This informed consent applies to adults.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. You may discuss your decision with your family and friends and with any of your doctors or your health care team. If you have any questions about the study, you should ask the study doctor. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have just had a transient ischemic attack (TIA) or a minor stroke. A TIA is a condition that produces stroke-like symptoms like sudden weakness on one side of the body or trouble speaking, but the symptoms are temporary.

Patients who have had a TIA or minor stroke have a higher risk of developing a stroke. Recognizing and treating TIAs can reduce that risk. Medicines that prevent blood clots from forming are often used to help prevent another stroke in patients with blockage of one of the arteries in the brain. Two commonly used drugs are being used in this study.

- Clopidogrel (also known as Plavix) is a type of medication called an antiplatelet drug. This helps blood flow more easily, and provides more protection against a future heart attack or stroke. Antiplatelet drugs are also known as blood thinners. Clopidogrel is approved for the prevention of a second stroke or TIA, and is taken once per day. This drug is also FDA approved for use after a stroke or TIA.

- Aspirin has also been shown to be effective in helping to prevent a second stroke or TIA, and is approved in doses ranging from 50 to 325 mg per day. This drug is also FDA approved for use after a stroke or TIA.

This study looks at whether the combination of low-dose aspirin and clopidogrel increases the effectiveness in reducing the risk of stroke, heart attacks and other complications in patients who have just had a TIA or a minor stroke. The study will also compare the risks of the combination of clopidogrel with aspirin with the risks from aspirin alone. These two drugs are often used together but not immediately after a stroke or TIA.

Several studies that tested the combination of clopidogrel and aspirin have shown that taking these two medications together may protect patients even more from major stroke and heart attack after a TIA than taking aspirin alone. A single trial in China studying patients with stroke and TIA suggested that the combination of clopidogrel and aspirin was safe and effective. However, there are differences in the treatment of patients, the types of stroke, and the design of the trial, so it is not clear whether these results would apply to you. The POINT research study has been designed to find out whether the combination of aspirin and clopidogrel taken within 12 hours of time last known free of new ischemic symptoms reduces the risk of stroke, heart attacks and other complications compared to aspirin alone in patients like you.

This study is sponsored by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke (NINDS). A total of 4,150 patients in about 210 hospitals will participate in this research study with 10 here at Vanderbilt Medical Center.

2. What will happen and how long will you be in the study?

Before you begin the main part of the study...

If you agree to be in this study and sign this consent, you will be assessed to see if you meet the entry criteria for the study. A study doctor will check to see if you are eligible by reviewing the results of the following tests and procedures that were done as part of your routine care:

- A complete medical history (including any medications you are currently taking, since there are some medications you cannot take while you are in this study).
- Blood drawing (venipuncture): Laboratory tests, including glucose and platelet count.
- An electrocardiogram (ECG) heart tracing (measures the electrical activity of the heart).
- Because the drugs in this study can harm a fetus, pregnant women should not take these drugs. If you are female and not post-menopausal or have not had a prior hysterectomy, you will have urine pregnancy test.
- A type of brain scan called a CT (computed tomography) or an MRI (Magnetic Resonance Imaging) that takes a picture of your brain.
- A physical examination and neurologic assessment (a focused physical examination of neurologic functioning including strength, sensation, coordination and speaking, and a series of 2 evaluation scales – the modified Rankin Scale and the NIH Stroke Scale).

You may not enroll in this study until all of these tests and procedures have been done and a study doctor has reviewed the results. Again, these will all have been done as part of routine stroke care before you start in the study.

If you are female and not post-menopausal or have not had a prior hysterectomy, you will undergo a blood or urine test to determine if you are pregnant. The drugs in this study can negatively affect a fetus, so pregnant women may not participate in this study.

During the main part of the study (everything from here to the end of the study is for research only) Day 1

After those procedures are completed, and it has been determined that you are eligible for this study, you will be randomized. Randomization means that you are put into a group by chance. You will have an equal (a 50:50) chance of being placed in group 1 or group 2. This visit will take about 30 minutes.

This is a double-blind study, which means that neither your study doctor nor you will know which of the study drug groups you are in. However, this information will be available in the case of an emergency. If you are in group 1, you will take 8 tablets of 75 mg clopidogrel on day 1, and 1 tablet daily of 75 mg clopidogrel, and a daily dose of 50 - 325 mg of aspirin for the next 89 days. If you are in group 2, you will take 8 tablets of 75 mg placebo (a substance that has no active drug) on day 1, and 1 tablet daily of 75 mg placebo and a daily dose of 50 - 325 mg of aspirin for the next 89 days. In both groups the dose of aspirin will be determined by your study doctor.

Just before your discharge from the hospital, an appointment for your next visit in about 90 days from the day you enrolled will be made. Information about how to contact the study doctor in case of an emergency will be given to you on a card to keep in your wallet. This wallet card advises emergency responders (EMTs or paramedics) that you are in a study using blood thinners. The study doctor or staff will try to contact your regular doctor to inform him or her that you are in this study.

You will also be given a list of medications to be avoided while taking study medication, as well as a study medication log and study information sheet. This list does not replace the advice of your medical provider. You should discuss this list and any medications you are taking with your health care provider before you make any changes.

Study Visits:

One Week

About 1 week after you enroll, the Study Coordinator will call you or ask you in person whether you've been taking your study medications. You will be asked about any side effects or possible problems you might be having. The Coordinator will also collect information about your other medications and will ask you to complete a short survey about any neurological symptoms you may have had since your discharge. This call should take about 15 minutes unless you have questions that need to be addressed.

Thirty Days

About 30 days after you enroll, the Study Coordinator will call you or ask you in person whether you've been taking your study medications. You will be asked about any side effects or possible problems you might be having. This call should take about 5 minutes unless you have questions that need to be addressed.

Event Visit

If you think you have had another event (a stroke, TIA or heart attack) call 911 or have someone take you to the emergency room immediately. After that, call or ask someone to call the study number listed on your wallet card as soon as possible. You will be scheduled for a follow-up evaluation. At the follow-up visit you will:

- answer questions about your study medications and any side effects or adverse events
- be evaluated using two scales (the modified Rankin Scale and the NIH Stroke Scale)
- have your blood pressure and pulse taken by the study coordinator
- complete another survey about any neurological symptoms you may have had since enrolling in the study

This visit would not replace a visit to your regular doctor.

90 Days

You will need to return to Vanderbilt Medical Center for a study visit 90 days after starting the study. The follow-up visit will include the same questionnaires and tests described under the Event Visit.

At the end of the study, your study doctor will discuss with you the best choice for antiplatelet drugs like those in the study. You will not be told which treatment you were on for this study until everyone has completed the study and the results are known. This visit will take about 30 minutes.

How long will I be in the study?

The total length of your participation in this study is approximately 3 months.

3. Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. You will also be given the aspirin and the Plavix or placebo while you are in this study. For this study it includes the research only procedures noted in section 2 above.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:
These side effects can be rare, uncommon, or common and some are serious.

a. Side effects from study drugs: patients who have a known hypersensitivity (allergic reaction) to clopidogrel or aspirin should not participate in this study.

b. Side effects from clopidogrel: clopidogrel works by thinning the blood in order to the help blood flow more easily.

Common side effects are
- Longer bleeding from cuts
- Bruising

Uncommon side effects are
- Abdominal or stomach pain
- Diarrhea
- Rash or itching
- Aching muscles and/or joints
- Dizziness
- Fever
- Headache
- Stomach bleeding causing dark, tarry stools and/or stomach pain
- Severe skin rash

Rare and serious side effects are
- Internal bleeding
- Brain bleeding
- Decrease in neutrophils (type of white blood cell)
- Thrombotic thrombocytopenic purpura (TTP) (a serious bleeding disorder) This side effect is most likely to happen in the first two weeks in the study

c. Side effects from aspirin: The side effects of aspirin are generally dose-related, and tend to occur more often in doses that are higher than the dose of aspirin taken in this study.

Common side effects with higher doses:
- Stomach pain
- Heartburn
- Nausea and/or vomiting

Rare and serious side effects in patients taking aspirin for a long time:
- Bleeding

- Hemorrhagic stroke (bleeding in the brain)

d. Side effects from aspirin and clopidogrel: Both drugs thin the blood. Combining them is likely to increase that risk. This combination has not been tested right after a TIA, so rates of hemorrhage must be estimated from other studies of stroke and acute heart syndromes. It is likely, based on the results of those studies, that clopidogrel combined with aspirin has a slightly higher risk of major bleeding. The combination of aspirin and clopidogrel may increase the risk of complications with surgeries or other procedures, or may delay the performance of these procedures due to concerns about bleeding risk, or make accidents worse.

***Note: Other blood thinning drugs should not be taken without first contacting the study doctors or nurse. This includes extra aspirin.**

5. Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

6. Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt or the sponsor to pay for the costs of any additional care. There are no plans for Vanderbilt or the sponsor to give you money for the injury. You do not give up your legal rights by signing this form.

7. Good effects that might result from this study:
a) The benefits to science and humankind that <u>might</u> result from this study. Your participation in the study may help the investigators better understand the safety and effectiveness of clopidogrel when used to prevent stroke in patients with a TIA or minor stroke, and the knowledge gained from participation in this research study may help other TIA patients in the future.

b) The benefits you might get from being in this study. If you are in the group that receives clopidogrel and it proves to treat your condition more effectively and with fewer side effects than the placebo, you may benefit from your participation.

8. Other treatments you could get if you decide not to be in this study:
If you do not want to join this study, you will get the usual therapies that the doctor prescribes following a TIA or stroke. There are several drugs approved by the Food and Drug Administration (FDA) for the prevention of a stroke, including aspirin and clopidogrel. Aspirin is available without a prescription, and

clopidogrel is available off the study. Other drugs are available to you by prescription from your doctor without participating in this study.

You may also choose not to receive any treatment. You may wish to discuss your treatment options with your doctor who usually cares for you before you decide to participate in this study.

9. Payments for your time spent taking part in this study or expenses:
There is no payment for participating in this study.

10. Reasons why the study doctor may take you out of this study:
The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped. 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. If you are taken out of the study you will be told why.

11. What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way. You can decide to stop at any time. Tell the study doctor and your doctor who usually takes care of you if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. Even if you stop the study medication we would like to contact you at day 7 and day 90.

12. Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Dr. Howard Kirshner** at **615-936-1354** or **Diane Brown, RN, BSN, CCRP** at **615-936-0062**. If you cannot reach the research staff, please call 615-936-0060 and ask to have the stroke doctor on call paged.

For additional information about giving consent or your rights as a person in this study, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. All identifying information will be removed from study records and the code will be kept confidential. The study coordinator will be the only person who has access to the code. It will be on her password protected computer.

14. Authorization to Use/Disclose Protected Health Information:
All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your

healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Kirshner and his study team may share the results of your study and/or non-study linked lab tests, x-ray reports, and other tests, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, Food and Drug Administration, University of California, NINDS Neurological Emergencies Treatment Trials (NETT) Network, POINT Clinical Research Collaboration (CRC). Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The sponsor and/or Vanderbilt may give or sell your health data, without identifiers, to others or use it for other research projects not listed in this form. The sponsor, Vanderbilt, Dr. Kirshner and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.
The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Kirshner in writing and let him know that you withdraw your consent. His mailing address is1161 21st Avenue South, MCN A-0118, Nashville, TN 37232-2551. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____

Consent for Sample and Data Storage and Future Research

You are being asked to give a blood sample for research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. The secondary study is optional and you can decide to participate in just the main study.

This blood sample is to test for Biomarkers. Biomarkers are molecules found in blood, other body fluids, or tissues that are signs of a specific condition or disease. If you agree to participate in the secondary study, we will collect about 2 teaspoons of blood (two 5 mL tubes) from you for a type of test called a “biomarker test” on your blood. The biomarker test will help us learn if you have specific biomarkers for the genes named ABCB1 and CYP2C19 which may affect how your body responds to being treated with clopidogrel, the medication being studied in this trial. The results of the biomarker tests can help us learn more about how effective clopidogrel can be for preventing stroke in people who have had a TIA and also have those specific biomarkers in their blood.

The blood will be prepared for genetic analysis and stored at the Neurogenetics Laboratory at the Mayo Clinic in Jacksonville, Florida (MCF) for 20 years. The stored blood samples may be used in future studies for TIA and stroke. We will do our best to make sure that the personal information that we have collected is kept private. We will assign numbers to label the blood samples and no personal information will be on the tubes used to store the blood samples. The genetic test results will be provided to the Principal Investigator and statistician in the study. You will not receive the genetic test

results. The use of samples by other researchers for other research might result in loss of confidentiality out of the control by the POINT research team.

A single blood sample of 2 teaspoons will be drawn from a vein in your arm using a needle. This will take about 10 minutes of your time.

Blood samples – You may feel bothered or pained from the needle stick. You may have a bruise or the site may get infected. It is rare, but some people faint.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Kirshner and Diane Brown will have access to your name.

Your sample will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, and/or others. If this happens, there are no plans to provide money to you.

Your samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for future research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Kirshner at 615-936-1354 or Diane Brown at 615-936-0062 to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. Insert if applicable: You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for research.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future research in _____.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature: _____ Date: _____