Mass General Brigham

Research Consent Form
General Consent Form Template
Version Date: March 2026

Subject Name:

MRN or DOB:

Subject Identification

Protocol Title: Beta-2 adrenergic receptor polymorphic variants: an endotype of salt sensitive hypertension

Principal Investigator: Gordon H. Williams, MD

Site Principal Investigator:

Description of Subject Population: Hypertensive Volunteers Screening Visit 2 and Main

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.

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

We are asking you to be in a research study. This form will tell you what you should expect if you agree to be in the study. You will find more information about each of the following points later in this form.

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 Mass General Brigham 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.

We are asking you to be in this study because you have high blood pressure and your cheek swab showed that you have the risk form of the B2AR gene.

[NOTE TO INVESTIGATORS: Add a one-sentence summary in lay language of why the subject is eligible for the study.]
We are doing the research to to determine if different forms of the B2AR gene and the level of salt intact act together to cause high blood pressure.
[NOTE TO INVESTIGATORS: Add a one-sentence overvew in lay language of the purpose of the study.]

If you agreeand your screening tests are normal, at home you will measure your blood pressure daily and eat a liberal and a low salt diet for 7 days each at the end of which you will be hospitalized overnight to measure kidney function and obtain hormone blood tests.
[NOTE TO INVESTIGATORS: Add a one-sentence overview in lay language of what will happen in the study.[

You will be in the study for 4 weeks after completion of the medication washout and home blood pressure monitoring **[NOTE TO INVESTIGATORS: Include timeframe**] if you decide to stay for the whole study.

The main risks of being in the study are, those associated with blood draws and IV catheters, potential changes to your blood pressure medications that might increase your blood pressure briefly, and other unknown risks.
[NOTE TO INVESTIGATORS: Include a one-sentence overview in lay language of the risks that are most relevant to the potential subject's decision about whether or not to join the study.]

You will not benefit from taking part in this research study. If you take part in this study, your participation may help people in the future.

You will be paid up to $2,000 for taking part in this research study. You will find more information about the payment amount for each visit and a plan if you do not complete all study visits later in this form.

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

Gordon H. Williams, MD, is the person in charge of this research study. You can call him/her at 617-732-5666, M-F 9-5.

If you have questions about the scheduling of appointments or study visits, call Kristen Foote at 617-525-9585**.**

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. You can call them at 857-282-1900.

You can talk to them about:

- A complaint, problem, or concern
- Ask questions, offer input, or obtain information
- Your rights as a research participant

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?

[NOTE TO INVESTIGATORS: Include a brief description of the purpose of the study in lay terms.] We are doing the research to to determine if different forms of the B2AR gene and the level of salt intact act together to cause high blood pressure.

[NOTE TO INVESTIGATORS: Consider incorporating this detailed information about genetic testing into the section "What will happen in this research study?"]

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 affect your health. DNA is the material in the cells that makes up your genes and your particular make-up is call your genotype. Changes or differences in a gene (your genotype) may affect your chances of developing a particular disease, or how a person responds to a particular drug. Your genes are passed down from your parents and then passed on to your children. Different forms of certain genes in your body, for example, the B2AR gene, can increase your blood pressure. The form of the gene that could raise your blood pressure is called the risk allele or risk genotype. Taking too much salt in your food or drink also can increase your blood pressure. In this research study we want to determine if different forms of the B2AR gene and the level of salt intake act together to cause high blood pressure.

Who will take part in this research?

We are asking you to take part in this study because you are an individual with high blood pressure and are age 18 – 50 years. About 100 subjects will take part in this research study at Brigham and Women's Hospital/.Mass General Brigham. The National Institutes of Health is paying for this research to be done.]

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

SCREENING VISIT:
There will be two screening visits associated with this study. You have already participated in the first one with a research coordinator. That visit determined that you have the B2AR risk genotype.

The second screening visit will take about 90 minutes and you will meet with both the research coordinator and a study physician. At this second screening visit, we will:

- Ask you questions about your medical history and whether you have kidney problems, diabetes, or heart problems. You also will be asked about your family's medical history and what meds you take, both prescribed and over the counter.
- Perform a physical
- Ask you for a urine sample for routine tests.
- Draw a blood sample for routine tests. About 60 cc (2 ounces) of blood are drawn at this screening visit.
- If you are a woman and able to become pregnant, a urine pregnancy test will be done. You cannot take part in the study if you are pregnant. All women will use effective contraception, but not birth control pills, shots or skin patches. Allowable contraceptive approaches include condoms, diaphragms, cervical caps, contraceptive sponges, tubal ligation, hysterectomy, abstinence (no sexual intercourse), or a partner who cannot father children (e.g., vasectomy or female partner).
- Perform an electrocardiogram (EKG). Small stick-on pads with wires attached will be placed on your skin. The wires are attached to a machine that will look at the electrical activity of your heart.
- We may also check your genotype with a blood test to confirm that you have the risk form of the B2AR gene.

The study doctor will review the results of these tests and procedures. If you don't qualify, the study doctor will tell you why. If you are eligible, you can then take part in the following study:

RESEARCH DIETARY SALT STUDY

The study is divided into four (4) parts. At the end of the fourth part, more details of the **special procedures** that will be performed are provided. Procedures will be performed using resources from the Center for Clinical Investigation (**CCI**), following techniques established over three decades in our > 1,000 person HyperPATH cohort.

Run-In Period (performed in outpatient and home over approximately 35-125 days)

1. To start the study, you will have a 10-15 minute visit to the research office at 221 Longwood Ave., Boston, MA.
2. We will give you a blood pressure cuff.
3. You will be trained to obtain and record home Blood Pressures and e-mail them to the study team daily. Additionally, a 1-1 live contact with a coordinator will be made every 3 days throughout the washout and Assessment Protocol.
4. Beginning approximately one month after your initial Run-in visit, medications that you were taking to treat your high blood pressure will be discontinued following standard procedures.
5. ACE inhibitors (**ACEi**), angiotensin receptor blockers (**ARB**), or Mineralocorticoid Receptor Antagonist (MRAs) will be withdrawn approximately 3 months after your initial Run-in visit.
6. If your home blood pressures increased to greater than 145/95 on two consecutive days or you have any symptoms, we will start another blood pressure lowering medicine, amlodipine. This will continue until 1 month before the start of study when all blood pressure medicines are stopped.
7. The study is stopped, and previous therapy restarted for the onset of heart or head symptoms, a rise in diastolic BP (the lower number) >15 mmHg or systolic BP (the upper number) >30 mmHg, or an absolute BP >160/100 mmHg on 2 consecutive days.

Pre-dietary Sodium Assessment Study (performed in outpatient/ home over approximately 7 days)

a) At home, you will complete two nearly identical 7-10 day dietary protocols. usually separated by 0-6 days of a regular diet.

b) If you are a woman, the separations of the two protocols may be longer because of the need for the two studies to be performed during the same phase of your menstrual period.

c) The two diet protocols are:

d) 7 days of a Liberal (LIB) salt diet containing the average amount of salt you eat each day (approximately 2.2 tablespoons). We will provide menus for you to develop your own meal plan to contain the correct amount of salt for the study.

e) 7 days of a Restricted (RES) salt diet (1/4 of a tablespoon/day). We will provide the meals for you to take during these seven days.

f) Both diets have the same number of calories/ body weight, regular dietary potassium intake plus 3 large tomatoes or bananas or 12 oz of orange or tomato juice daily, one calcium carbonate tablet, and are caffeine and alcohol-free.

g) If you are a woman, the diet's start is timed so that Day 7 coincides with a particular phase of your menstrual cycle. We will confirm this by measuring your hormones in a blood test.

h) On the final morning of each diet, you will begin a 24-hr urine collection

i) Also on the final morning of each diet, you will begin to wear a 24 hr Ambulatory Blood Pressure Monitor (**ABPM**) (**ST-1**) that we will provide.

In patient dietary Sodium Assessment Study (performed in-patient unit over approximately 24 hours)

A. You will then be admitted overnight to the in-patient Clinical Research unit arriving between 4-7 PM.

B. A spot urine will be obtained for sodium and creatinine to confirm the sodium content of your diet.

C. You will be kept on the same diet that you were taking outside the hospital and then kept without food or fluids from midnight until the next morning.

D. At ~ 7 AM, tubes are place in a vein in each arm and a BP monitor is placed on one arm to collect and record BP every 2 minutes.

E. Approximately 30 minutes later, approximately 60 ml (4 tablespoons) of blood is obtained to measure various hormones, lipids markers of inflammation and a basic metabolic panel, *Para-aminohippurate* (*PAH),* and to isolate from the blood one of its components (Peripheral Blood Mononuclear Cells (PBMC) (**ST-2**)

F. ***Aldosterone and kidney blood flow (KBF) response to angiotensin II (ANGII) Procedure****:*

   a. In one of your arm veins, a substance called *PAH* is infused for 45-60 minutes, that is used to measure the blood flow to your kidneys. At the end of this infusion approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. **(ST-3)**

b. The PAH infusion is continuing in one arm and an angiotensin II (ANGII) infusion is begun in the other arm. These two infusions run together for 30-45 minutes. At the end of this infusion approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. **(ST-3)**

c. For 60-90 minutes after the completion of the PAH/AngII infusion, the PAH but not AngII infusion is continued. At the end of the 60-90 minute approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. **(ST-3)**

d. A captopril (25 mg) tablet is then given (the PAH infusion is continuing); 60 minutes later approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. **(ST-3)**

e. After the blood draw, with the PAH infusion continuing in one arm, an ANGII infusion is begun in the other arm. These two infusions run together for 30-45 minutes, starting approximately 60 min after captopril administration. At the end of this infusion approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. (**ST-3**).

G. You will then be given lunch. If you are not scheduled to start the alternate diet right away, you will eat your usual food at home until your scheduled admission on the ***Pre-dietary Na^+ Assessment Study*** on the opposite diet.

H. If you are to immediately start the opposite diet, then your lunch will contain the sodium content of the opposite diet and you will be discharged home to follow the ***Pre-dietary Na^+ Assessment Study*** protocol and 7 days the ***In-patient dietary Na^+ Assessment Study*** protocol as noted above on the diet containing the opposite sodium content.

I. At study completion, you are discharged on pre-study medications to the care of your local physician.

We have successfully completed this three-part core study in ~1000 subjects. The inpatient protocol runs between 6-7AM and 12-1PM.

Elective Out- Patient Dietary Sodium Assessment Study (performed in outpatient and home over approximately 3-10 days)

1) If you have agreed to participate in an additional study, you are discharged from the inpatient unit but maintained on the same diet for 2-3 days.

2) Then, you return to the outpatient unit. **a)** If on LIB diet, a ***Superficial Inferior Epigastric Artery (SIEA) isolation procedure*** is performed (**ST-4**). **b)** If on RES diet, an ***Acute Salt Load protocol*** is performed (**ST-5**).

3) At study completion, you are discharged on pre-study medications.

Special Techniques (ST)

1. ***24-hour ambulatory Blood Pressure:*** The Brigham and Women's Hospital (BWH) Ambulatory Blood Pressure Core will perform this measurement using Microlife WatchBP.

2. ***PBMC cell study:*** 40 ml of whole blood will be obtained supine after overnight fast. The PBMC will be separated by gradient density centrifugation and stored at -80C until studied within one week of isolation.

3. ***Aldosterone and kidney blood flow (KBF) response to angiotensin II (ANGII) Procedure****:* KBF is assessed by para-aminohippurate (**PAH)**—a stable chemical excreted by the kidney. Therefore, KBF is measured as clearance of PAH from the blood by the kidney. The study begins with a 60-minute infusion of PAH alone through a tube in one arm vein. Blood is then collected at the end of this infusion approximately 20 ml (1 and 1/4 tablespoons) to measure various hormones and PAH. Then ANGII (3 ng/kg/min) is infused through a vein in the opposite arm for 45 minutes. ANGII is a naturally occurring hormone that contracts blood vessels and stimulates aldosterone. This dose affects KBF and aldosterone (a salt retaining hormone) levels with minimal effects on blood pressure. At the end of this infusion approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. Immediately following obtaining the blood, the ANGII infusion is stopped, but the PAH infusion continues for 60-90 minute, and approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH. Captopril (25 mg tablet) is then given by mouth. Captopril is an ACEi that blocks the production of ANGII. To assess the effect of captopril on tissue sensitivity to ANGII, the ANGII infusion is repeated for 30-45 minutes after captopril is given, and approximately 20 ml (1 and 1/4 tablespoons) of blood is obtained to measure various hormones and PAH.

4. ***SIEA (superficial inferior epigastric artery) isolation procedure*****:** This procedure involves obtaining human vessels from a fat biopsy taken from your abdomen. Your SIEA will be isolated by a plastic surgeon in the plastic surgery outpatient unit. SIEA (located by Doppler ultrasound) is easily harvested under local anesthesia in under 30 minutes. The area is prepped, draped in sterile fashion, and infiltrated with 0.5% lidocaine with epinephrine, 1:200,000. A low transverse (horizontal) incision of ~2 cm (about ¾ of an

inch) is made over the Doppler mark, a 2-4 cm^3 dissection of fat, including the SIEA, is taken, placed in a sterile cup with saline, and delivered immediately to the laboratory. Bleeding will be stopped using electrocautery (heat from a mild electric current) or dissolvable sutures. Site is checked in 1week.

5. ***Acute salt study:*** At seven o'clock in the morning, you will drink distilled water, 5 ml/kg body weight (approximately 12-13 oz. for the average man), over 30 min and urinate within 30 min. A 0.45% saline infusion is started to give 26 oz. of fluid over 1 hour. At time 0, blood is drawn for salt and creatinine. Voided urines are collected for 5 hours.

Leaving the study early

The study doctor sometimes needs to end your participation in this study before it is finished. The doctor may do this if you miss study visits, for health reasons, or for administrative reasons. If this happens, the reason will be explained to you.

Mass General Brigham Alert System

Mass General Brigham has an electronic system that lets your study doctors know if you are admitted to a Mass General Brigham Hospital, or if you visit a Mass General Brigham Hospital Emergency Department. 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.

OPTIONAL STUDY: Acute Salt Load Procedure- Clinical Research Center Outpatient

After the completion of the primary study, would you like to participate in an optional Acute Salt Load Study? If so, you will stay on the same Low Salt Diet that you were on during the main study at home for 1-2 days. You will return to the ambulatory research center at seven o'clock in the morning. You will be asked to drink distilled water, approximately 12-13 oz. over 30 min and void within 30 min of completion. Then, a saline infusion is started to give 26 oz. of fluid over 1 hour. Blood is drawn at the end of the hour. Voided urines are collected for 5 hours.

YES: NO: Initials:

OPTIONAL STUDY: SEIA Isolation Vessel Procedure

After the completion of the primary study, would you like to participate in an optional SEIA Vessel Study? If so, you will stay on the same Liberal Salt Diet that you were on during the

main study at home for 1-2 days. You will go to the plastic surgery ambulatory suite at seven o'clock in the morning. Details of this procedure are provided in section Special Techniques #4 in this consent form.

YES: NO: Initials:

OPTIONAL STUDY: FUTURE RESEARCH STUDY OPPORTUNITIES

We would like to contact you about future research studies that you may be interested in. Do you want to be notified by someone from our research group about future studies here at Brigham and Women's Hospital?

YES: NO: Initials:

OPTIONAL STUDY: USING YOUR DNA

We will perform a whole genome analysis on your DNA sample unless you opt out. 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 hypertension and cardiovascular health.

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.

This DNA testing is being done for research purposes only. Results of DNA study tests will not be placed into your medical record.

Do you wish to opt out of the use of your DNA for whole genome analysis?

YES: NO: Initials:

If later you change your mind and want your samples destroyed, contact the study doctor.

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

The 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 identifiable samples and health information with researchers at Mass General Brigham for other research related to cardiovascular, metabolic and renal disease areas. If we share your samples and/or health information with other researchers outside of Mass General Brigham, 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/locked 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 have extra blood samples saved to test for hormones and chemical markers of cell damage?

YES: NO: Initials:

Do you agree to let us store your samples for future research related to cardiometabolic diseases?

YES: NO: Initials:

If later you change your mind and want your samples destroyed, contact the study doctor.

Will you get the results of this research study?

No. The research study we are doing is only a stepping stone in understanding cardiovascular, metabolic and renal diseases**.** Therefore, no information about the results of this research study or the results of your individual participation in the research study will be given to you or your doctor. Tests done for the research using your samples will not be useful in directing your medical treatment. The results of the tests will not be placed in your medical record.
you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

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

We identify several potential risks associated with participation in this study.

Alteration of anti-hypertensive medications. You will be followed without specific anti-hypertensive therapy for approximately 2-4 drug-free weeks during the high and low salt diet study periods. You will closely monitor your blood pressure at home daily and be in close contact with study investigators to ensure prompt and careful control of blood pressure (described below).

Hypertensive medication washout. To ensure that the results we see are due to our study interventions and not due to your previous hypertensive treatment, if you have been on are on anti-hypertensive medications prior to the study, you will enter a washout phase that lasts for at least 2-4 weeks. If you are on an angiotensin converting enzyme inhibitor, angiotensin receptor blocker or a mineralocorticoid receptor antagonist, they are washed out for 3 months prior to starting the study diets.

Since you have hypertension, you have an increased risk of stroke or heart attack particularly when your blood pressure is elevated. We have safely and effectively performed blood pressure medication washouts using the methods below in over 2,000 individuals over the past 25 years. Over this time, we have never had a stroke or heart attack during the washout phase of our studies. To accomplish these results, we use our IRB approved Standard Operating Procedure for Blood Pressure Research Protocols during this washout period.

During the medication washout phase and throughout the entire protocol, you are supervised by the study staff. You are trained on how to use an automated blood pressure cuff so you can take daily morning blood pressure recordings at home and report them to study staff daily. Every three days, you will directly (in person or via Zoom) contact with a study staff member. If your blood pressure is equal or above 160/100 mmHg, you will be asked to contact the study staff. If blood pressure is still increased on two separate occasions 24-hours apart throughout the washout phase or study protocol or you develop clinical symptoms of chest, arm, head pain or weakness of side of face, arms or legs, go to an emergency room as soon as possible. Also call the research physician and research coordinator. In our experience over the past 25 years, these steps have never been necessary. If they occur, you will be removed from the study and asked to follow up with your Primary Care Physician and resume taking your prior antihypertensive medication(s).

Risks associated with performing the study procedure
Blood Collection. Blood draws may cause tenderness, hematoma formation, and rarely infection. Alcohol swabs to sterilize the skin and blood collected by skilled nurses or phlebotomists are employed to minimize these risks. Total blood volume obtained will be less than that permitted by the Mass General Brigham IRB for study of disease populations.

Risks associated with PAH infusions
Para-aminohippurate (PAH) infusions may rarely cause flushing, tingling, nausea, vomiting and cramps. Very rarely PAH may cause a hypersensitivity reaction (including angioedema and urticaria) or vasomotor disturbances. Subjects may have a sensation of warmth or the desire to defecate or urinate during or shortly following initiation of infusion. Discontinuation of the PAH infusion leads to the resolution of these symptoms.

Risks associated with Captopril
Captopril is a specific inhibitor of angiotensin I converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Administration of Captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in kidney blood flow following administration of Captopril Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of Captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. A fall in blood pressure or a fast heart beat when standing are infrequent. Abrupt withdrawal of Captopril has not been associated with a rapid increase in blood pressure.

Counterindications. Captopril should not be used in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

Warnings and precautions. Angiotensin-converting enzyme inhibitors affect the metabolism of certain substances in the body. Because of this, patients receiving ACE inhibitors (including Captopril) may have a variety of adverse reactions (side effects), some of them serious. Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Infrequently, an increase in potassium can occur. More common is a cough.
Since you will only be taking a small dose of Captopril one or more weeks apart, very rarely would any of these effects occur with you.

Risks associated with Angiotensin II infusions
ANGII increases blood pressure. The increase in BP can be accompanied by chest discomfort and rarely cardiac damage. The doses that you will receive, however, generally increase mean arterial pressure by only 6-10 mm Hg in subjects on a high salt diet. We have extensive experience with these techniques, having performed such infusions in over 2,000 subjects in the past 25 years. Using these doses of ANGII and monitoring BP every two minutes during the infusion of ANGII we have had only minor adverse events (<0.5%) and only two episodes of chest discomfort, neither of them cardiac in origin. We believe the potential risks of these infusions are minimal. A clinical investigator will be present for each of the infusions.

Risks associated with study diets
You will be asked to consume a liberal salt diet and a low salt diet. Increasing dietary sodium can elevate BP in some individuals. However, the liberal salt diet used in this study (calculated diet to 200 mEq/day) is similar to the "normal" salt diet (150-250 mEq/day) in the United States. We have performed over 2 dozen similar studies in ~2,000 hypertensive and normotensive individuals without adverse events. The liberal and low salt diets will be constructed by CCI Nutrition and Metabolic Core Kitchen and provided to enrollees after they have been interviewed by a research Registered Dietician to calculated caloric needs. You will be instructed on how to check your blood pressure at home with a study-provided automatic BP device. You will check your blood pressure daily and report results to study staff every 2-3 days. The study diet will be stopped if systolic BP is >160100 mmHg on 2 occasions. As described above, you will consume a low salt diet during another phase of your study. You will be warned about signs and symptoms related to low blood pressure and instructed to refrain from strenuous physical activity

while on the low salt diet. You will also be encouraged to drink water freely to maintain hydration and minimize low blood pressure symptoms particularly in hot weather.

Unexpected laboratory results
A risk from participating in this study is the inadvertent discovery of abnormal laboratory tests that lead to anxiety, distress and added cost to you. This could include laboratory tests obtained at screening.

Risks associated with 24hour Ambulatory blood pressure
You will undergo two 24hr Ambulatory BP studies (ABP). ABP requires placing a BP cuff on the arm which is attached to a pump device. It records BP at set intervals during the day with lower frequencies at night. Discomfort from wearing the device includes those associated with arm constriction and disrupted sleep.

Risks of genotyping
You will undergo genotyping to determine genotype status related to the B2AR gene. This procedure involves a cheek swab sample obtained under direct observation. The sample is identified with your unique code only. Samples are sent via express overnight mail service to Transnetyx for rapid genotype determination. Results are reported back to the study team in under 48hrs.

Vascular Biopsy
For the SIEA biopsy procedure, the area will be numbed with an anesthetic (Lidocaine). The risks associated with the Lidocaine injection include burning, itching, pain, redness, or swelling at the injection site. The size of the vessel removed will be about the diameter of a drinking straw and about 1.5 inches long. Some risks associated with the biopsy procedure include mild discomfort/pain, swelling, bleeding, and scarring at the biopsy site. Bruising and a temporary small depression in the skin and/or bumps under the skin where the vessel has been removed will likely occur. The discomfort lasts for 12-36 hours. We have performed 30 of these procedures without any other adverse events. You will be asked to return 1 week after the biopsy to have the surgical site inspected and to contact study staff if you have any concerns. Removal of this vessel likely occurs more than 1000 times daily in the US as it occurs with abdominoplasty, reconstructive breast surgery, and hernia repair.

What other treatments or procedures are available for your condition?

This is not a treatment study. You can continue to receive treatment for your hypertension before and after the study is completed.

Can you still get medical care within Mass General Brigham 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 Mass General Brigham 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?

You will be paid up to $1,500 for completion of the primary study. This amount includes stipend, travel and parking. If you consent to the randomized optional study, you will be paid up to an additional $500. You will be paid on a prorated basis for the visits that you complete. The breakdown is as follows:

Study	**Stipend**	**Duration of Visit**
Screening Visit 1 (already completed)	$75	30-60 minutes
Screening Visit 2	$150	90-120 minutes
Run in Period	$75	30-60 minutes
High Salt Pre-Assessment	$100	30-60 minutes
High Salt Inpatient	$500	24 hours
Low Salt Pre-Assessment	$100	30-60 minutes

Low Salt Inpatient	$500	24 hours
Randomized optional Acute Salt Load Study or, Randomized optional SIEA Vessel Study	$250 $500	5-6 hours 3-4 hours

You may be asked to provide your Social Security number to be paid for taking part in this study. Money received from participating in research is considered taxable income according to federal tax law. If your total payments from Mass General Brigham are over $2000 per year, Mass General Brigham will report these payments to the Internal Revenue Service. If this happens, you will receive a 1099 form from Mass General Brigham. If you have questions about this, please contact the person in charge of this study.

Compensation could potentially jeopardize your eligibility for public assistance programs such as MassHealth, SNAP, and ACA subsidies. If you receive certain public benefits (for example Medicaid (MassHealth) Health Connector subsidies, Medicare Savings Program, SNAP) please consider whether research payments could impact your eligibility for such programs. You do not have to accept payment for research participation, and you may be in the study whether or not you choose to receive payments."

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples or information are used for this purpose."

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

All the study drugs, tests, and procedures that are done as part of this research study will be paid for by study.

Charges for any ongoing or routine medical care you receive outside this study will be billed to you or to your insurance company in the usual way. 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 Mass General Brigham 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 they may need to do so:

- Mass General Brigham 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 Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research

- A group that oversees the data (study information) and safety of this study
- Non-research staff within Mass General Brigham 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:

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any legal action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.
There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.
Researchers may release information about you when you say it is okay, including as described in this form. For example, you may give them permission, as you are doing in this form, to release information to insurers, medical providers or other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

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 study 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 health information to be used and shared as described above.

Print Name

Subject Signature | 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.

Print Name

Signature of Study Doctor or Person Obtaining Consent | Date | Time (optional)

Consent Form Version Date: 08/20/26