NON-INVASIVE TREATMENT OF ABDOMINAL AORTIC ANEURYSM CLINICAL TRIAL

(Consent Form)

1. Nature and Purpose of the Study

The main artery (aorta) from your heart has a small bulge (aneurysm) in its wall as it passes through your abdomen. Because of its location this is called an abdominal aortic aneurysm or AAA. Small bulges can stay the same size for a time; most grow slowly; some grow quickly. No one knows exactly why there are these differences. When a small bulge is present, the usual course is to check its size every 6 months to see if it enlarges to a size that should be fixed. If the bulge grows to this larger size, there is a danger it will burst, which would be a threat to your life and well being. Your doctors would recommend fixing the bulge if it becomes large enough to pose a risk to you.

The purpose of this study is to learn the effect of a medicine called “doxycycline” on the growth of this blood vessel bulge. If the drug slows the growth of the bulge in blood vessels, in future years it could be used to prevent the need for surgery or repair to the blood vessel. Doxycycline may block an enzyme that acts to take apart proteins in the bulge wall.

The time it might take for the bulge to reach this large size could be short (6 months) or long (years). Because bulge growth varies, it can be hard to tell if a new medicine really works. To find out if doxycycline can make the bulge slow its growth, we have to test it along with an inactive “look-alike” capsule. Because these bulges typically grow at a slow rate, we will need to follow the growth for 2-3 years to see if there is a difference.

Doxycycline is used to treat other sicknesses. The other sicknesses doxycycline is used to treat include rosacea (red face rash), gum loss, and infections. Doxycycline is an FDA approved drug for some of these uses, but not for treatment of bulges like the ones we will study.

There is a lot of work in science labs that shows that the drug we will use in this study is good at slowing or stopping the growth of artery bulges in mice and rats. We do not know the effect of this drug on small bulges, like yours, in human patients. The tests that have been done in people, so far, have not been as detailed as this one. We know of two studies in people.

- In one small study in Finland the drug seemed to slow growth of small bulges in human patients, but the doctors who led that study stated that the effect could have been due to chance.
- A large, recent study in Holland tested doxycycline in people with both small and large bulges. The doctors who led the study report that the bulges grew slightly faster in the patients who got the drug instead of the placebo (inactive look alike) with no effect noted on rupture or other outcomes that are of concern for the care of patients.

This study is a clinical trial funded by the National Institutes of Health. About 250 patients with small bulges of the main artery are expected to join this study.

2. <u>What to Expect</u>

If you agree to join this study you will be asked to take two capsules every day, one in the morning and one at night. Half of the patients will get capsules of doxycycline and the other half will get a capsule with the inactive “look-alike”. This will be decided by chance, like a lottery. Neither you nor your doctor will know which of the two kinds of capsules you are taking. However, central study offices will keep a record of what you are taking should your doctors need to know this to take care of you. You will be asked to take your capsules twice a day for 2-3 years or as long as you are in the study. You should not join the study unless you are ready to continue for 2-3 years. As long as you are in the study, you will be seen in our clinic every three months. If traveling to our offices is a hardship for you, you may ask us to conduct the visits at 9, 15, 21, 27 and subsequent visits that do not call for a CT scan by telephone. We will record the study form parts of these calls for data quality control. Each visit will take about half an hour.

Twice a year we will fill out a form about how much you can do and how well you feel and take a special X-ray study to measure the size of the bulge in your aorta, and collect a blood sample from a vein in your arm with a needle into a test tube to be sure that your treatment is safe or to check your blood for levels of the study drug or learn what the blood findings have to do with the growth of blood vessel bulges. Each sample will be no more than three tablespoons of blood. We will collect no more than three-quarters of a cup over the course of the study, seven blood collections at most.

This blood will be frozen and may be tested later to find out how much study drug or what changes due to study drug are seen in any blood. These blood samples will be sent to and stored at Washington University in St. Louis. The frozen tubes of blood will not contain your name, birth date, or other data that could be used by people outside the study to recognize you.

Dr. _____ and the study staff will ask about your health in the past. You will be asked to sign forms so that we can get records from your private doctor or hospitals where you have been treated if we find out that you have been ill while in our study.

3. Risks of Taking Doxycycline and This Study

The most common undesirable effects seen in patients taking doxycycline are stomach and bowel problems such as nausea, vomiting, diarrhea, stomach discomfort or abdominal pain. Fewer than 10% of patients will have any one of these problems. Your skin will be more sensitive to the sun. So, you may be more likely to get sunburn. You can avoid or reverse most of these side effects by taking the medication as instructed and cutting down the amount of sun you get. Other less common side effects (1% or less) include tooth discoloration, skin rashes, liver injury or changes in blood count. As with any medication, there are very rare (<0.1%) problems that could lead to permanent, serious injury. You could have an allergic reaction or drug interaction which could be severe. We are going to ask you about the drugs you use before starting the study to keep people who take drugs that could cause bad reactions out of the

study. We will review your other treatments with you in the course of this study to avoid drug reactions.

As part of this study we will take an X-Ray picture (CT scan) of your aorta every six months (at least five and no more than seven times while you are in the study). Some doctors take CT scans at six-month intervals on their patients who have bulges in their aorta, others take CT scans less frequently or take other pictures that do not use X-rays (for example, ultrasound pictures). CT scans are recommended but are not the only choice for taking care of patients like you whether or not you are in a research project. The amount of radiation in seven CT scans could increase your lifetime risk of developing a fatal cancer by 1/1000. Cancer from radiation usually takes 20-30 years to develop. Among the 250 patients who will join the trial, we do not expect to see any one develop a fatal cancer because of this study, but it could happen. If you do not want to have any radiation exposure related to research on your condition, you should not join this study. Your doctor may choose to use X-ray dye at the time of CT scans to see blood vessels better. This study does not ask for your doctors to use dye. If your doctor wants to use the dye for you (for example, because he or she thinks that the dye picture will be helpful in deciding how to treat you), this study will accept those images.

Rarely (1% per year) a bulge in an artery will burst even though it is a small bulge. Some patients are expected to have this problem whether they join this study, take the study drug or look alike, or not.

You may feel some pain or get a black and blue mark at the site of needle puncture for blood sample collection. Very rarely (less than 1% of the time) these puncture sites may become infected.

As with studies of all new treatments, there may be other risks to using doxycycline that are not now known. If any new bad effects are observed, patients in the study will be told as soon as possible; we will take action to protect your safety as needed.

4. <u>Benefits</u>

You may not receive direct benefit from participation in this study. The treatment used in this study may have no effect on growth of the bulge size, may decrease the rate of growth or increase it. You would not notice this yourself. Only on medical pictures (for example, X-ray pictures) could the change be seen. It may take up to two years to see any effect of being on the drug. We will send X-ray reports and any important medical information about you (for example, high blood pressure levels) that we found on a clinic visit to the doctors who take care of you. At its end, the doctors in this study will be able to use the data they collect from you to tell other patients who have small bulges in that artery whether or not taking doxycycline might help them. This advice will be useful to these patients, to their families and to their doctors.

5. Privacy

In this study only your clinic will know your name. Clinic staff will make note of your age, ethnicity, sex, weight, and height. That information will be stored in the study computer. You will not be identified personally in any report from this study. Your personal medical reports will be kept private. At the end of the study, a computer file of the study results will be made for future use. It will not include any information that could identify you directly. Information may be given to the National Institutes of Health, but your name will not be used in such files.

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.

6. Other Choices

If you join this study, it is your own choice. You may refuse to take part in it or you may leave it at any time. The study doctors may decide to stop your study treatment any time they think it would be in your best interest or in the best interest of the study. If you do not join, or if you leave the study, doing so will not harm your present or future care at the hospital or clinic. Instead of taking part in this study you may go to your doctor for your usual treatment. Your doctor could add doxycycline to your treatment, but until studies such as this are done, your

doctor will not know whether doxycycline will be helpful to you. There have been other studies that have examined the effect of doxycycline on small artery bulges. So far no study has been able to be sure whether the drug slows the growth of a small bulge or not.

7. Costs Paid for by the Study

You will not be charged for any of the visits that are part of the study and not part of your routine care. You will not be charged for the study drug. Clinic visits and imaging studies that are part of your routine care will be billed to you and your insurance company as has been done in the past.

8. Costs Not Paid for by the Study

If you need medicine other than doxycycline the study will not pay for it. Your routine CT scans are not paid for by the study. If you must visit your private doctor or emergency room, or must stay in the hospital, those costs will not be covered by this study. If the bulge in your aorta grows to a size for which stent-graft or surgery is the standard of care, your study doctor will notify you and your personal doctor. The cost of stent-grafts or surgery will not be covered by the study.

9. Payments to You

You will be paid at least $40.00 every three months for travel costs. You will receive this money from the clinic after each of your study clinic visits. If you do not attend study clinic visits or become unable to take part in the study then you will no longer be paid that money. We will cover allowable, documented transportation costs that exceed the $10.00 that we anticipated in the $40.00 reimbursement. For example, travel of 100 miles by car at a cost approved for one recent year by the US government of $0.56/mile amounting to $56.00 exceeds $10.00. We will approve and reimburse those excess costs when you give us advance notice and receipts or other acceptable information such as a description of your driving route from current home to the clinic. In our example, $40.00 + $56.00 - $10.00 = $86.00 would be paid.

10. Use of Left Over Blood Samples

If you agree, the left over blood sample may be stored and used in future research projects to help discover causes of or new treatments for bulges in arteries or other health concerns.

Please initial each one of the following sentences that applies:

(If you do not initial next to a statement we will assume that your answer is NO)

_____ I agree to use my blood for future research.

_____ I do not agree to use my blood for future research.

I understand that if I do not want my samples used for future research this will not affect my ability to take part in this study or in future studies.

11. Studying Your Genetic Information

To collect your DNA or perform genetic studies on your DNA, we need you to give us specific consent. There are different risks that go along with studying your genes that do not apply to the rest of your participation in the study. You do not have to participate in the genetic portion of the study to participate in the other portions of the study.

Why are we collecting genetic information as part of the N-TA^{3}CT?

Genes are the basic "instructions" for the development and activities of our bodies. Genes are made out of DNA. The DNA of a person is about 99.9% the same as the DNA of any other person. But no two people have exactly the same DNA except identical twins. Differences in DNA are called genetic variations. They explain some of the differences among people, like eye colors and blood groups. They also partly explain why some people get diseases like cancer, diabetes, as well as aortic aneurysms. It may also partially explain why some aneurysms grow faster than others.

How will the samples be used?

The DNA samples will be stored with the other blood samples drawn over the course of the study. We anticipate that researchers will study the samples to find places in the DNA

where people are different. For each sample, this may include information on hundreds of thousands (eventually millions) of genetic variations.

The sample will be linked to other data from the study. All of these data are put in one place called a database. All of this information together lets us see patterns that tell the story of how genes affect health. This database will include features of your health and your aneurysm disease such as the size and growth rate of the aneurysm over the course of the study. The final research database will not include any identifiable medical information about anyone who gave a sample.

We may use the data on the differences between the genes of people in this study to map out the ways genes connect with each other to do their work. Researchers can then look for specific genes and study how they work. This will help them figure out better ways to prevent, diagnose, and treat aortic aneurysm disease. They can also learn how to make drugs that work better in more people.

It is possible that studying your genes may reveal information about the risk of aneurysms or some other unrelated disease. *However, it will be very hard for anyone to learn anything about you personally from any of this research because none of the samples or the database will include your name or any other information that could identify you or your family.*

What will happen if I decide to give a sample?

At one of the routine blood draws as part of the N-TA^{3}CT study, we will set aside one tablespoon of blood from your arm for DNA tests. It will not require any additional effort on your part. We will send your sample to the N-TA^{3}CT Biomarkers Core Laboratory (BCL) at the Washington University School of Medicine in St. Louis [U.S.A.], which is overseen by the National Institutes of Health (NIH), the main government agency in the U.S. that funds medical research.

Who will be studying these samples?

Any researchers who will study the samples, data obtained from the samples or data in the database will have to follow U.S. laws and guidelines that apply to research. All studies using the genetic information will have to be approved by an Institutional Review Board (IRB). An IRB is a committee similar to the one that approved the N-TA^{3}CT study to make sure that your safety is protected. Doctors who propose to study the samples must write up their plans for review by the leaders of the study. Their plans must be worthy of permission to use the samples.

The results generated by these researchers may be shared, without any identifying information, with large national databases of genes and diseases such as the Database of Genotypes and Phenotypes (dbGaP) which is maintained by the NIH.

How will you protect my privacy?

While [insert name of institution] will keep your signed consent form, nobody else will see it. We will not keep your name with your sample or give your sample a code number that could identify you. So nobody at the BCL or who studies your sample will know that it came from you.

What are the benefits of giving a sample?

You probably will not directly benefit from giving a sample, because of the long time this research will take to produce results that would change treatment. But researchers will study these samples for many years to learn about health and disease. This research will eventually benefit the health of people around the world.

What are the risks of giving a sample?

The risks at the time of drawing the blood are as described in the main study consent form. If your sample is used for genetic analysis, a large amount of genetic information from your sample may be generated, and many researchers may have access to that information. However, there are few ways anybody could trace the information back to you. One is if they thought your information might be in the database, got another sample from you, did many tests

on that sample, and then compared the genetic information from those tests with the information in the database. The other way is if somebody compared genetic information from samples in the BCL with genetic information known to be from you that was in another database and figured out who you were. The risk of either of these things happening is very small, but it may grow in the future.

We cannot always predict the results of research, so new risks to you may come up in the future that we are unable to predict now. Your sample will not be used to make a clone of you.

Can I change my mind after I give a sample?

Giving a sample is completely up to you. You will not lose any benefits if you choose not to give a sample, including the opportunity to participate in all other aspects of the N-TA^{3}CT study. However, since nobody will know which sample came from you, after you give a sample you cannot take it back or take any information out of the database.

How will I find out what happens with this project?

We do not plan to give you individual results from any of the research performed on the genetic samples. There will be publication of the results of the studies in peer-reviewed medical journals and other publications about what they are learning about health and disease. You can obtain copies of these public reports by seeking them out on the Internet or asking the research staff here for help finding them.

Consent and Signature

Please read the paragraph below, think about your choice, and sign if you agree:

I agree to give a blood sample to obtain my DNA, for researchers to use for future studies of the type described in the form. I have read or listened to the information, I have asked any questions I had, and all my questions were answered. I know that giving a sample is my choice. I understand that after I give a sample, I cannot withdraw my sample from the Repository.

_____ _____
Signature Date

I do not agree to give a blood sample to obtain my DNA, for researchers to use for future studies of the type described in the form.

_____ _____
Signature Date

12. Rights

You will be given a copy of this consent form to keep. If at any time you have questions or concerns about the study you may call (give study staff name and telephone number) _____, the study staff, or (give IRB contact or ombudsman name and telephone number) _____, a person whose job is to watch over the well being of patients in medical research projects. Should you have any bad effect of treatment or medical emergency during the study, care will be provided to you. The cost of treating such bad effects is not covered in the study, and no money has been set aside to pay for these bad effects.

13. Questions

This study has been explained to you by _____ and your questions were answered. If you have any other questions about this study you may call Dr. _____ at _____.

Signature Print

Patient: _____ Name: _____ Date: _____

Investigator: _____ Name: _____ Date: _____

Witness: _____ Name: _____ Date: _____