Brief Title: The ENCHANTMENT HIV Study

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Protocol Title: ENding subClinical Heart failure using an Aldosterone and Natriuretic peptide Targeted treatMENT in HIV (The ENCHANTMENT HIV study)

Principal Investigator: Suman Srinivasa, MD

Site Principal Investigator:

Description of Subject Population: Persons with and without HIV with abnormal heart structure and function (LONGITUDINAL STUDY)

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Partners now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

In this research study we want to learn more about heart disease before symptoms present among persons with and without HIV. In addition, we want to understand if the study medication sacubitril/valsartan can improve heart disease in people with HIV disease. HIV disease has been linked to an increased risk of heart disease, abnormal heart structure and function, and inflammation.

How long will you take part in this research study?

Baseline Study
Both persons with and without HIV will participate in a baseline study to look at the heart structure and function.

If you decide to join this baseline study, the duration of this part of the study will be approximately 2-3 months from time of enrollment (signing consent) to completing the final study visit, which is dependent on the scheduling of the visits. During this time, we will ask you to make up to 4 study visits to Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH).

Treatment Study
Persons with HIV will participate further in a treatment study that will last approximately 6 months. If you decide to join this research study, the duration of the study will be approximately 8 months from time of enrollment (signing consent) to completing the final study visit, which is dependent on the scheduling of the visits. During this time, we will ask you to make up to 11 study visits to Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH).

What will happen if you take part in this research study?

If you decide to join this research study, the following things will happen: physical exam, blood sampling, ultrasound of the heart, magnetic resonance imaging (MRI) of you heart. If you are in the treatment study, you will be assigned to take study medication (sacubitril/valsartan) or placebo for 6 months. A placebo looks exactly like the study drug, but it contains no sacubitril/valsartan.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. During this study, you will receive regular physical exams with blood pressure monitoring, lifestyle counseling to improve nutrition and physical activity, and screen testing that will evaluate for

clinically significant heart disease. Others with heart disease may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include:

You will have two imaging scans of the heart—an ultrasound of the heart and magnetic resonance imaging of the heart.

In the treatment study, you may be assigned to take the study medication (sacubitril/valsartan) or placebo. Sacubitril/valsartan is approved by the U.S. Food and Drug Administration (FDA) for the treatment of heart failure with reduced ejection fraction.

A placebo looks exactly like the study drug, but it contains no sacubitril/valsartan. We use placebos in research studies to learn if the effects seen in research subjects are truly from the study drug or from other reasons.

A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called "What are the risks and possible discomforts from being in this research study?"

Other things to consider are if you are in the treatment study, you will be participating for approximately 8 months and will be asked to take study medication for 6 months.

What other treatments or procedures are available for your condition?

There are no other current treatments or procedures that are available to specifically improve heart structure and function among persons with HIV with no known symptoms or history of heart disease.

Your alternative is to not take part in this research study. If you choose not to take part in this study, you will receive standard medical care to optimize your risk factors as prescribed by your doctor.

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Suman Srinivasa, MD is the person in charge of this research study. You can call her at [redacted]. You can also call the nurse practitioner [redacted] or study coordinator [redacted] with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call the study coordinator [redacted]

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study

Detailed Information

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.

Why is this research study being done?

In this research study we want to find out if sacubitril/valsartan can improve heart structure and function among people with HIV who do not have a known history of heart disease or symptoms. HIV has been linked to an increased risk of heart disease, abnormal heart structure and function, and inflammation. If you are in the treatment study, you will be assigned to take study medication (sacubitril/valsartan) or placebo for 6 months. A placebo looks exactly like the study drug, but it contains no sacubitril/valsartan.

Who will take part in this research?

Your participation in this study is voluntary. We are asking you to take part in this study because you are an adult without known heart disease. About 20 persons without HIV and 50 persons with HIV will take part in this research study. We anticipate that up to 120 subjects will be screened to arrive at the 50 persons with HIV and 20 persons without HIV who will complete the study. We expect to enroll all the subjects at MGH and BWH.

To qualify for this study, you must be an adult with or without HIV and no known prior history of heart disease with evidence of abnormal heart structure or function on imaging studies. We use transthoracic echocardiography (TTE) scans (ultrasounds) of the heart to look for changes in the structure and function of the heart.

The National Institutes of Health (NIH) is paying for this research to be done.

What will happen in this research study?

For persons with HIV (Visits 1-11):
You will be asked to come to MGH for 7 study visits, which will take place at the MGH Translational and Clinical Research Center (TCRC), located on the 12th floor of the White building (55 Fruit Street, Boston, MA 02114) or the MGH Metabolism Unit (2 Longfellow, Boston, MA 02114).

You will also be asked to come to BWH for 4 study visits, which will take place at the BWH Center for Clinical Investigation (CCI), located on the 9th floor of the main tower, Section 9A (75 Francis Street, Boston, MA 02115) or the Outpatient Center located on the 3rd floor of 221 Longwood Ave, Boston MA 02115.

- Screening Visit 1 (V1) and all and Safety Visits (V5, V6, V7, V8, V9, V10) will take place at the Translational and Clinical Research Center (TCRC) or the Metabolism Unit at MGH.

- Screening Visit 2 (V2), Baseline Visits (V3, V4) and 6 Month Visit (V11) will take place at the Center for Clinical Investigation (CCI) at BWH. Baseline Visits (V3, V4) and 6 Month Visit (V11) are inpatient visits that require you stay overnight (overnight portion may be omitted pending investigator's approval).

You will be escorted to each of the procedures by a member of the study staff.

You will also need to follow a special diet before the Baseline Visits (V3, V4) and 6 Month Visits (V11).

All of the study procedures including the special diet are explained in more detail following the description of study visits.

If you are a woman who can become pregnant, we will collect a urine sample for a pregnancy test at each visit. You cannot take part in the study if you are pregnant.

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures. After you have signed this consent form, we will do some tests and procedures over two screening visits to find out if you qualify to take part in the study. The study doctor or nurse practitioner will review the results of these tests and procedures. If you don't qualify, the study doctor or nurse practitioner will tell you why.

NOTIFICATION OF CHANGES DUE TO COVID 19

We are providing this notification because you are participating in a research study and we are making changes to study visits to comply with public health efforts to address COVID- 19 (coronavirus). MGH and BWH have instituted restricted visits for research purposes in response to the evolving COVID-19. These restrictions have prompted the following changes to the study:

Regarding Remote Study Visits

Going forward, visits may be done remotely until the restrictions are lifted at your study site. Remote visits will be conducted over Zoom video conferencing or telephone and every attempt will be made to keep the visit schedule the same. Changes may occur to the visit schedule due to factors related to COVID19. During these visits, someone from the study staff will contact you (via Zoom video conferencing or telephone) and may conduct the following research activities:

- Consenting
- Obtaining information about past and present health
- Questionnaires
- Lifestyle Counseling
- Obtaining information related to safety assessments

Study staff will provide you information on how to access the video conferencing platform. We will launch the video conferencing in a private and secure area. To protect your privacy, we ask that you do not take screenshots, photographs, or recordings of any kind with any electronic equipment.

We would like to remind you that a video meeting is similar to us visiting you at home. We may learn more about your home and the people living with you than we would during a visit at the hospital. For example, we may learn information from you that must be reported to public health or public safety authorities. We are required by law to report known or suspected child or elder abuse. If we make such report, the public health and safety authorities can use the information as they see fit and may end up sharing it with other government agencies. Please ask the research staff if you have any questions about this prior to your video visit.

Regarding Study Drug

Study drug shipments may be made directly to you. The courier responsible for delivering study drug to you will require your contact information in order to arrange shipments. During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator [redacted]

Regarding Laboratories

If blood work cannot be obtained at the study site, we may ask that you have your labs performed locally. It is important to assess safety labs while you are on study drug. We will provide you with an order for the labs and the study staff can assist with finding a location.

Regarding Scheduling of Visits

It may be that we are unable to conduct an in-person study visit due to policies related to COVID19. We will try to arrange for assessments to occur remotely and continue to follow the visit schedule. Some study procedures require a visit to the study site, for example, imaging procedures. We may provide you with additional study drug until we are able to perform the study procedure, and this may extend your visit schedule. If a study procedure requires an in-person visit and cannot be scheduled at the study site due to COVID19 policies, then the procedure may be omitted.

Description of study visits:

Screening Visit 1 (V1)

The Screening Visit 1 is an outpatient visit at MGH and will take about 2 hours.

At Screening Visit 1:

- We will ask you questions about your past and present health;
- We will perform a physical exam;
- You will meet with a nurse for measurement of your vital signs (blood pressure, temperature and pulse);
- If you are a woman who can get pregnant, urine will be obtained for a pregnancy test. You cannot be in the study if you are pregnant; and,

- The nurse will also draw your blood. The blood tests we will do include tests for potassium, kidney and liver function, complete blood count (measuring the amount of blood cells in your blood), HbA1c (measuring your sugar levels over the past 3 months), and HIV viral load (if you have a history of HIV); and,
- You will meet with the nutritionist who will take body composition measurements. You will be given a diet record which we will ask you to return at V5 if you qualify for the study.

If you qualify to take part in this research study after you complete Screening Visit 1, we will ask you to return for Screening Visit 2. You will be given a urine container. You will need to start a urine collection 24 hours prior to the morning of your next visit only if you qualify to participate in Screening Visit 2.

Screening Visit 2 (V2)
The Screening Visit 2 is an outpatient visit at BWH and will take about 1.5-2 hours. We will ask that you start collecting your urine the day before this visit and bring with you to the visit. The study staff will provide you with a special container to use for the collection. You will need to fast overnight for 12 hours before your second visit. Fasting means that you cannot have anything to eat or drink, except for water and your medication. We will give you a lunch voucher at the end of this visit.

At Screening Visit 2:

- If you are a woman who can get pregnant, urine will be obtained for a pregnancy test. You cannot be in the study if you are pregnant;
- We will collect urine to measure your salt balance;
- The nurse will draw your blood after you have fasted overnight. The blood tests we will include tests for markers of heart disease and inflammation stored for research if you have given permission; and,
- You will have an ultrasound scan of the heart, or transthoracic echocardiogram (TTE) to evaluate changes in the heart structure and function.

Based on the results of the TTE scan, we will determine whether you qualify for the study. If you qualify for the study, we will invite you to return for the remainder of the study if you would like to.

If you qualify for the study and decide to participate, we will ask you to fill out the diet record and bring this to V5.

Baseline Visits (V3,V4)
V3 (Baseline Visit Part 1)

This visit is an inpatient visit and will occur at the BWH. You will be asked to stay overnight. The visit will last approximately 18 hours. For 3 days before V3, we will ask you to follow a special high salt diet. On the morning of the visit, we will ask that you start collecting your urine in a special container provided by study staff. You will bring this container to the visit and we will continue the collection. You will fast except for water for approximately 3 hours on the day of the visit before we meet you.

At V3:

- If you are a woman who can get pregnant, urine will be obtained for a pregnancy test. You cannot be in the study if you are pregnant;
- We will also collect urine to measure your salt balance. The study visit will continue if you are in high salt balance;
- You will meet with the study doctor or nurse practitioner to review your past and present health and any medication you are taking;
- You will have a physical exam by the study doctor or nurse practitioner;
- You will meet with a nurse for measurement of your vital signs (blood pressure, temperature and pulse) while lying flat and standing;
- You will have an ultrasound scan of the heart, or transthoracic echocardiogram (TTE).
- We will have you fast overnight except for water for 8 hours. We will ask that you remain lying down in bed overnight;
- An IV catheter will be inserted;
- In the morning, we will draw your blood for several hormones and markers of heart disease and inflammation;
- We will draw blood for DNA testing for genes that are associated with heart disease if you have given permission;
- A member of the study staff will take you to another location at BWH for cardiac MRI scan of your heart;
- You will receive your meal after completing the MRI;
- We will have you meet with a member of the nutrition staff. The nutritionist will provide you with low salt meals and snacks. You will be asked to eat a low salt diet for 6 days before V4; and,
- You will be given a urine container for use during the next study visit.

V4 (Baseline Visit Part 2)

This visit is an inpatient visit and will occur at the BWH. You will be asked to stay overnight. The visit will last about 16 hours. For 6 days before V4, we will ask you to follow a special low salt diet and refrain from exercise. On the morning of the visit, we will ask that you start collecting your urine in a special container provided by study staff, so we can measure your salt

balance on the low salt diet. You will bring this container to the visit and we will continue the collection.

At V4:

- If you are a woman who can get pregnant, urine will be obtained for a pregnancy test. You cannot be in the study if you are pregnant;
- We will continue to collect urine to measure your salt balance. The study visit will continue if you are in low salt balance and may be rescheduled if you are not in low salt balance;
- You will meet with the study doctor or nurse practitioner to review your past and present health and any medication you are taking;
- You will have a physical exam by the study doctor or nurse practitioner;
- You will meet with a nurse for measurement of your vital signs (blood pressure, temperature and pulse) while lying flat and standing;
- We will have you fast overnight except for water for 8 hours. We will ask that you remain lying down in bed overnight;
- An IV catheter will be inserted;
- In the morning, we will draw your blood for several hormones while lying flat;
- You will then stand for 45 minutes and we will measure some hormone levels in your blood after you have been standing for 45 minutes. This is called a posture study;
- You will receive your meal after this blood draw; and,

Overnight stays may be omitted pending investigator approval. If overnight stay is omitted, you will still be asked to complete the high sodium diet, imaging, and blood draw.

You will start the study medication following completion of the baseline procedures.

For participants in the treatment study:

In the treatment study, you may be assigned to take the study medication (sacubitril/valsartan) or placebo. Sacubitril/valsartan is a combination of two medications in the form of one pill. The FDA has given us permission to evaluate the benefit of sacubitril/valsartan to treat heart disease among persons with HIV. Sacubitril/valsartan works by blocking the action of aldosterone, a natural substance in the body that raises blood pressure and sodium, and increasing brain natriuretic peptide, a natural substance in the body that protects the heart structure and maintains blood volume. In this study we would like to see if by blocking the action of aldosterone and increasing brain natriuretic peptide will improve the heart's structure and function and other markers of heart disease and inflammation.

Assigning you to study drug (sacubitril/valsartan or placebo)

At the end of V4, we will assign you by chance (like a coin toss) to either the sacubitril/valsartan group or the placebo group. You and the study doctor cannot choose your study group. You will have an equal chance of being assigned to the sacubitril/valsartan or to the placebo group. You and the study doctor will not know which study group you are in, but we can find out that information if we need it.

We will give you a supply of the study drug to take home with you. The study drug is taken twice a day. For the first week you will take 24/26 mg twice a day. At V5 (approximately 1 week after V4), we will increase the dose of sacubitril/valsartan to 49/51mg twice a day.

The Lifestyle Modification Program

All subjects in this research study will take part in the lifestyle modification program. As part of this program you will participate in counseling sessions. You will meet with study staff for about 45 minutes during your visits to MGH.

The counseling sessions will include information on topics such as different kinds of nutrients, helping you to identify "good" and "bad" nutrients in your diet, and the importance of exercise recommendations.

As part of this program we will encourage you to do at least 3 hours of physical activity a week. We will also ask you to fill out four day food diaries and activity questionnaires during the study.

Safety Visits (V5, V6, V7, V8, V9)

Safety visits will occur approximately around 1 week, 2 weeks, 4 weeks and 2 and 3 months after starting study medication. There are a total of 5 safety visits. We call these visits "safety visits" because we want to assess if you are having any side effects from the study drug. These are outpatient visits that will take place at MGH. These visits will take about 45 minutes.

You will need to fast overnight for 12 hours before the V9 (3 Month Safety Visit). You do not need to fast before the other safety visits. We will give you a lunch voucher at the end of this visit only.

At the Safety Visits:

- If you are a woman who can get pregnant, we will ask you for a urine sample. We will test your urine for pregnancy;
- You will meet with the study doctor or nurse practitioner to review your past and present health and any medication you are taking;
- You will have a physical exam by the study doctor or nurse practitioner;
- You will meet with a nurse for measurement of your vital signs (blood pressure, temperature and pulse);

- The nurse will draw your blood to check potassium, kidney function, blood counts, and a protein related to the study medication and only at V9, we will draw blood for markers of heart disease and inflammation;
- You will receive lifestyle modification counseling;
- At V5, you will be asked to bring in your diet record. The nutritionist will review the diet record and an activity questionnaire;
- At V5, you will be asked to participate in an optional beginning of study nutrition education and lifestyle counselling survey. If you choose not to participate in this survey, it will not affect your participation in the study; and,
- At V5, V6, V7, V8, and V9, we will collect any unused study drug and give you a new supply of study drug.

Final Safety Visit (V10)
This is an outpatient visit that will take place at MGH approximately 2 weeks prior to the end of study 6 Month Visit. This visit will take about 45 minutes.

At this Safety Visit:

- If you are a woman who can get pregnant, we will ask you for a urine sample. We will test your urine for pregnancy;
- You will meet with the study doctor or nurse practitioner to review your past and present health and any medication you are taking;
- You will have a physical exam by the study doctor or nurse practitioner;
- You will meet with a nurse for measurement of your vital signs (blood pressure, temperature and pulse);
- The nurse will draw your blood to check HbA1c (measuring your sugar levels over the past 3 months) and HIV viral load (if you have a history of HIV);
- You will meet with the nutritionist who will take body composition measurements, review a diet record and an activity questionnaire. You will also receive lifestyle modification counseling;
- You will be asked to participate in an optional end of study nutrition education and lifestyle counselling survey. If you choose not to participate in this survey, it will not affect your participation in the study.
- You will be given a urine container for use during the next study visit.

6 Month Visit (V11)
This visit will be the same as V3.

Description of Study Procedures

TTE Scan of the Heart (V2, V3, V11)

You will have an ultrasound scan of your heart. The ultrasound technician will apply a clear gel to your chest area. An imaging device will be placed on your chest area to obtain images of your heart. We will ask you to lie on a bed on your back and side for about 60 minutes. You may be asked to change positions in order to look at the heart from different angles. The total duration of the TTE of the heart and stomach is about 45-60 minutes.

MRI Scan of the Heart (V3, V11)
If you are able to get an MRI with contrast, you will have an MRI scan of your heart. We will ask you to lie still on a table. The table slides into a tunnel slightly wider than your body. There is little room in the tunnel. You will be in constant voice contact with the MRI staff.

An (IV), a very thin, flexible tube which will be put in a vein using a needle) will be placed in your forearm. During the MRI scan, we will give you a small injection through an IV of contrast called gadolinium, which allows us to image blood flow of your heart muscle. Approximately 15-30 minutes later, you will receive a small injection through an IV of regadenoson which is used to dilate your blood vessels. While you receive regadenoson, we will repeat the blood flow imaging of your heart muscle. During and after the regadenoson, we will monitor your heart rate and blood pressure every minute. We will also check your heart rhythm with an ECG. During the MRI scan, we will also obtain an image of your abdomen to measure belly fat. This will not require IV contrast. The total duration of the MRI of the heart and stomach is about 45-60 minutes.

High Salt Diet (V3, V11)
For 3 days prior to the Visit 3 and Visit 11, you will be placed on a high salt diet similar to the everyday diet consumed by many people in the United States. During your in-patient portion of the study, we will provide you with high salt meals. During your outpatient portion of the study, you will consume your normal daily meals at home and we will supplement them with high salt broth, and suggestions for high salt meals and snacks. Your dietary plan will be provided to you before you start your high salt meal plan.

Low Salt Diet (V4)
We will ask you to follow a special prepared low sodium diet for approximately 6 days before Visit 4. We are controlling the amount of salt that you are eating since dietary salt will change the levels of hormones in your body, which we are studying. A dietician (a food and diet expert) will call you to talk about your food choices for the controlled diet. We will ask you to eat all the food that is provided and do not perform any exercise while on the low salt diet. It is very important that you do not eat anything other than the food provided for you for these few days.

24 Hour Urine Collection (V2, V3, V4, V11)
At least one week before V2, V3, V4, and V11 we will mail or give you a urine collection container and instructions on how to collect your urine for the 24 hours before your visit. We

will use the urine you collect to determine the amount of potassium, sodium, and aldosterone (a hormone) in your urine. We will ask you to bring the collected urine on the day of your visit.

Blood Drawing
The total amount of blood drawn for the baseline portion will be approximately ¾ pint over approximately 2-3 months. If you participate in the treatment study, there will be about an additional ½ pint drawn over approximately 6 months. By comparison, the Red Cross allows a healthy adult to donate 1 pint of blood every 8 weeks.

Food Diary/Diet Record (V5, V10)
For 4 days prior to the V5 and V10, we will ask you to write down everything that you eat (all meals and snacks) in a food diary. This will take you about 15 minutes each day to complete. You will need to bring the food diary with you when you return for your visit.

Activity Questionnaire (V5, V10)
We will also ask you to complete an activity questionnaire that will ask you to record the ty types of activities you do. You will complete this questionnaire at visits V5 and V10.

Optional Nutrition Education and Lifestyle Counseling Survey (V5, V10)
We will also ask you to complete a questionnaire that will help us understand if your nutrition education and lifestyle changed from the beginning to the end of the study. You will complete this questionnaire at visits V5 and V10. You may chose not to complete these surveys.

Fasting
Before specified visits, you must not eat or drink anything, including food, beverages, candy, and gum before your visit. Depending on the study visit, we may ask you to fast for approximately 8-12 hours. You are allowed to take your prescription medications and you are encouraged to drink water while you are fasting.

Stopping the Study Early

If you decide to stop taking part in the study for any reason, we will ask you to make a final study visit. You will need to return all unused study drug at this visit. The final study visit will be the same as V11. You will be reimbursed for you time and travel depending on the study procedures that will take place as detailed in the renumeration section.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- Your blood potassium level is increased. We will check your blood potassium level at every visit during the study. If your level is increased we will have you return to the MGH TCRC to have an additional blood draw to recheck your level. If your potassium level remains elevated we will take you out of the study.

- You have any serious side effects from the study drug.
- You have abnormal kidney function tests.
- You develop anemia (decreased number of red blood cells).
- The study doctor thinks it is best for you to stop taking the study drug.
- You need to take a new medication that is not allowed in this study.
- You become pregnant.
- The Sponsor decides to stop the study.
- We stop doing the study for other reasons.

If you are taken out of the study, we will ask you to come in for a final study visit. This visit is the same as V11. We ask that you return for a final visit to be able to assess for any changes that you may have experienced related to the study drug during your study participation.

Study Information Included in Your Electronic Medical Record
A notation that you are taking part in this research study will be made in your electronic medical record. Information from the research that relates to your general medical care and study related care will be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs, and imaging tests).

Partners Alert System
Partners has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department for any reason. This alert will let the study doctors know why you are there. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

How may we use and share your samples and health information for other research?

The samples and information we collect in this study may help advance other research. If you join this study, we may remove all information that identifies you (for example your name, medical record number, and date of birth) and use these de-identified samples and data in other research. It won't be possible to link the information or samples back to you. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses.

At the completion of this research study, we would like to store and be able to use and share your deidentified samples and health information with researchers at Partners for other research related to heart disease. If we share your samples and/or health information with other

researchers outside of Partners, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer/file.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to heart disease?

YES NO Initial _____

OPTIONAL PARTICIPATION

Communication with Your Doctor
With your permission, we may obtain medical history from your primary care doctor that we think may be important to this study.

Do you agree to have your primary care doctor discuss your medical history?

Yes ☐ No ☐ initials:_____

With your permission, we may contact your primary care doctor to make them aware of your participation and to send results of standard clinical findings of the medical tests that are done in this study that we think may be important to your health.

Do you agree to have your primary care doctor receive test results?

Yes ☐ No ☐ initials:_____

DNA Collection
Some of the blood we collect will be used to look at your genes (DNA) or inflammatory cells. All living things are made of building blocks called cells. Genes are the part of cells that contain the instructions which determine important things about you, like your height or hair color, and

also influence your health. Your genes are passed down from your parents and then passed on to your children. DNA is the material in the cells that makes up your genes. The genes that we will be looking at include ones that can change the way blood vessels or the heart react or contribute to inflammation and metabolic disease.

Since we are not studying other members of your family, this information will only be useful as part of a group analysis rather than an individual assessment. After the active enrollment phase of this study is complete, continued analysis of the samples will be performed, therefore all samples will be stored.

We may also perform a whole genome analysis on your DNA sample. Usually researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome studies, all or most of your genes are analyzed and used by researchers to study links to cardiovascular disease, diabetes, and HIV. In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

We would like to use some of the blood we collect to look at your genes (DNA). Do you agree to this genotyping? This will require us to draw an additional 20mL (less than 1.5 tablespoons) of blood total during visit 3? Do you agree to this collection?

Yes ☐ No ☐ initials:_____

We would like to collect white blood cells in order to look at the genes involved in inflammation and heart function. This will require us to draw an additional 20mL (less than 1.5 tablespoons) of blood total each during visits 3, 4 and 11. Do you agree to this collection?

Yes ☐ No ☐ initials:_____

Future Studies
There may be future studies that you may qualify to take part in. Can we contact you in about future research studies?

Yes ☐ No ☐ initials:_____

Will you get the results of this research study?

- Generally, we will not give you or your doctor information about the results of your individual participation in the research study. The research we are doing is only a stepping stone in understanding heart disease. Most of the findings that come from studying your samples or information will not be relevant to your personal health. However, in the future, this may change.
- It is important to remember that research results are not always meaningful and are not the same as clinical tests. While you should not expect to get any information about the results of your participation in this research, if experts from the study decide that research results from your samples are of high medical importance, we will attempt to contact you. In some situations, follow-up testing might be needed in a certified clinical lab. You and your medical insurer may be responsible for the costs of these follow-up tests and any follow-up care, including deductibles and co-payments.
- It is possible that you will never be contacted with individual research results. This does not mean that you don't have or won't develop an important health problem.

What are the risks and possible discomforts from being in this research study?

Risks of Taking Sacubitril/Valsartan
Possible side effects include:

- low blood pressure (common)
    - symptoms of low blood pressure may include:
        - tiredness or weakness
        - feeling dizzy
        - confusion

      During all safety visits, we check your blood pressure to make sure it remains in a normal range on the study medication. We may ask that you stop the medication or decrease the dose if your blood pressure is too low.
- increases in potassium levels (common)

- symptoms of increased potassium levels may include:
  - tiredness or weakness
  - a feeling of numbness or tingling
  - nausea or vomiting
  - trouble breathing
  - chest pain
  - palpitations or irregular heartbeats

  During all safety visits, we check your potassium level to make sure they remain in a normal range on the study medication. We may ask that you stop the medication or decrease the dose if your potassium level is high. If your potassium levels are too high, we may additionally speak with your PCP about giving you a potassium lowering medication and/or you may need to be observed under the levels are reduced.

- decreases in kidney function (common)
- anemia or low red blood cell counts (common)
- cough (uncommon)
- rash (uncommon)
- lip or tongue swelling (uncommon)

Rare but serious side effects include: chest pain, tingling in arms and legs, loss of muscle tone, weakness or heaviness in legs, confusion, lack of energy, cold, gray skin, or irregular heartbeat. If you experience any of these possible side effects, chest pain, tingling in arms and legs, loss of muscle tone, please call the study doctor immediately.

People who are pregnant, on certain medications for high blood pressure, potassium supplementation, or severe liver or kidney function will not be allowed to take part in the study.

As with any drug, an allergic reaction may occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of Taking Sacubitril/Valsartan with Other Medications (uncommon)
Certain medications may cause serious side effects when taken with sacubitril/valsartan. The study doctor will review your medications to make sure that it is safe for you take sacubitril/valsartan.

For your safety during this study, call your study doctor or nurse practitioner BEFORE you take any:

- New medications prescribed by your own doctor
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

Risks to an Embryo or Fetus, or to a Breastfeeding Infant (rare but serious)
The effect of sacubitril/valsartan on an embryo or fetus (developing baby still in the womb) or on a breastfeeding infant may be harmful. Use of this medication during the second and third trimesters may affect kidney function of the fetus or cause death. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are a woman who is able to become pregnant you must use an appropriate birth control method for the entire study. We require using two forms of birth control for the duration of this study.

Acceptable birth control methods for use in this study include:

- intrauterine device
- barrier method such as diaphragm with spermicide, condom
- complete abstinence

If you become pregnant or think you are pregnant during the study, you must stop taking the study medication. Please tell the study doctor immediately.

Risks of TTE Scan (uncommon)
The TTE is an ultrasound and has no known side effects. If you feel uncomfortable during the positioning of the TTE, the TTE can be stopped at any time at your request. There may be critical incidental findings on the TTE study. If any of these findings are clinically interpreted as critical, you may be withdrawn from the study and referred to the primary care physician for further evaluation**.** You may receive a referral to address the findings.

Risks of MRI Scan (common)
MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the

MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped. There may be incidental findings on the MRI study. If any of these findings are clinically interpreted as critical, you may be withdrawn from the study and referred to the primary care physician for further evaluation**.** You may receive a referral to address the findings.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

Risks of Contrast (Dyes) (rare but serious)
Some people are allergic to contrasts (dyes). Gadolinium is used for the cardiac MRI scans. If you experienced an allergic reaction in the past using similar contrast, you will not undergo the MRI. Mild allergic reaction involves redness and irritation of the skin. In rare cases, severe reactions cause shortness of breath and a blood pressure drop. If you have such a reaction, you will be treated immediately.

In some people with decreased kidney function, gadolinium can cause a rare side effect called Nephrogenic Systemic Fibrosis. In this condition, painful scarring can develop throughout the body that can lead to death. Your kidney function will be checked as part of the screening laboratory studies for participation. If you have decreased kidney function, you will not be able to participate in this study.

During the procedure, in rare circumstances, contrast may leak into the tissues surrounding the vein in your arm where the IV catheter was placed. If this complication occurs, it may cause discomfort, swelling and bruising of the skin.

Risks of Regadenoson (common)
Regadenoson will be administered to you during the MRI study. Regadenoson stress has been used routinely for many years for evaluating patients with known or suspected heart disease. The most common side effects associated with the regadenoson infusion include: flushing, chest pain/pressure, shortness of breath, palpitations, headache, low blood pressure and low heart rate.

These side effects are usually mild and self-limiting. If they are severe in intensity, aminophylline IV (1 mg/kg) will be given as per standard protocol. You will have your blood pressure and heart rate monitored closely by a physician and/or nurse in attendance at all times. The protocol will be immediately discontinued if clinically significant irregular heart rhythm is observed.

Risks of High and Low Salt Diet (uncommon)
Increases in dietary sodium may cause elevations in blood pressure, but usually only by a small amount. Your blood pressure will be monitored frequently during your high salt diet visit. Symptoms of severely elevated high blood pressure include headaches, changes in vision, chest discomfort, heart attack and stroke. Decreases in dietary sodium may cause mild reductions in blood pressure, but usually only by a small amount. Blood pressure will be monitored frequently during study visits. When you resume your usual home diet, your blood pressure will likely return to its baseline. The food items may taste different to you, but these amounts of salt for a few days should not pose a risk.

Risks of Intravenous (IV) Catheter Placement (common)
An IV catheter may cause:

- Pain
- Bleeding
- A bruise where the needle was put into your vein. The bruise is usually temporary and goes away on its own.
- Swelling or redness, which could be a sign of an infections. Infections related to IVs are rare and can be treated.
- Feeling faint

Risks of Blood Draws (common)
You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Posture Study (common)
You will be asked to stand for 45 minutes followed by some blood draws. During the 45 minutes, you will be encouraged to walk around to prevent orthostasis or lightheadedness. If you do begin to feel lightheaded or dizzy, you can sit down.

Genetic Information (rare but serious)
Genetic information from this study cannot be used to make decisions about medical treatment at this time. However, information about participation in a genetic study may influence insurance and/or employers regarding your health status. Not sharing information about your participation

in this study with others will help minimize these risks. Information about your participation and results from this study will not be placed in your medical records. Your samples will be deidentified with a code, and the key to the code kept in a separate locked file. After the active enrollment phase of this study is complete, continued analysis of the samples will be performed. Therefore, all samples will be stored.

Additional Risks (uncommon)
The TTE and MRI scans are designed to answer research questions, not to examine you medically. These scans are not a substitute for one your doctor would order. They may not show problems that would be picked up by medical scans. However, if we believe that we have found a medical problem in your scans, we will ask a doctor who is trained in the reading of scans, a radiologist, to help us review the scan. If the radiologist thinks that there may be a critical abnormality in your scan, we will contact you and will help you get medical follow-up for the problem. If you have a primary care doctor, we can contact your doctor, with your permission, and help him or her get the right follow-up for you. You may receive a referral to address the findings. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

You will be asked whether you would like us to inform your Primary Care Provider (PCP) about your study participation and results from this study. After the initial screening TTE, we will inform you and your PCP with your permission of critical heart findings and any other critical incidental findings. We will relay only critical imaging findings to you and your PCP unless you do not want us to notify your PCP.

Unknown Risks
There may be other side effects, in addition to those described in this consent form, that are not known at this time.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this research study. During this study, you will receive regular physical exams with blood pressure monitoring, lifestyle counseling to improve nutrition and physical activity, and screen testing that will evaluate for clinically significant heart disease. While you are taking sacubitril/valsartan, it is possible that there could be improvement in your heart health.

What other treatments or procedures are available for your condition?

Your alternative is to not take part in this research study. If you choose not to take part in this

study, you will receive standard medical care to optimize your risk factors as prescribed by your doctor. Currently, there are no targeted FDA approved treatments to help improve heart structure and function among persons with and without HIV with no known symptoms or history of heart disease.

Can you still get medical care within Partners if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

1. Transportation
   We will pay you for your travel expenses and parking for each study visit. If you drive, we will pay for your parking per visit by providing parking vouchers for the designated MGH or BWH parking lot; or if you take public transportation, we will reimburse your travel expenses per visit. Please save your receipts whenever possible and provide them to the Study Coordinator.

2. Meals
   For every visit where you are required to fast, we will give you timed meals prepared on the research floor during your inpatient visits or a voucher to have a single meal in the cafeteria for outpatient visits.

3. Payment
   A breakdown of how you will receive payment is listed below.

   - You will receive $15 for completing Screen Visit 1 (V1).
   - If we ask you to return for Screen Visit 2 (V2), you will receive $75.

   - If you qualify, you will receive:
     $125 for Baseline Visit Part 1 (V3),
     $75 for Baseline Visit Part 2 (V4),

   - If you qualify and invited to enroll in the treatment study, you will receive:
     $25 for completing Safety Visits (V5, V6, V7, V8, V10),
     $30 for completing the 3 Month Safety Visit (V9),
     $150 for completing the final 6 Month Visit (V11),

   - We will pay you up to $595 for taking part in the study. You will receive part of this total amount for each study visit you complete as outlined above. If you do not complete the study, you will not receive the full payment.

All payments will be in the form of a check that will be given to you at your visit or sent via the mail. Alternatively, you can opt to receive payments via a reloadable credit-card based system. This would be enabled by our partnership with an approved, outside vendor (Advarra) employing a system called Advarra Participant Payments. This secure system is similar to a gift card or credit card. If you are paid by the Advarra Participant Payments system, you will be given a Participant Payments Visa card when you enroll in the study. Once the card is activated, the study team will add a payment after each paid visit you complete. The payment should be available to you within a day. You may use the card anywhere Visa cards are accepted, such as at a grocery store. We will need to collect your Social Security number in order to make these payments, and this number will be shared securely with the company that runs the credit card-based system. Payments like this are considered taxable income. If you receive more than $600, the payment will be reported to the IRS as income by the hospital. If you provide a receipt for something like travel expenses and we can cover that, that is not considered taxable income. Travel expenses cannot be reimbursed via the payment card.

Payment for V4 is dependent upon adherence to the low salt diet and demonstration of salt balance. Your salt balance will be verified by urine testing on the day of your visit. If you are not in salt balance, you may be given the option of repeating the diet and returning for the visit at our discretion. You will not be paid if you do not adhere to the high or low salt diets.

If a portion of a visit is not completed due to a scheduling conflict on our part, you may be asked to return to complete this portion of the visit and may be eligible to receive payment of up to $25 for your inconvenience.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

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

If you take part in this research study, how will we protect your privacy?

Federal law requires Partners to protect the privacy of health information and related information that identifies you. We refer to this information as “identifiable information.”

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Partners researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Partners ethics board or an ethics board outside Partners that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Partners who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside Partners, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for

you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

_____	_____	_____
Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____	_____	_____
Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name	Date	Time (optional)

Consent Form Version Date: 3/7/2024