Inclusion Criteria:	**Yes**	**No**
Acute focal symptoms or signs of any duration associated with imaging, pathological, or other objective evidence of arterial infarction OR clinical evidence of cerebral, spinal cord, or retinal focal arterial ischemic injury based on symptoms persisting >24 hours that occurred within 30 days prior to randomization	☐	☐
Index stroke in 1 above is attributed to 70-99% stenosis (or flow gap on MRA) of a major intracranial artery (carotid artery, middle cerebral artery (M1 or M2), vertebral artery (V4), basilar artery, posterior cerebral artery (P1), or anterior cerebral artery (A1)) documented by CTA, MRA, or catheter angiography. *The method for determining percent stenosis will be by WASID criteria:66,67* *Percent stenosis = (1 – [Ds / Dn]) x 100% with Ds (diameter of stenosis) and Dn (diameter of normal vessel).* *These measurements will be made using CTA, MRA, and catheter angiographic systems software*	☐	☐
Modified Rankin Scale score of ≤ 4, at time of consent	☐	☐
Ability to swallow pills	☐	☐
At least 30 years of age, inclusive, at time of consent	☐	☐
Subjects 30-49 years are required to meet at least one of the following additional criteria (1-6) below to qualify for the study. This additional requirement is to increase the likelihood that the symptomatic intracranial stenosis in subjects 30-49 years is atherosclerotic. (*indicate which criteria apply*) 1. diabetes treated with insulin for at least 15 years 2. at least 2 of the following atherosclerotic risk factors (*indicate*) (a) hypertension (BP > 140/90 or on antihypertensive therapy); (b) dyslipidemia (LDL > 130 mg /dl or HDL < 40 mg/dl or fasting triglycerides > 150 mg/dl or on lipid lowering therapy); (c) smoking; (d) non-insulin dependent diabetes or insulin dependent diabetes of less than 15 years duration; (e) any of the following vascular events occurring in a parent or sibling who was < 55 years of age for men or < 65 for women at the time of the event: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, stroke, carotid endarterectomy or stenting, peripheral vascular surgery for atherosclerotic disease 3. personal history of any of the following: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, carotid endarterectomy or stenting, or peripheral vascular surgery for atherosclerotic disease 4. any stenosis of an extracranial carotid or vertebral artery, another intracranial artery, subclavian artery, coronary artery, iliac or femoral artery, other lower or upper extremity artery, mesenteric artery, or renal artery that was documented by non-invasive vascular imaging or catheter angiography and is considered atherosclerotic 5. aortic arch atheroma documented by non-invasive vascular imaging or catheter angiography 6. any aortic aneurysm documented by non-invasive vascular imaging or catheter angiography that is considered atherosclerotic	☐	☐ **n/a** ☐

Inclusion cont.	**Yes**	**No**
Negative pregnancy test in a female who has had any menses in the last 18 months and has not had surgery that would make her unable to become pregnant	☐	☐
Subject is willing and able to attend all follow-up evaluations required by the protocol	☐	☐
Subject is available by phone	☐	☐
Subject understands the purpose and requirements of the study and can make him/herself understood	☐	☐
Subject has provided informed consent (**use of a LAR is not permitted**)	☐	☐

Exclusion Criteria:	**Yes**	**No**
Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, including mechanical thrombectomy for the qualifying stroke, or plan to perform one of these procedures	☐	☐
Plan to perform concomitant endarterectomy, angioplasty or stenting of an extracranial vessel tandem to the symptomatic intracranial stenosis	☐	☐
Intracranial tumor (except meningioma) or any intracranial vascular malformation	☐	☐
Thrombolytic therapy within 24 hours prior to randomization	☐	☐
Progressive neurological signs within 24 hours prior to randomization	☐	☐
History of any intracranial hemorrhage (parenchymal, subarachnoid, subdural, epidural); *asymptomatic radiographic microhemorrhages or hemorrhagic conversion of infarction are not exclusions, but the latter requires delaying randomization for 2 weeks from onset of qualifying stroke*	☐	☐
Intracranial arterial stenosis due to: arterial dissection; MoyaMoya disease; any known vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with CSF pleocytosis; radiation induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; postpartum angiopathy; suspected vasospastic process; reversible cerebral vasoconstriction syndrome (RCVS); suspected recanalized embolus	☐	☐
Presence of any of the following unequivocal cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, left atrial spontaneous echo contrast	☐	☐
Known allergy or contraindication to aspirin, rivaroxaban, clopidogrel, or ticagrelor	☐	☐
Uncontrolled severe (systolic pressure > 180 mm Hg or diastolic pressure > 115 mm Hg), active peptic ulcer disease, major systemic hemorrhage within 30 days prior to randomization, active bleed or bleeding diathesis, platelets < 100,000, hematocrit < 30, INR >1.5, clotting factor abnormality that increases the risk of bleeding, current alcohol or substance abuse, severe liver impairment (AST or ALT > 3 x normal, cirrhosis), or CrCl < 15 mL/min or on dialysis	☐	☐

Exclusion cont.	**Yes**	**No**
Major surgery (including stenting of any vessel; open femoral, aortic, or carotid surgery; or cardiac surgery) within 30 days prior to randomization or planned within 90 days after randomization	☐	☐
Any condition other than intracranial arterial stenosis that requires the subject to take any antithrombotic medication other than aspirin (NOTE: exceptions allowed for subcutaneous heparin for deep vein thrombosis (DVT) prophylaxis)	☐	☐
Dementia or psychiatric problem that prevents the subject from following an outpatient program reliably	☐	☐
Co-morbid conditions that may limit survival to less than 12 months	☐	☐
Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study, or currently breastfeeding. If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately	☐	☐
Current or anticipated concomitant oral or intravenous therapy with strong CYP3A4 inhibitors or CYP3A4 substrates that cannot be stopped for the course of this study	☐	☐
Enrollment in another study that would conflict with the current study	☐	☐

Name of Investigator: _____

Signature: _____ Date: _____

National Institutes of Health (NIH) / Protocol Number CAPTIVA

CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Sponsor / Study Title:	**Dr. Brian Hoh, University of Florida / "Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis (CAPTIVA)"**
Protocol Number:	**CAPTIVA**
Principal Investigator: (Study Doctor)	**Brett Cucchiara, MD**
Telephone:	**215-662-6738** **215-349-5990 (24Hr.)**
Address:	**The Hospital of the University of Pennsylvania** **3400 Spruce Street** **Philadelphia, PA 19104**

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

This form is for use in a research study in which only participants who have the capacity to consent can take part in the study. The pronouns "you" and "your" should be read as referring to the participant.

KEY INFORMATION

Purpose of the Study:	The purpose of this research study is to see whether ticagrelor and aspirin or rivaroxaban and aspirin compared to clopidogrel and aspirin may have the most success in preventing another stroke, bleed in the brain, or death in participants who have already had a stroke from a narrowed brain artery. This research is important to future patients, as this knowledge may help doctors do a better job of preventing stroke in patients with major narrowing of brain arteries.
Study Participation:	If you choose to participate in this study, you will be randomly assigned (like drawing straws) to one of three study treatments: ticagrelor and aspirin, rivaroxaban and aspirin, or clopidogrel and aspirin. You will receive Intensive Medical Therapy: treatment of your blood pressure, cholesterol, diabetes if you are diabetic, program to stop smoking if you smoke, and program for weight loss if you are obese. You will also have a mouthwash or cheek swab sample collected to look at the makeup of one of your genes. Some studies have shown that a person's genetic makeup may reduce the beneficial effect of clopidogrel, one of the medications that will be used in this study.
Study Length:	You will be in the research study for up to 12 months.
Risks:	The most common risks with the medications used in this study (aspirin, clopidogrel, ticagrelor, and rivaroxaban) include bleeding, which can be severe or fatal; nausea; diarrhea; and skin rashes or itching. A complete list of potential risks is included in the RISKS AND DISCOMFORTS section below.
Benefits of the Study:	Your participation in the study may help the study doctors better understand the effectiveness and safety of ticagrelor and rivaroxaban when used to prevent stroke in patients with a narrowed brain artery.

Alternative procedures:	The alternative to participating in this study is to not participate. If you choose not to participate in the research study, you will receive standard medical care.

INTRODUCTION AND SUMMARY OF THE STUDY

You are being asked to participate in this research study because you had a stroke within the last 30 days. From the tests that have already been done, it is thought that a major (70-99%) narrowing of one of the large arteries in your brain was the cause of your stroke.

Currently, the best way to avoid having another stroke is to use medications such as aspirin and clopidogrel to prevent blood clots from forming in the narrowed artery and to manage and treat other risk factors for stroke by:

- Keeping the blood level of LDL (the bad form of cholesterol called low density lipids) under 70;
- Keeping blood pressure under 140/90;
- Keeping the hemoglobin A1c blood level under 7% for diabetics;
- Stopping cigarette smoking;
- Exercising 30-45 minutes at a time, 3-5 days a week (walking, jogging, cycling or other aerobic activity); and
- Controlling weight, which is measured by BMI (body mass index). BMI is found by putting your height and weight together in a formula. The goal is to have your BMI under 25.

A plan for this kind of treatment, which we call Intensive Medical Therapy, is part of this study. However, we still need to develop better treatments to lower the risk of stroke in participants like you with a narrowed brain artery.

One possible treatment that we will be testing in this study is to use different medications to prevent blood clots. The currently accepted standard medications used for preventing blood clots in your condition are clopidogrel and aspirin. There are some preliminary studies suggesting that substituting clopidogrel with different medications, such as ticagrelor or rivaroxaban, may lower the risk of having another stroke in the following year but could also cause more bleeding events. Ticagrelor is approved by the US Food and Drug Administration (FDA) to reduce the risk of another stroke in patients with a recent stroke, and rivaroxaban is also approved by the FDA at a higher dose than is being used in this study to prevent stroke in patients with an irregular heart rhythm called atrial fibrillation. While rivaroxaban at a higher dose is FDA-approved for stroke prevention in patients with atrial fibrillation, low dose rivaroxaban in this study is investigational. An investigational use is one that is not approved by the United States Food and Drug Administration (FDA). In this study, we are evaluating how effective and safe ticagrelor and lower dose rivaroxaban are in preventing stroke from a narrowed brain artery when combined with aspirin.

As such, there is not enough certainty about the benefits and risks of ticagrelor or rivaroxaban for patients that have had a stroke from a narrowed brain artery. Likewise, doctors do not have enough certainty to routinely recommend it for this condition.

You are being asked to be in this research study evaluating ticagrelor and aspirin or rivaroxaban and aspirin or clopidogrel and aspirin as a study treatment for participants who have had a stroke from a narrowed brain artery in preventing another stroke in the next 12 months.

If you agree to be in this research study, you will have blood drawn for routine standard lab tests to help in stroke prevention after you have been enrolled in the study.

You will also have a mouthwash or cheek swab sample collected. You will swish about 2 teaspoons (10 ml) of mouthwash in your mouth for 60 seconds and spit the liquid into a collection container. If you have difficultly swishing, we will collect a cheek swab sample by rubbing the inside of both of your cheeks with two pencil-sized q-tip swabs. This sample will be sent to a laboratory at the University of Florida where it will be tested for different makeups of one of your genes called variants. You may be asked to provide a second sample if the first sample was inadequate. In some studies, these variants have been shown to reduce the beneficial effect of clopidogrel, one of the medications that will be used in this study. Based on these studies, the FDA has issued a Boxed Warning (strictest warning) regarding the effects of certain gene variants on clopidogrel. However, other studies have shown that gene variants do not alter any of the beneficial effects clopidogrel provides. Because of this uncertainty regarding the effect of gene variants, the test for gene variants is not currently recommended or performed as part of standard care in deciding treatment for participants with stroke. That is why we are studying gene variants as part of this study. You will not be told the results of the gene testing until the end of the study. If you already know that you have a gene variant from a previous test you can still participate in the study on the understanding that there is a 1 in 3 chance you could be assigned to take clopidogrel in the trial and that there is a boxed warning on the use of clopidogrel in patients with a gene variant.

This research study will be paid for by the National Institutes of Health and Janssen Scientific Affairs, LLC. The study medication ticagrelor is being supplied by AstraZeneca Pharmaceuticals **OR** another pharmaceutical company that makes ticagrelor; and rivaroxaban is being supplied by Janssen Scientific Affairs, LLC.

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.

PURPOSE

The main purpose of this study is to see whether ticagrelor and aspirin or rivaroxaban and aspirin compared to clopidogrel and aspirin may have the most success in preventing another stroke, bleed in the brain, or death in participants who have already had a stroke from a narrowed brain artery.

The plan is to have approximately 150 medical centers and about 1683 people participate in this study. We are looking for 15-60 people at this center to be part of the study. Each person would participate in the study for up to 12 months.

You will only be in this study if you want to. You do not have to do it.

If you are an employee or relative of an employee of this research center, you are under no obligation to participate in this study. You/your family member may withdraw from the study at any time and for any reason, and neither you/your family member's decision to participate in the study, nor any decision on your/their part to withdraw, will have any effect on your/your family member's performance appraisal or employment at this clinical research center. You/your family member may refuse to participate or you/your family member may withdraw from the study at any time without penalty or anyone blaming you.

If you are a student of the researcher, you are under no obligation to participate in this study. You may withdraw from the study at any time and for any reason, and your decision to participate in the study, nor any decision on your part to withdraw, will have any effect on your performance or standing as a student. You may refuse to participate, or you may withdraw from the study at any time without any penalty.

HOW THE STUDY WILL WORK

You have been given this form to read because the study doctor has determined that you qualify for the study. Signing and dating this form means you consent to be a participant in this study.

If you agree to participate in the study, the study coordinator will ask you about your medical history and the medications you take. You will also see a study medical provider.

You will be randomly assigned (like drawing straws) to one of three study treatments. Approximately one-third (1 of 3) of study participants will be assigned to each study treatment.

Regardless of which study treatment you are randomly assigned to, you will receive Intensive Medical Therapy to treat the risk factors described above and aspirin and the study medications described below for one year.

To make sure no one in the study favors one study medication over the other, your study medications will be "blinded", meaning neither you nor your study doctor will know what study medications you are receiving. If needed, your doctor will be told what type of medication you are receiving.

To achieve this blinding, we have to use real medication and placebo medication in the study. A placebo is an inactive pill that looks like and is given in the same way as the real medication.

Depending on which study treatment you are assigned, you will take aspirin and one of the following three medications: ticagrelor, rivaroxaban or clopidogrel. It is important that you keep all medications in a secure place and take them as instructed by the study staff. The study medications and aspirin will be provided at no cost to you.

INTENSIVE MEDICAL THERAPY

The Intensive Medical Therapy to treat risk factors for stroke will be the same for everyone in the study.

If not already performed as part of your regular care, you will have routine blood tests done at the beginning of the study to check your cholesterol, liver and kidney function, and Hemoglobin A1c, which is a test for diabetes. You might need to take medications to correct some or all of your risk factors for stroke.

- If your LDL cholesterol is greater than or equal to 70 mg/dL, you will be started on atorvastatin (also known as Lipitor) at no cost to you, and the blood test will be repeated approximately 30 days later. If your LDL cholesterol is still greater than or equal to 70 mg/dL, the dose of atorvastatin (Lipitor) will be increased, and the blood test will be repeated approximately 30 days later. Adjustments of your cholesterol medications and testing will be repeated every 30 days until your LDL is below 70 mg/dl. If you are already on another cholesterol lowering medication like a statin, you can continue those medications but you will also have the option of switching to atorvastatin. Only the atorvastatin will be provided at no cost to you. You will also have the cholesterol blood test repeated at month 12.
- Your blood pressure will be checked at each study evaluation. If your blood pressure is greater than or equal to 140/90, you will be given medications to lower it. If your blood pressure at the 30-day evaluation is still greater than or equal to 140/90, your medications will be adjusted and you will have your blood pressure checked in another 30 days. Adjustments of your blood pressure medications and testing will be repeated every 30 days until your blood pressure is less than 140/90. There are different kinds of blood pressure medications and some of them will be offered to you at no cost as part of the study. If you are already on blood pressure medications, you can continue them without switching to medications supplied by the study.
- If you smoke you will be asked to stop. At each evaluation with the study doctors, you will be asked a few questions about how much you are smoking. Your study doctor will tell you things you can do to help you quit.

- You will be weighed at each evaluation. If you are overweight your study doctor will tell you things that can help you have a healthy weight.
- You will be asked to exercise regularly if your study doctors think it is safe for you to do so. You will be asked to exercise at least 3 times per week for 30 minutes at a time. Your study doctor will help you decide what exercise you should be doing.

You will also be enrolled in a risk factor management program called INTERVENT. This is a healthy lifestyle coaching program that is used around the country and in other parts of the world that helps patients manage their risk factors for stroke. People who are not in this study pay to receive this help from INTERVENT, but it will be provided to you at no cost while you are in this study.

Help in managing your risk factors will be done through telephone calls with one of the INTERVENT staff members. These staff members, or coaches, are healthcare workers that are not physicians. These coaches have been specially trained to follow the medical management plan your study doctors have recommended for you and help you figure out ways to follow them as completely as possible.

You will have an initial intake call with INTERVENT and your first telephone conversation with your coach approximately one week after you enter this study. You will then talk with your coach once every 2 weeks for the following 11 weeks. Following this you will talk with your coach once a month as long as you are part of this study. Each coaching call usually lasts from 15-20 minutes. After some of the calls, your coach will send a report to your study coordinator and study doctor about how you are doing. Your study doctor will decide what types of changes should be made and when they should be made. Your study doctor or coordinator will talk with you about how you are doing and if you should change anything.

It is important that you participate in the INTERVENT coaching. Studies in the past have shown that patients who had this type of coaching had better results in controlling their risk factors than patients who were not coached. Having each participant in the study use the same program to manage their risk factors also makes it more likely that the people involved in this study are working on their risk factors in a similar way. This allows for a more accurate evaluation of the results of this study by the study researchers after the study is completed.

You will need to complete a study evaluation 30 days after starting the study and then at 4 months, 8 months, and 12 months. These evaluations are expected to last about 30 minutes. If in-person visits are not possible, some evaluations may be completed securely using video technology that is HIPAA-compliant. Prior to having any video evaluations, you will need to be trained and willing to take your blood pressure at home with a device provided by the study.

At each of these follow-up evaluations you will:

- Have your medical history reviewed, your study medications counted, and your blood pressure measured, and
- Be examined by the study medical provider.

All of these follow-up evaluations, as part of the study, will be provided at no cost to you.

If you have symptoms suggestive of a stroke during the study, immediately call 911 or go straight to an emergency department. Once you are doing better, contact the study coordinator so you can be seen as soon as possible by the study medical provider who will likely recommend a brain Magnetic Resonance Imaging (MRI) (or a brain Computed Tomography [CT] scan if you cannot tolerate an MRI) as part of your regular care. This MRI (or CT) will be billed to you and/or your insurance company. A copy of these scans, along with scans you had prior to joining the study, will be sent to a secure computer so that they can be reviewed. Any information that identifies you, such as your name or date of birth, will be removed before the scans are sent.

If you wish to stop being in the study before your last scheduled follow-up evaluation, you will be asked to have a final evaluation as soon as possible.

Once this research study is completed, any information that could identify you (protected health information (PHI)) will be removed from any data or biospecimens collected and that, after such removal, the data or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

RISKS AND DISCOMFORTS

As with any medical treatment and tests there are risks and discomforts that you need to know.

Blood Draws:
The most common risks associated with blood draws for the laboratory tests are mild pain and/or bruising where the needle is pushed into the skin.

Magnetic Resonance Imaging, (MRI):
If you have a possible stroke during the study, you will undergo an MRI of the head. An MRI is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body. The most common risk associated with MRI is claustrophobia, “the feeling of being closed in”. The study doctors can give you some medication to help with anxiety if this is a problem for you. There are risks with an MRI if you are pregnant, or have one of the following: an artificial heart valve, metal plate, pin or other metallic objects in your body (including a bullet or shrapnel). During an MRI, you will have to lie still on your back in the MRI scanner in a tight space. This may make you anxious. The MRI scan does not cause any pain and does not

expose you to x-ray radiation. If you cannot tolerate an MRI, a brain CT will be done instead.

Computed Tomography (CT):
If you have a possible stroke during the study, you may undergo a CT scan of the head. A CT scan is a computerized x-ray picture of your internal organs. You may feel some discomfort or anxiety when lying inside of the CT scanner.

Aspirin:
The most common risks with aspirin are irritation to your stomach and bruising on your skin. Other risks with aspirin are:

- Heartburn
- Ringing in the ears
- Nausea
- Vomiting

Less common, but more serious risks of aspirin are ulcers of the stomach or small intestine that can lead to serious internal bleeding. This bleeding could lead to hospitalization, blood transfusion and perhaps surgery to stop the bleeding. A previous study of patients with narrowed brain arteries who were treated with a much higher dose of aspirin (1300 mg per day) than you will receive (81 mg per day) showed a risk of major bleeding in 1.8 of 100 patients treated for 1 year.

Clopidogrel:
The most common risks with clopidogrel are:

- Skin rash
- Itching
- Nausea
- Vomiting
- Diarrhea
- Intestinal discomfort

Less common risks include:

- Nose bleeds
- Bleeding in the brain
- High blood pressure
- Swelling in the legs and feet
- Headache
- Dizziness
- Aching in the joints
- Back pain
- Coughing
- Nasal congestion
- Respiratory tract infection
- Mental depression

- Increase in blood cholesterol
- Chest pain
- Fatigue (tiredness)

The most serious risk with clopidogrel is a clotting disorder called thrombotic thrombocytopenic purpura (TTP). This condition is very rare and occurs in 1 out of every 15,000 to 20,000 treated patients. Recent studies have shown that the combination of clopidogrel 75 mg per day and aspirin (75 mg per day) is associated with a significantly higher risk of serious bleeding compared with clopidogrel or aspirin alone over 18 months. In one study these rates were 1.3% (1.3 in 100) on clopidogrel vs. 2.9% (2.9 in 100) on clopidogrel and aspirin. In another recent study of patients with narrowed brain arteries who were treated with aspirin (325 mg per day) and clopidogrel, the rate of a serious bleeding problem was 2.4 in 100 patients treated for 1 year.

Ticagrelor:

The most common risks with ticagrelor are:

- Dizziness
- Nausea
- Diarrhea
- Slow heartbeat rate
- Rash
- Feeling of spinning
- Low blood pressure
- Itching
- Increased blood creatinine (which can indicate kidney damage)
- Allergic reactions including swelling of the face, throat, lips, tongue, hands or feet

The most serious risks include bleeding and shortness of breath. Recent studies have shown that there was no difference in major bleeding between ticagrelor (0.5% or 1 in 200) and aspirin (0.6%), but a higher chance of shortness of breath: ticagrelor (6.2% or 6.2 in 100) compared to aspirin (1.4% or 1.4 in 100) (over a period of 90 days). Another recent study showed that combining ticagrelor with aspirin lowered the risk of a new stroke but increased the risk of major bleeding compared to aspirin alone. After 30 days of treatment, the rates of a new stroke were 5% (5 in 100) in patients treated with ticagrelor plus aspirin compared to 6.3% (6.3 in 100) in patients treated with aspirin only and the severe bleeding rates were 0.5% (1 in 200) in patients treated with ticagrelor plus aspirin compared to 0.1% (1 in 1000) in patients treated with aspirin only.

Rivaroxaban:

The most common risks with rivaroxaban are:

- Bleeding: Internal bleeding which may occur in your stomach and intestines may result in a low blood count (anemia) or decrease in your blood pressure (hypotension). Other common bleeding sites include eye bleeds, bleeding from your gums, nose bleeds, dark urine, heavy menstrual bleedings, hematomas (collection of blood) on the skin and small bleeds under the skin, coughing up blood, bleedings from wounds and after surgical procedures.
- Some enzyme levels in blood may increase (such as liver enzymes called transaminases)
- Upset stomach, nausea, vomiting, constipation or diarrhea
- Itching or skin rash
- Headache, dizziness
- Fever
- Pain in limbs
- Swelling
- Decreased general strength and energy
- Bruises
- Kidney problems*

*this was observed after major orthopedic surgery of the lower limbs

Less common risks include:

- Increased platelet count, Increased heart rate, dry mouth, feeling unwell
- Allergic reactions, hives
- Wound oozing
- Some liver enzyme levels in blood may increase
- Bleeding into your joints
- Brain bleeding or intracranial bleeding (especially in patients with high blood pressure and the elderly)
- Fainting

Rare risks include:

- Localized swelling, yellow skin, hematomas or bleeds in the muscle tissue
- Blood collection outside an arterial wall
- Elevation of bilirubin in the blood with or without an elevation of a liver enzyme called alanine aminotransferase

Since rivaroxaban is a blood thinner there is a risk of bleeding from anywhere in your body whether or not you have a cut or injury. This may include bleeding that you can see like bruising (black and blue marks), or dark stool, or bleeding that you cannot see, like a low blood cell count or bleeding into a body organ. There is also a risk of uterine bleeding that, if severe, could require surgery. Bleeding signs may also include weakness, pallor (paleness or whitish skin color), dizziness, headache, chest pain or angina, shortness of breath, low blood pressure, or unexplained swelling. Bleeding if severe, may require transfusion. In a recent study, 3.1% of patients (3.1 in 100) treated

with aspirin and rivaroxaban had major bleeding events compared to 1.9% (1.9 in 100) of patients treated with aspirin alone (over a period of 23 months). Bleeding from rivaroxaban is rarely fatal (seen in less than 1 out of 1000 patients).

After marketing authorization, the following side effects have been reported for rivaroxaban. Their actual frequency cannot be accurately estimated from post approval experience.

- Allergic edema (swelling of the face, lips, mouth, tongue or throat)
- Decreased bile flow, inflamed liver, including liver injury
- Low number of platelets which are cells that help blood to clot
- Severe kidney damage, known as anticoagulant-related nephropathy (ARN), that leads to blood in the kidneys and urine
- A lung disease, known as eosinophilic pneumonia, caused by the buildup of a type of white blood cell called eosinophils. It can cause shortness of breath, cough, fatigue, night sweats, and weight loss
- Stevens-Johnson Syndrome and/or DRESS (drug reaction with eosinophilia and system symptoms), which are severe skin reactions
- Hemiparesis or weakness on one side of the body

Rivaroxaban is not recommended for you if a doctor has told you that you have a severe form of antiphospholipid syndrome, a disease which can cause blood clots. Please discuss with your doctor if you have been told that you have this condition. If you have ever had an allergic reaction to rivaroxaban, you should not enroll in the study.

Atorvastatin:

The risks associated with atorvastatin, the cholesterol-lowering pill used if LDL levels are greater than or equal to 70 mg/dL, are increase in the blood levels of enzymes in the liver (less than 1% or 1 out of 100), muscle weakness and aches (less than 2% or 2 out of 100), and a very rare occurrence of a muscle disorder called rhabdomyolysis that can potentially lead to kidney failure (less than 1/10th % or 1 out of 1000). Atorvastatin can also interact with other medications. It is important that you notify the study doctors of all of the medications you take, whether prescription or over-the-counter, so problems can be avoided.

Blood pressure lowering medications:

The risks associated with blood pressure lowering medications include:

- Low blood pressure that may cause faintness
- Dizziness
- Headaches
- Weakness
- Abnormal metallic taste
- Allergic reactions
- Diarrhea
- Low or high potassium levels in the blood (depending on what type of blood pressure medication is being taken)
- Cough (with one category of these medications)

- Decrease in white blood cells
- Swelling of the tissues (angioedema)

These types of reactions occur in less than 10% (or less than 10 of 100) of the patients who take them. These medications can also interact with other medications. It is important that you notify the study doctors of all of the medications you take, whether prescription or over-the-counter, so interactions can be avoided.

It is important to tell the study doctor if you have an asthmatic reaction to aspirin, ulcers in your stomach or intestines and any bleeding or clotting disorders. You also need to tell the study doctor if you drink more than an average of 2 drinks per day of alcohol.

Tell your doctors or dentist that you are in a study and taking blood thinners. This is very important if you have any planned or emergency surgery, dental procedures, or other procedures such as a colonoscopy.

Unforeseen risks:
Since the study medications are investigational, there may be other risks that are unknown. Additionally, there may be unknown risks to a pregnancy, embryo, or fetus if you are female and become pregnant or if you are male and your female partner becomes pregnant.

Privacy Risks:
If your PHI and genetic research data are shared with unauthorized users, you may be at risk of loss of the privacy of your health data. This risk is minimized by protections described in the Confidentiality section below.

Pregnancy Risks:

If you are a female and are pregnant or are breastfeeding, you cannot join this study because the risks of the study medications to the human embryo, fetus, or breastfed infant are unknown and the use of the blood thinners in the study during pregnancy could cause serious bleeding resulting in emergency delivery. If you have had a period in the last 18 months and have not had surgery that would make you unable to become pregnant, you will have a pregnancy blood test done to be sure you are not pregnant. If you can become pregnant, it is important that you agree not to become pregnant while you are in the study and you must use birth control during the study. The type of birth control you use must be discussed with the study doctor before you begin the study. The study doctor must approve the method you use before you can enter the study. If you do become pregnant while in this study, it is very important that you tell your study doctor or study coordinator immediately. You will have to stop taking the study medications. The study doctor will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy, your delivery and the health of your baby.

If you are a man and your partner becomes pregnant in the time between when you start taking the study medications until your last dose of study medications, you must tell the study doctor immediately. The sponsor may ask you and your partner to allow them to collect information about her pregnancy, delivery, and the health of the baby. Your partner may be asked to sign a separate consent form.

BENEFITS

Your participation in the study may help the study doctors better understand the effectiveness and safety of the study medications when used to prevent stroke in patients with a narrowed brain artery. No direct benefit to you from joining this study can be guaranteed.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY

The alternative to participating in this study is to not participate. If you choose not to participate in the research study, you will likely be prescribed the usual therapy that is recommended following a stroke due to a narrowed brain artery. This consists of clopidogrel and aspirin daily. Additionally, any stroke risk factors you might have such as high blood pressure, high cholesterol, diabetes, smoking, and excess weight control should be managed. Stenting of the narrowed artery (placing a balloon and a wire tube into the artery to open it) has been shown to be less effective and more dangerous than intensive medical treatment alone.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law.

If you are or have been a patient at the study site Healthcare facility, then you will have a study site medical record. If you are not and have never been a patient at the study site then a study site medical record will be created for you just because you are participating in a research study.

Results from study tests and procedures that are performed, analyzed and/or read at or for the study site facilities that can be used for healthcare purposes will be placed in any medical record that you have with the study site facilities. In addition, a copy of the informed consent form and HIPAA authorization form that you sign and date will be placed in any study site medical record you may have. Persons who have access to your medical record will be able to have access to all results and documents that are placed there, and the results/documents may be used by the study site facilities to help provide you with medical care. Any results and documents that are kept as part of your medical record are not covered by certain state and federal laws and regulations that may prevent the disclosure of research data. However, the confidentiality of the results and other documents in the medical record will be governed by laws such as HIPAA that concern medical records.

The study site does not have any control over results from tests and procedures performed and/or analyzed or read at non-study site facilities. These results are NOT routinely included in medical records at the study site facilities, and they will not necessarily be available to the study site providers. The study site also does not have control over any other medical records that you may have with other healthcare providers and will not send any test or procedure results from the study to these providers without your permission. It is up to you to let these healthcare providers know that you are participating in a study.

Some tests and procedures that may be performed during this study by the study site Healthcare or other facilities or persons MAY NOT BE LOOKED AT OR READ FOR ANY HEALTHCARE TREATMENT OR DIAGNOSTIC PURPOSES. THESE TESTS AND PROCEDURES WILL ONLY BE LOOKED AT FOR RESEARCH PURPOSES AND THE RESULTS WILL NOT BE REVIEWED TO MAKE DECISIONS ABOUT YOUR PERSONAL HEALTH OR TREATMENT. The specific types of tests or procedures, if any, that fall within this category are listed below:

- The mouthwash or cheek swab test for the genetic variants. This test is called CYP2C19 genotyping.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

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

All health insurance companies and group health plans and all employers with 15 or more people must follow this law.

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

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The

researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information, we cannot withhold that information and we cannot hold responsibility for how that person may use your information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that information to appropriate authorities.

COMPENSATION AND COSTS

The study medications [aspirin and either clopidogrel, ticagrelor, or rivaroxaban], all scheduled follow-up evaluations that are performed as part of the study, and the INTERVENT coaching program and services will be paid for by the study.

You may also receive atorvastatin and certain blood pressure-lowering medications at no cost to you.

You may be provided with a blood pressure device for home measurements at no cost to you. If provided, you will need to return it to your study doctor at the end of your study participation.

You and/or your insurance company will be responsible for the costs of any lipid-lowering and/or blood pressure medications that are not provided by the study as well as blood tests and brain MRI or CT scans that are considered necessary as part of your regular care. If you and/or your insurance company cannot cover certain laboratory costs, let your study doctor know as assistance may be available.

The study will provide a $50 stipend to you per visit for the 1-month, 4-month, 8-month and 12-month visit, if the visit is conducted **in-person**. The stipend is intended to assist you with the cost of travel to the visit (gas, bus ticket, parking, etc.). You will be paid for each visit at the completion of each visit.

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

Please indicate below if you wish to receive the visit stipend described above:

_____ Yes, I want to receive the $50 stipend for in-person visits.
(INITIALS)

_____ No, I do NOT want to receive the $50 stipend for in-person visits.
(INITIALS)

COMPENSATION FOR INJURY

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

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

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

YOUR RIGHTS AS A STUDY PARTICIPANT

Your signature and date on this consent form means you have read this information and want to join the study.

You will be given a copy of this signed and dated form to keep. You are not giving up any of your rights by signing and dating this form**.** Even after you have signed and dated this form you can change your mind at any time and stop being part of the study. Let the study staff know right away if you want to do that.

The study doctor may decide that you need to stop study provided treatments. For example, if you have a serious reaction to study medications. The entire study could also be stopped on the recommendations of a safety committee that will monitor this study or by the sponsors of the study.

WHOM TO CONTACT ABOUT THIS STUDY

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 study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00050939.

NEW FINDINGS

If new things are learned during this study that might be important to you we will tell you right away.

ABOUT USING BIOLOGICAL SAMPLES AND DATA FOR RESEARCH

During this study, you will have a mouthwash or cheek swab sample collected and sent to the University of Florida Center for Pharmacogenetics and Precision Medicine Laboratory to test for the CYP2C19 genetic variant. After this test is complete, instead of discarding your leftover sample, with your permission, we will save (bank) it and the information (data) collected from this study for possible future research. Any leftover sample and your data will be identified with a code and stored indefinitely in the University of Florida Center for Pharmacogenetics and Precision Medicine Laboratory located in the College of Pharmacy.

Once this research study (CAPTIVA) is completed, any PHI will be removed from coded data or samples collected. Then after the information is removed, the data or sample could be used for future research studies or distributed to another investigator without additional informed consent from you.

The research that may be done is unknown at this time and may not be designed specifically to help you. It might help people who have had a stroke and other diseases in the future.

Reports about research done will not be given to you or your study doctor. These reports will not be put in your health record. The research will not have an effect on your care. If the research is published or presented at scientific meetings, your name and other personal information will not be used.

Things to Think About

If you decide now, that you wish for your sample and data to be used for future research, you can always change your mind at any time. Simply contact your study doctor, who will let the leader of the study know that you no longer want your sample and data used for research. The leader of the study will destroy the remaining sample and data as long as the PHI that identifies you has not already been removed. However, any research that has already been done using your sample and data will be kept and analyzed as part of those research studies.

In the future, people who do research may need to know more about your health. While your study doctor may give them reports about your health, he will not be able to give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your sample and data will be used only for research and will not be sold. The research done may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from the sample.

Benefits

The benefits of research using samples and data include learning more about what causes strokes and other diseases, how to prevent them, and how to treat them.

Risks

Any information that could identify you will be removed from any data or sample collected; therefore, the risk of release of your personal information is very small.

Making Your Choice

Please think about your choice. After reading, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your study doctor or study coordinator, or call our research review board at 877-992-4724.

Outside researchers may one day ask for a part of your sample and data for studies now or future studies.

The University of Florida has the right to destroy your sample and data and end their storage without telling you.

The choice to let us use your sample and data is optional and is up to you. No matter what you decide to do, it will not affect your care.

I agree that my leftover sample and data collected from this study can be banked for future research:

_____ Yes, I agree. (INITIALS) _____ No, I do not agree. (INITIALS)

Consent To Collect and Store Your Genetic Data For Future Research When Identity Of Subject Is Coded And The Codes Are Kept In Locked Files By The Person Conducting The Research

As part of the research project **Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis (CAPTIVA)** we are seeking your consent to store your genetic data.

Reason for Storing Your Data:
You have recently agreed to participate in the research study listed above, that is funded by the National Institute for Health (NIH). That research study involves determining certain genetic information about you. The NIH has a policy of sharing genetic information with other researchers to help further new discoveries on disease treatment and cures. Genetic factors are those that people are born with and that can affect other family members. What is included in the genetic information of yours that will be stored in this federal data bank, will be determined by the research study you have already agreed to.
The person in charge of the research project you agreed to (also known as the Principal Investigator) or a representative of the Principal Investigator will describe this data sharing to you and answer all of your questions. Your participation in allowing your data to be shared and stored in this NIH data bank is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. If you choose not to participate in this data banking and data sharing study, you will not be penalized or lose any benefits that you would otherwise be entitled to.

What will Happen to Your Genetic Data:
If you agree to this data banking and data sharing study, your genetic data and any other data that is collected in the study will be placed into a secure location (a large computer). Once the other study you agreed to (listed above) is completed, your genetic data and other data collected on you during that study will have all identifiable information removed and then be sent to the NIH data bank. Your de-identified data that is sent will be given a unique ID number so the NIH will not be able to match this unique ID number to identify you.

Who Can Use Your Stored Data:
At the NIH, de-identified genetic data that has been collected from you and other participants may be given to researchers from around the country who apply to the NIH to receive de-identified data to use in their research projects. This request will first have to be approved by an NIH committee that oversees the release of the data. Once the NIH committee approves the release of the de-identified data, the researcher will have to get local Institutional Review Board (IRB - an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research) approval before they can start their study.

At the NIH, since your data is de-identified in the data bank, you will not receive any information when data is used in future research or receive any results from that future research.

Benefits to You in Storing Your Data:
There is no direct benefit to you for participating in this data bank.

Risks to You in Storing Your Data:
At NIH:

- Risk of Identification: The genetic data being sent to the NIH Data Bank is de-identified, however there is a slight chance that identifiable information may be mistakenly sent.
- Risk Associated with the Freedom of Information Act: Your information that is sent to the NIH will be kept in an NIH data bank and will, thereby, become U.S. government records that are subject to the Federal Freedom of Information Act (FOIA). As an agency of the Federal government, the NIH is required to release government records in response to requests under the Federal Freedom of Information Act (FOIA), unless the records are exempt from release under one of the FOIA exemptions. The NIH believes that the only release of your data under such a request would be your data with the unique ID number removed.

- Risks Associated with Law Enforcement Access: It is possible that law enforcement agencies could request access to the de-identified genetic data within the NIH data bank and, for example, search for matches to DNA data collected as part of some criminal activity. While this is expected to be rare, such requests may be granted by the NIH. Law enforcement officials might then try to identify you by requiring your study doctor to release the key to the unique ID number which could identify you. However, the release of identifiable information by your study doctor may be protected by the Certificate of Confidentiality.

  Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect researchers from being forced to release research records, which in this case is your genetic information. These Certificates allow the researchers and others who have access to research information to refuse to release information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Risks to Specific Populations, Groups, and Communities: Medical research has already shown that some populations demonstrate a higher likelihood to develop certain medical diseases than others. It is possible that if you have some rare condition or rare physical characteristics, that someone could identify you based on the de-identified data in the NIH data bank.

Can You Withdraw Your Consent to Store Your Data?
If you decide that your genetic data can be kept for research but you later change your mind, tell your study contact who will ask the Federal Data bank to remove your de-identified data from the data bank. There will be no cost to you for this storage of your de-identified genetic data.

Do You Agree to Participate?
Please review statement below and initial by your choice:

I agree to have my de-identified genetic data shared with the NIH databank to be used for future unknown research.

_____ Yes, I agree. (INITIALS) _____ No, I do not agree. (INITIALS)

VOLUNTARY PARTICIPATION / WITHDRAWAL

You do not have to be in this study. You can also stop at any time if you start the study and do not want to continue. There will be no change in your relationship with your personal doctors if you stop being in the study. A copy of this consent form will be placed in your medical record. You will be given a copy of this consent form.

If you decide to stop being in the study, please tell the study doctor, at the telephone number on the first page of this consent form.

STATEMENT OF CONSENT

I have read this consent form and have been given the chance to ask questions about it. I am signing and dating this form because I want to join this study.

I give my consent to participate.

_____
Name of Participant (PRINT)

_____ _____
Signature of Participant Date

Person Obtaining Consent:

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the participant has been provided with the Experimental Subject's Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in non-technical terms all of the information contained in this informed consent document, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____
Name of Person Obtaining Consent (PRINT)

_____ _____
Signature of Person Obtaining Consent Date

WITNESS STATEMENT:

The participant is unable to read, sign and/or date this consent form because of the following reason(s):
___The participant is non-English speaking.
___The participant is illiterate.
___The participant is visually impaired.
___The participant is physically unable to sign and date the consent form. Please describe:_____
___Other (please specify): _____

I confirm that I was present as a witness for the consent process for this study. I confirm that the participant named above was read the information in the consent document and that the participant has agreed to take part in the research study.

_____
Name of Impartial Witness (PRINT)
(may be interpreter if participant is non-English speaking)

_____ _____
Signature of Impartial Witness Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health information about you to conduct the study. Health information may include:

- Your name
- Address
- Phone number
- Date of birth
- Medical history
- Information about your risk factors
- Information from your study evaluations, including all test results

Health information may come from your study records or from existing records kept by your study doctor or other health care workers.

For this study, the study staff may share health information about you with authorized users. Authorized users may include:

- Representatives of the University of Florida
- Representatives of the University of Cincinnati
- Representatives of the Medical University of South Carolina
- Representatives from the INTERVENT program, who will conduct the telephone coaching required as part of this study
- Representatives of AstraZeneca Pharmaceuticals or Janssen Scientific Affairs
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study)
- Representatives of the National Institutes of Health
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB
- United States governmental agencies which are responsible for overseeing research, such as the Food and Drug Administration (FDA), the Department of Health and Human Services, and the Office of Human Research Protections

- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study
- Other research doctors and medical centers participating in this study, if applicable
- A data safety monitoring board and independent medical monitor who oversees this study

Your health information will be used to conduct and oversee the research, including for instance:

- To see if the study medications work and are safe
- To compare the study medications to other medications
- For other research activities related to the study medications

Once your health information has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health information about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health information about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health information that identifies you will be gathered after your written request is received. However, health information about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health information in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health information.

If you decide not to sign and date this form, there will be no change in your relationship with your personal doctors; however, you will not be able to take part in the study.

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

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?
Information related to your participation in the research (e.g., laboratory tests, notes from your physician, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by Penn Medicine.
Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety and efficiency of your healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR?
The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your

participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Some information specific to this clinical research study may be shared with you in a delayed manner, shared with you at the end of the study, or not shared with you. Not sharing or delaying certain research information within your EMR may be necessary to protect the integrity of the trial results or for other reasons.

Results from your mouthwash sample will not be shared with you or placed in your medical record.

Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health information as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____
Name of Participant (PRINT)

_____ _____
Signature of Participant Date

WITNESS STATEMENT:

The participant is unable to read, sign and/or date this authorization form because of the following reason(s):
___The participant is non-English speaking.
___The participant is illiterate.
___The participant is visually impaired.
___The participant is physically unable to sign and date the consent form.
Please describe:
_____

___Other (please specify):
_____

I confirm that I was present as a witness for the authorization process for this study. I confirm that the participant named above was read the information in the authorization document and that the participant has agreed to take part in the research study.

_____
Name of Impartial Witness (PRINT)
(may be interpreter if participant is non-English speaking)

_____ _____
Signature of Impartial Witness Date