, ACEI, ARB, nitrates, and diuretics) for 48 hours before each of these visits. The investigators will review your medications with you to identify which medications should be held.
    - You will complete questionnaires
    - We will review your medical records for your medical history, medications, and past lab results.
    - We will collect your weight and vital signs (heart rate, breathing rate, blood pressure)
    - We will draw blood for lab tests and optional specimen banking
    - A 12 lead ECG if not done in the last 30 days
    - Cardiac MRI with adenosine or regadenoson stress testing
- At the 6 Week visit, you will receive a physical exam and complete questionnaires. This visit will take up to 2 hours.

What is the difference between being in this study and getting usual care?
All the procedures and tests described in this form are being done for research purposes only and would not be done as part of your usual care, unless you and your doctor determined they were a necessary part of managing your health.

If you have Type 2 diabetes, the medical provider who treats you for diabetes will be consulted regarding your participation in the study. This is because SGLT2i, in combination with medications that lower blood glucose, increase the risk of hypoglycemia. The study team will send your provider a copy of this consent form. Please tell your provider that you are considering participating in a SGLT2i study.

What other treatments may I receive if I decide to not take part in this study?
Instead of being in this study, you can choose not to participate. Being in this study will not alter any treatment for your condition. The following alternative treatments are available to you if you decide not take part in this study: Management of cardiac risk factors with medications and lifestyle changes.

How long will this study take?

Your participation in this study will require 3-4 study visits over about 3 months. Each visit will last about 4 hours.



Up to 50 people will be in this study at UVA.

What will happen if you are in the study?

SCREENING (visit will last about 30 -90 minutes)

Screening Visit ***(Can be done the same day as Baseline visit):***

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, screening will be performed. You will have tests and procedures to make sure you are eligible, and it is safe for you to participate. These include the following:

Screening for safety:

- If you have Type 2 diabetes, your diabetes care provider will be notified, and we will not assign study drug without their approval.
- You will be asked questions to determine if it is safe and appropriate for you to have an MRI. These questions ask about metal objects in your body, such as a pacemaker, implants, or metal from injuries, and ask about claustrophobia (fear of small places). This is standard procedure for anyone who is having an MRI.
    - If this questionnaire determines that it is possible that you have metal fragments in or near your eyes, we will use an X-ray machine to take pictures of your eyes to make sure there is no metal and therefor it is safe for you to have an MRI.
    - If this questionnaire or the X-ray determines that MRI is not safe for you, you cannot be in the study.
- Review of your medical history and medications. If this review shows it is not safe for you to receive the stress drug, you cannot be in the study.
- Limited physical exam and vital signs (blood pressure, heart rate). If your examination or vital signs show it would not be safe for you to receive stress drug, you cannot be in the study.

- **Blood & urine tests:** We will draw about 1 teaspoon of blood from a vein in your arm. We will perform the following tests on this blood sample:
    - Creatinine (to test your kidney function). If the blood test for kidney function shows that you have kidney dysfunction, you cannot be in this study. If you have had this test done as part of your usual care within the last 30 days, you will not need to have this test repeated. Instead, we will use the information in your medical records.
    - Urine pregnancy test: if you can become pregnant, you will have a urine pregnancy test. If you are pregnant, you cannot be in this study.

- **Electrocardiogram (ECG)**: this procedure will let us check the electrical activity of your heart. It will be done if you have not already had an ECG for your regular care within 30 days of the study visit. The ECG test will take place as follows:

- You will be asked to remove clothing from the waist up. The technician will ensure your privacy by covering you with a sheet or gown and exposing only the necessary skin.
- You will lie flat on a table or bed for the procedure. It will be important for you to lie still and not talk during the procedure, so as not to interfere with the tracing.
- Electrodes will be attached to your chest, arms, and legs. Leads will be connected from the electrodes to the ECG machine.
- The ECG will be started. It will take about one minute for the tracing to be completed.
- Once the tracing is completed, the technician will disconnect the leads and remove the skin electrodes.
- If the results show that it is not safe for you to receive the stress drug, you cannot be in the study.

Screening for obstructive CAD:

If you have not been tested for blockages of the coronary arteries within the last two years, we will perform a procedure called coronary CTA.

If you undergo coronary CTA on a different day than the baseline stress cardiac MRI, you will go to UVA main hospital radiology department and receive the following procedures:

- You will be asked to prepare for this test by:
  - fasting from food for 4 hours,
  - abstaining from caffeine (including caffeinated and decaffeinated coffee, colas, tea, and chocolate) for 24 hours
  - topping phosphodiesterase inhibitor drugs for 48 hours, which includes drugs such as theophylline, which the investigators will help you to identify
- Your vital signs will be taken, and an IV placed in your arm before the procedure
- Complete a standard questionnaire to be sure it safe for you to receive CT contrast
- If you can become pregnant, we will need a negative urine pregnancy test on the day of the visit.

If the coronary CTA is done on the same day as the baseline stress cardiac MRI, we will test you for kidney function and pregnancy only once. You will complete a safety screening questionnaire for each procedure.

CORONARY CTA PROCEDURE

(Will last up to 90 minutes)

- The CT will take pictures of your heart, including pictures of the arteries to look for blockages. CT is a way to make x-ray images of the inside of the body. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures that show structures inside your body more clearly than regular x-ray pictures.
- During the procedure, a technologist will take you into the CT scan room where you will lie down on the patient table (usually on your back) inside of the CT machine.
- You will have ECG leads placed on your chest to monitor your heart rate during the procedure.
- You will have a blood pressure cuff placed on your arm and have your blood pressure monitored during the procedure.



- You will have an intravenous (IV) catheter placed in your arm.
- Depending on your heart rate, you may be given a medicine (metoprolol) to slow down your heart rate. This medicine may be given orally 1 hour before your CT, or by IV at the time of the CT.
- You will also be given a medicine (nitroglycerin) under your tongue to dissolve which will dilate the blood vessels in your heart. These are standard procedures for the CT examination of the heart arteries.
- Since the CT examinations would be of your heart, a series of pictures will be taken from your lower chest to your upper chest/neck.
- During the study, you will be asked to hold your breath so that the pictures will not be blurred. The machine will make some noise, and the table will move during the scan. Also, you may receive signals from the technologist or from the machine about your breathing.
- Before or during the study, you will be given an injection of a contrast liquid in your vein to allow the radiologist to obtain clearer images of your heart. If you have any discomfort during the test or after the injection, be sure to tell the technologist.
- It will take about 20 minutes to take these pictures.

If the screening tests show you are eligible and that it is safe for you to be in the study, you will continue with the Baseline Visit procedures. The Baseline procedures can be continued immediately after Screening, or on another day within 2 weeks.

RANDOMIZATION and STUDY TREATMENT

(This part of the visit will take a few minutes**)**

You will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups. You have an equal chance of being assigned to either of the treatment groups (dapagliflozin or placebo). The placebo contains no active drug. Neither you nor the study doctor can choose which group you will be in. Neither you nor the study doctor will know which group you are in until the study is done. But if your medical provider needs to know, the people doing this study can find out.

GROUP 1: Dapagliflozin 10mg oral

GROUP 2: Placebo

*For the purpose of this study, we will refer to both dapagliflozin and placebo as the “study drug”

You will take one tablet of study drug once each day, preferably in the morning, with or without food. If you forget to take a dose, please take it as soon as you remember. However, if it is more than 6 hours later than your usual time, you should skip that day’s dose. Do not take more than 1 tablet at a time.

Monitoring glucose, if you have Type 2 diabetes: If you have T2DM and are taking insulin, sulfonylureas, or glinide medications, we will ask you to closely monitor your glucose for the first 4 weeks of the study. As part of your diabetes care plan, you may be conducting self-checks or laboratory-based monitoring of your blood



glucose. Conscientious adherence to your diabetes care plan is very important while you are in the study. This is because SGLT2i, in combination with these medications, increase the risk of hypoglycemia. If needed, T2DM treatments may be adjusted at the discretion of the Investigator or diabetes health care provider. Please contact the Investigator if you experience hypoglycemia while in this study.

STUDY VISITS

Baseline Visit (visit will last about 2 hours)

Before you come for the Baseline MRI, you will be asked to fast (have nothing to eat or drink but water), and to abstain from nicotine, for 4 hours. You will be asked to avoid caffeine, tea, cola and chocolate for 24 hours. You must stop taking certain cardiac medicines for 48 hours before the MRI. The Investigators will review your medications and let you know which medications would be affected.

Cardiac MRI (CMR) with stress test: uses a powerful magnet to create pictures of your heart.

- An intravenous catheter (IV) will be placed in each arm by trained staff. An IV is a small flexible tube inserted in a vein and guided by a needle.
- You will then be placed in the center of a large donut-shaped magnet on a padded stretcher, on your back, while pictures are being taken. You will need to lie still as much as possible during the stress cardiac MRI. Earplugs and an earphone will be supplied to reduce any discomfort from the knocking sound of the MRI machine. You will be asked to hold your breath for short periods of 10-15 seconds while different pictures of your heart are being taken.

- During the MRI stress test part of your study, we will give you a medicine called a "stress agent" (adenosine or regadenoson; you will only receive one of these drugs) through your IV. Stress drugs work by dilating the blood vessels on the heart. This allows doctors to determine if part of the heart is not getting enough blood flow. The stress drug will most likely make you feel hot and flushed. It will also probably make you feel like you are having chest pain and shortness of breath. If adenosine is used, all these side effects go away within 30 seconds after the medicine is stopped. If regadenoson is used, another drug called aminophylline will be given as soon as the “stress” pictures have been taken. Aminophylline usually relieves the symptoms of the stress drug within about 3 minutes.
- Once the stress drug is having its maximum effect, we will give you a contrast agent called Gadolinium (gadoterate meglumine or gadobutrol) through your IV and take more pictures to see the blood flow in your heart muscle. The gadolinium contrast agent allows us to visualize the blood flow in the heart muscle.
    - After we have turned the stress drug off, we will take some more pictures including a second set of pictures after giving you more contrast agent through your IV called gadolinium.
    - You will be in the MRI machine for about 45-60 minutes.

A cardiologist will be present during the cardiac MRI test and your heart rate, blood pressure, and electrocardiogram (EKG) will be monitored to see how your heart is working. The MRI will be stopped if you develop significant changes in the heart rhythm or blood pressure or if you are having other serious side effects.



Blood tests: We will draw about 2 teaspoons of blood from a vein in your arm. We will perform the following tests on this blood sample:

- Complete Blood Count (CBC). If you have had this test done as part of your usual care within the last 30 days, you will not need to have this test repeated. Instead, we will use the information in your medical records.
- Hemoglobin A1c (HbA1c – gives information about the average level of blood sugar over the past several months). If you have had this test done as part of your usual care within the last 90 days, we will use the information in your medical records.
- Blood lipids (measure of cholesterol and triglycerides in your blood). If you have had this test done as part of your usual care within the last year, we will use the information in your medical records.
- Basic Metabolic Panel (BMP) - includes testing for kidney function and blood chemistry. If you have had this test done as part of your usual care within the last 30 days, you will not need to have this test repeated. Instead, we will use the information in your medical records.

In addition to the tests above that may have already been done for your clinical care, the following additional blood testing will be performed for the study:

- **Inflammatory biomarkers:** about 20 teaspoons of blood will be drawn from a vein in your arm for study-specific tests. This blood will be analyzed for the presence of biomarkers that may be associated with inflammation in the body.
- **Cardiac Biomarkers:** about 1 teaspoon of blood will be collected for Troponin-1 and NT-proBNP tests. Cardiac biomarkers are substances that are released into the blood when the heart is damaged or stressed.
- **C-Reactive protein**: less than 1 teaspoon of blood will be collected for this test. C-reactive protein (CRP) is a protein made by the liver. The level of CRP increases when there is inflammation in the body.

Optional Genetic Testing & Specimen Banking: If you agree to be in the optional genetic testing and specimen banking sub-study, we will draw an additional 10 mL (about 2 teaspoons) of blood for this purpose. This blood will be collected with the blood taken for lab tests at the Baseline visit, described above. You may or may not be asked for another sample at the Week 12 visit, depending on the results of tests conducted on the Baseline sample. For more information see the section "**Optional Collection of Samples and Health Information for Genetic Research and Specimen Banking"** later in this consent.

Questionnaires: We will ask you whether you have symptoms, such as chest pain or discomfort and shortness of breath that can be caused by heart disease.

During this study, you will be asked to fill out some questionnaires. These questionnaires ask about:

- how you are feeling, including depressed or anxious mood
- your lifestyle habits and usual activities
- medicine use
- the impact of symptoms of heart disease on your quality of life

These questionnaires will take about 10 minutes to complete.



Week 6 Visit (will last about 1 hours)

You will be asked to bring your study medication with you to this visit. At the Week 6 visit, you will complete the quality-of-life questionnaires. We will collect your vital signs, ask you about changes in your health and medications, and the study doctor will perform an examination. We will give you study medication to last until the Week 12 visit.

Week 12 Visit (will last about 2 hours)

At the Week 12 visit, we will repeat the same procedures that were done at the Baseline visit.

Before you come for the 12 Week visit, you will be asked to fast (have nothing to eat or drink but water), and to abstain from nicotine, for 4 hours before the MRI. You will be asked to avoid caffeine, tea, and chocolate for 24 hours. You must stop taking certain cardiac medicines for 48 hours before the MRI. The Investigators will review your medications and let you know which medications would be affected.

At the week 12 visit, you will receive a physical examination, have blood drawn for laboratory and biomarkers testing, and undergo a second stress cardiac MRI. You will also complete quality of life questionnaires.

END OF STUDY:

At the completion of your week 12 visit, your participation in the study is complete. The study drug (dapagliflozin or placebo) will be given to you only during this study. After you have completed the study, you will be referred to your cardiologist for medical care.

What are your/and your parent/legal guardian's responsibilities in the study?

You have certain responsibilities to help ensure your safety. These responsibilities are listed below:

- You must come to each study visit.
- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Ensure that the study drug is taken as instructed, keep the study drug in a safe place away from other children, return any unused study drug at each visit, and report any lost or missed tablets.
- Ensure that the study drug is taken only by you, the person for whom it has been prescribed.
- Answer all the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over the counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications.

Blood Testing

We will take (or “draw”) up to 9 tablespoons) of blood per study visit. The total amount of blood we will take will be about 24 tablespoons for the entire study.

The blood we take will be tested to check your health. We will perform a complete blood count, blood lipids and hemoglobin A1c, and a panel of metabolic tests. Your samples will also be tested for biomarkers of inflammation and damage or strain to the heart.

When these tests are done any left-over sample will be thrown away or they will be de-identified. This means there is no information that could be used by anyone to determine who the sample came from.



STUDY

Study Procedures	**Visit 1 (Screening and Baseline)**	**Visit 2 (Week 6)**	**Visit 3 (Week 12)**
	(-14 days to Day 1)	(6 +/- 1 weeks) (42±7 days)	(12 +/- 2 weeks) (84±15 days)
Informed Consent	X		
Review study eligibility	X		
Randomization	X		
Complete blood count, Lipid Panel, HbA1c	X		X
Basic metabolic panel	X	X	X
Cardiac biomarkers (Troponin-1, NT-Pro BNP)	X		X
C-Reactive Protein	X		X
Pregnancy test (if applicable)	X	X	X
Urinalysis	X	X	X
Inflammatory biomarkers	X	X	X
Optional specimen banking	X		
Medical History/health status	X	X	X
Vitals signs	X	X	X
Physical exam	X	X	X
Study Drug Dispensed	X	X	X
Study Drug Collected		X	X
Questionnaires	X	X	X
Review current Medication	X	X	X
Cardiac MRI w/Stress & 12 lead ECG)	X		X
Coronary CTA (if not done within 2 years)	X		
Review health related problems (adverse events)		X	X
Volume of blood drawn (tablespoons)	9	7	8

If you want to know about the results before the study is done:

During the study your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.



Optional Collection of Samples and Health Information for Genetic Research and Specimen Banking

What Sort of Research Will Be Done On Your Sample(s)?



You are being asked to provide samples of your blood to be used for future research. We are interested in studying how the immune system affects the risk of developing blockages in the arteries around the heart, called coronary artery disease. This research involves testing cells in your blood for gene and/or protein variations to determine if they may be associated with blockages in heart arteries. Along with specimens, researchers may need to collect some health information about you. Combining information from the specimen with information from your health records may be useful for this research. For this research, the following types of information could be included: height, weight, BMI, and medications.

Genetic Testing

We plan to do genetic research on the DNA in your specimen sample. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics, such as hair and eye color and disease risk. Genes are passed from parent to child. We will be testing your genetic code or the genes you express in your blood cells to discover associations between genes and heart artery disease.

Genomic Research and Broad Sharing of Genomic Data

Genomic studies examine genetic differences across the human genome (set of human genes). Researchers study the association between genes and health conditions or personal characteristics like vision, obesity, or behavioral traits. As part of this study, we will be collecting information about your health and/or your individual genes. We will use this information for our study objectives. In addition, if you agree, the data will be entered into external scientific databases so that it can be broadly shared with other researchers performing other genomic studies. For example, the National Institutes of Health (NIH, an agency of the federal government) maintains a database called “dbGaP.” Databases like this serve as a repository of all kinds of genomic data from studies funded by the NIH and conducted in the US and around the world. The aim of collecting this information in a repository is to allow qualified researchers to look for genetic connections for a range of topics in the future. The information may be used to learn if certain genes are associated with certain traits, diseases and /or treatment effects. Making data broadly available in this way, means that your contribution and the data generated in this study could be helpful in advancing other areas of scientific research.

Traditionally used identifying information about you (such as name, phone number, address) will NOT be included in these databases or shared with others. De-identified genomic data generated in this study may be deposited in databases that will be publicly accessible via the Internet. Researchers with an approved study may access and utilize your de-identified genetic, genomic and/or health information deposited in the database (dbGAP) after approval by the regulatory authority (NIH). Strict safety measures are in place to protect the privacy of your information. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you or your family. The risk of this happening is very small but may grow in the future. Researchers will always have a duty to protect your privacy and keep your information confidential.

Specimen Banking



Specimens collected for research will be added to a research specimen bank. The purpose of a specimen bank is to process and store samples until researchers need them for future research. The long term goals of the samples collected in this bank will be mainly used for research on cardiovascular disease. Is it not possible, however, to list every research project that will include the samples because we cannot predict all of the research questions that will be important in the future. As we learn more, new research questions and new types of research may be done.

What will you have to do to give samples for research?
Research samples will be collected at the Baseline and Week 12 visits. We will take (or "draw") up to 6 ½ tablespoons of blood at the Baseline visit. You may or may not be asked for another sample at the Week 12 visit, depending on the results of tests conducted on the Baseline sample.

How Will Your Sample(s) Be Labeled?
Your sample(s) will not be labeled with your name or other information that would identify you directly. Instead, it will have a unique code that allows for it to be linked to some of your health information. This link means that your specimen can be identified but only indirectly. We can find out if we need to know which sample is yours in the event you wish the sample to be removed at a later date.

Angela Taylor, MD and Coleen McNamara, MD will be responsible for storing your sample and for protecting your privacy.

This research specimen bank is located at the University of Virginia under the leadership of Angela Taylor, MD and Coleen McNamara, MD. There is no set limit to the number of people who will provide samples to this bank.

Which researchers can use your samples and what information about you can they have?
Your sample may be shared with researchers at the University of Virginia and at other institutions or with the sponsor (if applicable). Dr. **Patricia Rodriguez-Lozano** will not give your name to other researchers who want to use your sample but will only give them information like your age and what disease/condition you have. Those who would see the information would include researchers and the others listed under "Who will see your private information?" section of this consent document.

What Are the Benefits To Donating Your Sample(s) For Genetic Research and Specimen Banking?
The genetic research and specimen banking that is done with your sample is not meant to help you. But, doctors hope that in the future it will help people who have other diseases or conditions.

It is very unlikely that any future research (specimen banking) performed using your specimen(s) would benefit you directly, but it may provide important medical knowledge that could help other patients with your medical condition or other medical problems in the future.

What Are The Risks of Donating Your Sample(s) For This Study?



Risks to Privacy from Genetic Research and Specimen Banking: The main risk of allowing us to store and use your samples and certain limited health information for research is a potential loss of privacy. One of the risks to you is the release of information from your health records. The University of Virginia will do its best to protect your records so that facts about you and your health will be kept private. The chance that information identifying you will be given to someone else is very small. However, we cannot *guarantee* it will be safe. To further safeguard your privacy, information obtained from future research will not be placed in your medical record.

There are certain risks of having health information given to other people by mistake. In the unlikely event that this happens, it could cause discrimination or mental harm to you or your family members if others were to see this information. The results could be that you may not be able to get or keep certain kinds of insurance. It could also hurt family relationships.

Your doctor will explain the risks of the routine medical procedure you are having. In some cases, your doctor will ask you to sign a separate clinical consent form that explains the risks of the procedure. Allowing your samples to be placed in the bank for future research will not change the risks of the medical procedure itself.

Because everyone has unique DNA, it is also possible, although very unlikely, that someone could identify you through your DNA if they have another sample of your DNA.

Information about your genetic make-up could mean that you and your family members could face problems that could lead to getting or keeping some kinds of insurance or affect your ability to get or keep a job. To keep this from happening, the results of these tests will not be given to anyone outside of the study staff. There is no way to predict all the possible risks of this research.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.



Will You Find Out the Results of the Research on Your Sample(s) for Genetic Research and Specimen Banking?

Neither you, your health care provider**,** nor anyone in your family will receive the results of any research done on your sample(s). The results will not be put in your health records. Therefore, results from any research done on your sample(s) will not affect your medical care. This helps protect you and other members of your family from harm that might be caused by this information.

What If You Change Your Mind About Donating Your Sample(s) for Genetic Research and Specimen Banking?

If you decide now that your sample(s) can be kept for genetic research and specimen banking, and later change your mind, you can simply withdraw the sample(s) at that time. To withdraw you will need to write to the Principal Investigator listed on the first page of this form. We will then destroy any of your tissue that has not already been used. However, if your sample has been used in genetic research, the information that we have learned will remain in the study, even if you withdraw. Unless you withdraw from the study, permission for researchers to use your tissue and to use and share your private health information for this study will never end.

Will You Be Paid For Donating Your Sample(s) for Genetic Research and Specimen Banking?

You ***will not*** be paid to donate your sample(s) for genetic research and specimen banking.

Will Donating Your Sample(s) Cost You Any Money?

There is no cost to you to have your samples collected or used for genetic research and/or specimen banking.



Genetic Research/Specimen Banking Options:

You do not have to participate and agree for specimens to be collected for genetic research and specimen banking in order to be in the main part of this study. No matter what you decide to do, your decision will not affect your medical care. You can tell us your choice by placing your initials in one of the options below:

GENETIC RESEARCH & SPECIMEN BANKING:
Please indicate your choice by placing your initials

_____ YES **Your sample(s) may be used for genetic research. Your sample(s) may be saved for future research and stored in a specimen bank.**

_____ NO **Your sample(s) may not be used for genetic research or saved for future work in a specimen bank.**

What are the risks of being in this study?

A risk of allowing us to collect information about you is a potential loss of privacy. The University of Virginia will do its best to protect your records so that facts about you and your health will be kept private. The chance that information identifying you will be given to someone else is very small. However, we cannot *guarantee* it will be safe.

Risks and side effects related to the study drug being tested (dapagliflozin) include:
Likely (up to 4 in 100 people)

- Urinary tract infections
- Runny nose and/or sore throat
- Genital mycotic infection ("yeast infection")
- Back pain
- Increased urination

Less Likely (1 to 3 in 100 people)

- Gastrointestinal disorders (constipation/nausea)
- Dyslipidemia (abnormal levels of one or more fatty substances in the blood)
- Discomfort with urination
- Influenza
- Pain in extremity

Rare but serious (frequency not known)

- Severe hypotension also called volume depletion (occurs as a result of the loss of the body's salt). Symptoms include weakness, fatigue, fainting and dizziness.
- Ketoacidosis (a serious, life-threatening metabolic condition, which can occur even if blood glucose is normal or elevated). Symptoms include nausea, vomiting, abdominal pain, general malaise, and shortness of breath.



- Acute kidney injury (sudden onset kidney failure). Symptoms include reduced urine output, fluid retention, shortness of breath, fatigue, confusion, nausea, weakness, irregular heart rate.
- Urosepsis and pyelonephritis (serious urinary tract infections). Symptoms include kidney pain, fever/chills, and fatigue/malaise.
- Hypoglycemia (low blood glucose) more likely if you are taking insulin or certain other drugs;
- Fournier's gangrene: fever, tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum.
- If any of these occur you will need to seek immediate medical attention: either your physician or go to the ER.

Risks of having an MRI:

MRI scanning is a painless procedure that only requires that you lie quietly on a padded table that gently glides you into a large magnet.

While the scanner is performing your scan, you will hear some humming and thumping sounds. These are normal and should not worry you. Because of the magnetic field and radio frequencies people with any type of metal in their body should NOT have an MRI. This may include things like pacemakers, aneurysm clips or shrapnel. It is important that you inform the technologist if you have any of these metallic appliances. Please inform the technologist if you are pregnant or think that you may be pregnant.

There is a low risk of experiencing symptoms of anxiety or claustrophobia while lying in the scanner. Should you experience these symptoms or otherwise become uncomfortable you can voluntarily stop your participation in this study. There will be NO consequences to your clinical care should you choose to stop your participation.

Risk of using gadolinium:

You will receive or are scheduled to receive a contrast called Gadolinium for your MRI/MRA. This substance will help the tissues show up better.

The following risks are associated with gadolinium contrast:

- Allergic reaction. Some people experience temporary itching after receiving MRI contrast. Less than one person in 300,000 will experience severe allergic reaction which requires treatment. Severe allergic reaction may include s difficulty breathing or wheezing, tightness in the throat, swelling of lips, tongue or throat, fast heartbeat.
- Contrast infiltration. Contrast that is injected outside the vein into other tissues can cause local pain and swelling at the injection site. Treatment generally consists of hot or cold packs and elevation of the affected arm. Infiltrations most often get better over time.
- Temporary metallic taste in the mouth, tingling in the arm, nausea, or headache occurs in less than 1 in 100 people.
- The FDA has received information about an extremely rare disease called Nephrogenic Systemic Fibrosis (NSF) is a rare disease that is linked with the use of Gadolinium in people with severe kidney disease.



NSF causes hardening and thickening (fibrosis) of the skin, connective tissues like muscles, tendons, ligaments, and blood vessels throughout the body. In addition, those who develop NSF may have scarring of their body organs. The signs of NSF also include:

- burning, itching, swelling, hardening and tightening of skin;
- red or dark patches on the skin;
- yellow spots on the whites of the eyes;
- stiffness in joints with trouble moving or straightening the arms, hands, legs or feet;
- pain deep in the hip bones or ribs;
- Muscle weakness.

In most of the cases reported to the FDA, symptoms of NSF started between 2 days to 18 months after a person received the Gadolinium-based contrast agent. NSF may get worse and may lead to death. There is no known treatment for NSF.

If you have any of the symptoms listed above after receiving Gadolinium-based contrast for a study MRI/MRA, please contact the study team immediately. The study team will review your symptoms and perhaps recommend a skin biopsy, which is the only way to determine if you actually have NSF.

The FDA has received information indicating that gadolinium may deposit in the brain and other organs of some people who have had four or more gadolinium contrast-enhanced MRI scans and it may remain for a long time. Although no signs or symptoms of negative health effects or changes to organs have been seen with these deposits to date, it is not known if these deposits may lead to negative health effects in the future.

Before you receive gadolinium/additional gadolinium for research:

- You will be screened by UVA Department of Radiology staff prior to getting gadolinium. If radiology screening shows that it might be unsafe for you to receive this contrast, then you will not be able to receive the contrast.

Risks and side effects related to the stress drug adenosine usually only last while you are receiving this medicine and typically go away in less than one minute after the infusion stops. **The side effects include:**

Likely

- Chest pain/tightness (resolves quickly after the test)
- Shortness of breath (resolves quickly after the test)
- Flushing feeling (resolves quickly after the test)
- Increase in heart rate (resolves quickly after the test)

Less Likely

- Dizziness (resolves quickly after the test)
- Nausea (resolves quickly after the test)
- Decrease in heart rate or change in heart rhythm (resolves quickly after the test)



- Low blood pressure (temporary)

Rare but serious

- Abnormal heart rhythm (usually temporary)
- Difficulty breathing (extremely rare)
- Heart attack (extremely rare)
- Death (extremely rare)

Risks and side effects related to the stress drug regadenoson:

Incidence not known

- Urticaria and Rashes

Likely

- Shortness of breath
- Headache
- Flushing feeling
- Angina or abnormal electrical activity in the heart as measured by ECG

Less Likely

- Dizziness (resolves quickly after the test)
- Chest pain
- Nausea
- Discomfort in your abdomen
- Loss of sense of taste
- Feeling hot

Rare but serious

- Abnormal heart rhythm
- Hypersensitivity (allergic anaphylaxis), angioedema, and decreased oxygen saturation
- Abnormally low blood pressure

Frequency not known, serious:

- Myocardial ischemia (heart attack)
- Respiratory arrest
- Atrial fibrillation/atrial flutter (abnormal heart rhythm)
- Hypertension (high blood pressure)
- Bronchoconstriction (difficulty breathing)
- Seizure
- Cerebrovascular accident (stroke)

In order to reverse the effects of regadenoson, you will be given another drug, called aminophylline, after the stress pictures have been taken. Aminophylline reverses the effects of regadenoson, and most people will experience complete relief from stress symptoms within 3 minutes.

Risks and side effects related to aminophylline, which is given to reverse the effects of regadenoson:

Mild effects, Incidence not known

- Headache
- irritability
- restlessness
- sleeplessness
- trouble sleeping
- unable to sleep

Moderate effects, Incidence not known

- Chest pain or discomfort
- dizziness
- fainting
- fast, slow, or irregular heartbeat
- increase in urine volume
- lightheadedness
- persistent vomiting
- pounding or rapid pulse
- seizures
- shakiness

Risk of x-ray of your eyes (if needed):

This study may involve radiation exposure from an x-ray of your head to ensure that there is no metal in your eyes prior to your MRI exam. As part of everyday living, everyone is exposed to a small amount of background radiation. Background radiation comes from space and naturally occurring radioactive minerals. The radiation dose you will receive from this x-ray will give your body the equivalent of about 2 weeks' worth of this natural radiation. This radiation dose is what you will receive from this x-ray only and does not include any exposure you may have received or will receive from other tests. The risk from this dose is considered small. This radiation exposure is not necessary for your medical care but is necessary to obtain the research information desired.

Risks and side effects related to the Coronary CTA (if applicable):

As a participant in this study, you could receive radiation exposure from a Computed Tomography Angiography (CTA) scan of your heart. Although each organ will receive a different dose, the total effective radiation dose you will receive from this scan is approximately 6 mSv. For comparison this dose is roughly 12% of the annual radiation dose safely allowed for a radiation worker such as the person performing your CTA. The precise risk from this dose is not known but is thought to be small. This radiation dose is what you could receive from this scan only and does not include any exposure you may have received or will receive from

other tests. This radiation exposure is not necessary for your medical care but is necessary to obtain the research information desired. If you are pregnant, you may not participate in this research study. It is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults.

Risks of IV Contrast given during the coronary CTA:
Likely

- Flushing

Less Likely

- Nausea, vomiting
- Discomfort, bleeding or bruising from IV insertion

Rare

- Rash/Hives

Rare but serious

- Allergic reaction to the contrast dye which could cause you to have a drop in blood pressure, difficulty breathing, increase in heart rate
- Kidney failure from IV contrast
- Fluid leaks from IV into your arm causing pain

Risks and side effects related to receiving nitroglycerin under your tongue during the coronary CTA:
Likely

- Headache

Less Likely

- Dizziness
- Nausea
- Flushing
- Burning/tingling under tongue

Rare

- Fainting
- Fast/irregular/pounding heartbeat

Rare but serious

- Serious allergic reaction to drug (rash; itching or swelling of the face or throat; severe dizziness; trouble breathing).

Risks and side effects related to receiving metoprolol during the coronary CTA:
Likely

- Slow heart rate- for short time after receiving drug



Less Likely

- Dizziness- for short time after receiving drug
- Drop in blood pressure- for short time after receiving drug

Very Rare: (less than 1 of every 100 subjects may experience)

- Wheezing
- Shortness of breath

Risks of Holding Medications Prior to Testing:

You are being asked to hold (stop taking) certain medications prior to cardiac imaging test for this research. Holding doses of your medications may include some risk. The specific risks and the likelihood of experiencing any symptoms will depend on which medications you are taking, and are summarized below. The Investigators will review your medications and tell you which medications would be affected. You will be able to resume these medications immediately following the cardiac imaging tests described in this consent form.

Risks of Holding Specific Cardiac Medications:

- **Beta blockers**
  - Risks of Hold:
    - Chest pain
    - Hypertension
    - Arrhythmias
    - Elevated heart rate
    - Feeling anxious
  - Frequency: Less likely
- **Alpha blockers**
  - Risks of Hold:
    - Difficulty with urination
    - Hypertension
  - Frequency: Likely
- **Calcium-Channel blockers**
  - Risks of Hold:
    - Chest pain
    - Hypertension
    - Arrhythmia
  - Frequency: Likely
- **Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin Receptor Antagonists**
  - Risks of Hold:
    - Hypertension
  - Frequency: Likely
- **Diuretics**
  - Risks of Hold:



        - Swelling
        - Hypertension
    - Frequency: Likely
- **Phosphodiesterase inhibitors**
    - Risks of Hold:
        - Chest pain
        - Dizziness
        - Shortness of breath
    - Frequency: Likely
- **Long-acting nitrates**
    - Risks of Hold:
        - Chest pain
    - Frequency: Likely

Risks of Sharing the Drug

Do not share the study drug with anyone. It is prescribed only for you and could hurt someone else. Keep it out of reach of children and people not able to read or understand the label.

Risks from Placebo:

Some participants in this study will receive a placebo. Taking a placebo is the same as not taking any active study drug. If you receive placebo, your known or suspected heart disease may get worse, stay the same, or improve, just as it may have done without any treatment.

Risks from Completing Questionnaires:

Some of the questions asked may be upsetting, or you may feel uncomfortable answering them. If you do not wish to answer a question, you may skip it and move on to the next question.

During the research, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your response, the staff may provide you with help to get treatment. This may include working with you to contact your doctor or therapist, referral to a therapist to discuss your thoughts, contact a trusted family member, significant other or clergy or work with you on a plan that may include getting you to a hospital for safety and treatment.

Risks of having your blood drawn:

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and
- ✓ infection (rare).

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or
- ✓ other infections.

You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV or any other infection that may affect your clinical care, we will tell you the results and help you understand what the results mean for you.

Risks for women:
Being in this study might hurt your unborn or nursing baby, so you will not be able to join or stay in the study if you are pregnant or breastfeeding. You must use an effective method of birth control during the study. If you have questions about birth control, please ask the study leader. If you are pregnant now, or get pregnant during the study, please tell us right away.

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?
You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?
You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include:

- Management of risk factors with medication and lifestyle modification

If you are an employee of UVA, your job will not be affected if you decide not to participate in this study. If you are a student at UVA, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?
You will be paid $300 for finishing this study. If you do not finish the study, you will be paid $100 for each study visit that you complete.

You may be reimbursed for travel expenses. If your round-trip distance to UVA is 120 miles or more, your mileage will be reimbursed at the IRS rate.

If you need overnight accommodation at the study site, please talk to the study team.



You may choose to receive these payments by check or as gift cards. If you choose to be paid with gift card(s), the study team will collect your social security number. Gift card payments will be given to you at study visits or mailed to your address. If you choose to be paid by check, you will need to register as a Vendor of UVA. The study team will collect your email address and telephone number for Vendor registration. You should get your check within 30 days after each visit. Whether received as checks or gift cards, these payments will be reported to the IRS as income.

By agreeing to be in this study, you are donating your blood samples for research, and giving up any property rights you may have in them. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

Will being in this study cost you any money?

The following procedures/tests, which are being done for research purposes (refer to Study Schedule), will be provided at no cost to you or your health insurance:

- Coronary CTA (if applicable)
- Electrocardiogram ("EKG")
- Stress Cardiac MRIs with gadolinium-based contrast
- Blood and urine testing
- Examinations by study staff
- Study drug

You and/or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and/or your health insurance may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan. You may be responsible for any co-payments or deductibles. You may wish to ask your insurance company for an estimate of what these costs might be or if pre-approval is required.

Your travel costs may also be reimbursed. See the "Will you be paid for being in this study?" section of this form for more information.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study, you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?



You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health
b) Your condition gets worse
c) The side effects of the treatment are too dangerous for you
d) New information shows the treatment will not work or is not safe for you
e) You do not follow your doctor's instructions
f) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to return to UVA as soon as possible for and end-of-treatment visit. Please contact Dr. Rodriguez, or the study coordinator as soon as you decide to stop participating in the study.

Any data collected about you up until the time you leave the study must be kept in order to determine the results of the study.

How will your personal information be shared?

The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address, and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers.
- Tissue or blood samples if you agree to provide them for genetic testing for this study

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)

- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the blood collected for ***inflammatory biomarkers*** (as described on page 9) will be shared with researchers outside of UVA. No one outside of UVA will receive information that could identify you directly. Instead, your samples will be sent with a code. Only the UVA team will know which coded samples are yours.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

Information obtained from you during this study may be used in future research. Your information may be shared with other researchers inside or outside of the University of Virginia. They will not be sent information that could identify you such as name, address or phone number.

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 if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Your information, collected for this study, will be protected by a Certificate of Confidentiality from the federal government. If UVA receives a subpoena or court order demanding information from the study records that would identify you, we will use the Certificate to resist the demand. However, UVA will not use it in the following cases.

- You have agreed in writing to allow UVA to share the information with your employer, your insurance company for billing purposes, or someone else
- Reports to authorities where there is a danger that you may harm yourself or others, or if there is evidence of probable child or elder abuse or neglect.

In addition, the Certificate does not prevent government authorities who oversee research from reviewing this study. This Certificate does not mean that the government either approves or disapproves of this study. It just helps protect your privacy.



Please contact the Principal Investigator listed earlier in this form to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22903 Telephone: 434-924-2620

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the UVA Study Tracking Number (at the bottom of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

You may also report a concern anonymously by calling the UVA Compliance Hotline phone number at 1-800-235-8700.

Would you like the study team to communicate with you by email or text message?
If you choose to communicate with the study team by unsecure email (email that is not encrypted) or text message to your personal phone, there is some risk that your health information could be read or accessed by someone else while the information is sent or saved by your email or phone provider.

Your personal email or phone provider may also share or release your information because they do not have to follow the privacy laws that UVA follows. Sometimes email and phone providers release information to marketing companies for use in direct advertising. If you choose to communicate by email or text messaging, UVA cannot control this potential loss of privacy, but we want to tell you about this possible risk.

You do not have to agree to communicate with the study team by email or text message to be in this study. If you agree to texting or emailing, the study team will collect your phone and /or email address from you that you would like them to use to contact you. Please note, if you agree to text messaging, charges may apply depending on your data/text plan with your phone provider.



Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form, it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below, you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Notification of My Health Care Provider

Please indicate below whether you want us to notify your health care provider that you have agreed to take part in this study.

_____ Yes, I want the study doctor to notify my health care provider that I have agreed to take part in this study.

Health Care Provider Name:
Health Care Provider Address:
Study team will send a copy of the consent form to the health care provider.

_____ No, I do not want the study doctor to notify my health care provider that I have agreed to take part in this study or I do not have a health care provider.



Leaving the Study Early

Signatures should be obtained in this section if the subject decides to leave the study early.

If you leave the study early the study leader will keep the data collected about you up until the time you leave the study to help determine the results of the study.

Check one option below:

_____ I am withdrawing my consent from the intervention or treatment part of this study but agree to continue to have follow up information about me collected by the study team.

The follow up information will be collected by:

- Obtaining information from my medical records
- In person follow up visit including physical examination, blood testing, and quality of life questionnaires.
- If you are unable to return to UVA for a follow up visit, we will conduct this visit by phone. The study team will provide you with a pre-paid mailer to return your study drug containers and questionnaires.

_____ I am withdrawing my consent for this study. No additional information may be collected about me including follow up information from my medical records.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below, you confirm that you have fully explained the implications of withdrawing from the study to the subject and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE