Protocol Title: The Effect of Exercise Training on Skeletal Muscle Metabolism in Peripheral Arterial Disease

Principal Investigator: Reena Pande, MD

Site Principal Investigator:

Description of Subject Population: Adults With Peripheral Artery Disease

About this consent form

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

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

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

We are doing this research study to find out if abnormal creation of energy stores in the leg muscles may contribute to leg muscle pain in patients with peripheral arterial disease (PAD). In PAD the arteries (blood vessels) in the legs are narrowed because of the build up of plaque. The leg muscle can hurt in patients with PAD and this is usually described as a cramp or tiredness.

This pain is called intermittent claudication. We also want to find out if exercise improves walking distance by making the leg muscles create more energy.

We are asking you to take part in this research study because you have leg muscle pain with walking caused by a narrowing of the arteries in your legs.

We will enroll 40 subjects with PAD and intermittent claudication, and 15 healthy subjects who will serve as a control group at Brigham and Women's Hospital (BWH).

How long will I take part in this research study?

It will take you about 4 months to complete the study. The length of time and the number of visits will depend upon your ability to perform the exercise test during Visits 3 and 4, as described below. The study involves 10 or 11 visits at the Vascular Medicine Research Center (Research Center). Some subjects will also have 36 exercise training sessions at the Research Center.

What will happen in this research study?

Screening Visit

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures. This visit will take about 30 minutes. This visit is required only for study participants who are on aspirin. At this visit, we will go over the study and the risks of stopping your aspirin, and we will contact your physician to make sure it is ok for you to stop your aspirin. If it is ok, we will schedule you for study visit 1.

Study Visit 1 – Baseline Biopsy

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

During the Screening visit, we will do some tests and procedures to see if you qualify to take part in this study. The study doctor will review the results of these tests and procedures. If you do not qualify, the study doctor will tell you why.

Visit 1 will take about 3 ½ -4 hours.

You cannot eat or drink (other than water) for 8 hours before this visit. You may take all of your medications except for aspirin. Aspirin must be stopped 5 days prior to this visit.

At this visit, we will:

- Ask you questions about your/your family's health history
- Ask you to complete 3 questionnaires about how you feel about your health and well being. You can skip any questions that you are not comfortable answering~~)~~.
- Give you a physical exam
- Draw a blood sample
- Give you a sugary drink which helps us measure how quickly glucose is cleared from the blood. We will measure your glucose (blood sugar) before you have the drink and again 2 hours after.
- Measure the ankle brachial index (ABI). For this test we will measure the blood pressures in your arms and legs while you are lying down. This is done by inflating a blood pressure cuff on your arms and legs and listening to the blood flow as the cuff is released.

Lastly, we will take a small muscle biopsy from your calf muscle. This sample will be tested to measure levels of proteins and genes in muscle tissue that control how muscle cells generate (create) energy. All living things are made of building blocks called cells. Genes are part of cells that contain the instructions which determine important things about you, like your height or hair color, and also influence your health. Changes or differences in a gene may affect a person's chances of developing a particular disease, or how a person responds to a particular drug. Your genes are passed down from your parents and then passed on to your children. DNA is the material that makes up genes.

The muscle biopsy takes about 30 minutes. After washing your skin and muscle with a brown soap that kills germs, we will inject numbing medicine into your skin and muscle to lessen the discomfort. One of the study doctors will insert a needle and "snip" a piece of the muscle near your calf. The sample is frozen immediately. The needle puncture will be covered with a bandage and/or steri-strip (a thin adhesive that is used to close small wounds). You can take the bandage off the next day.

The biopsy samples will be sent to Joslin Diabetes Center for analysis. The samples will be labeled with a code and not with information that could be used to identify you.

We may also perform a whole genome analysis on your DNA sample. Usually researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome studies, all or most of your genes are analyzed and used by researchers to study links to the disease under study (Peripheral Artery Disease) and related disorders.

Although we do not currently plan to send your samples, we would like you to know that in order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks would store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data would be sent with only your code number attached. Your name or other directly identifiable information would not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

Visit 2-Biopsy Check
Visit 2 will take about 15 minutes and will take place within 2-3 days after Visit 1.

At this visit, we will ask you to return so we can check where we did the biopsy. We want to make sure there is no sign of infection or other complications.

Study Visit 3-Baseline 6 Minute Walk and Treadmill Testing

Visit 3 will take about 1.5 hours. This visit will take place within 1 week of Visit 1.

At this visit, we will:

- Have you perform a 6 minute walk test**.** With this test we will measure how far you can walk up and down a flat hallway in a 6 minute time period. This is done at the Research Center. You can rest at any time during this test if you need to.
- Perform an electrocardiogram (ECG) to record the rhythm of your heart. We will place 10 small sticky pads on your chest, shoulders and lower abdomen. Each pad has a wire attached. The wires connect to a machine that records the electrical activity of your heart rhythm.
- Have you do the exercise treadmill testing. This test is done on a treadmill to see how long you can walk before you feel symptoms of leg muscle pain (cramping, tiredness, etc.). We will ask you to keep walking until you have to stop due to the leg pain. The treadmill will be flat at the beginning. Gradually, over time the incline (the tilt of the treadmill) will increase. During this test we will monitor your heart by ECG. We will also check your blood pressure every few minutes.
- We will measure your ABI's before and after you performed the exercise treadmill testing, as described under Study Visit 1.
- We will measure your oxygen uptake and carbon dioxide production at rest and while you walk. We will measure this by having you breathe into a tube at rest and while walking on the treadmill.

Study Visit 4--Repeat 6 Minute Walk Test and Treadmill Testing

Visit 4 will take about 1.5 hours. This Visit will take place within 1 week of Visit **3**.

At this visit we will:

- Have you repeat the 6 minute walk test as described under Study Visit 2
- Have you repeat the exercise treadmill testing as described under Study Visit 2

Study Visit 5-Repeat 6 Minute Walk Test and Treadmill Testing

Depending on the test results of the exercise treadmill test done during Visit 2 and 3, we may ask you to return for Visit 5. Visit 5 will take about 1.5 hours and will take place within 1 week of Visit 4.

At this visit we will perform the same tests as described under Study Visit 4.

Study Visit 6-Baseline PET scan

Visit 6 will take about 6 hours and will take place within 2 weeks of Visit 5.

We will do a blood pregnancy test if you are female able to become pregnant. If the test is positive, you will be asked not to participate in the study because we don't know if the exposure to radiation would harm your unborn child.

During this visit you will undergo a positron emission tomography (PET) scan in the Nuclear Medicine/Radiology Department at BWH. The PET scan will show us how your muscles use glucose (sugar) for metabolism (energy).

In order to get the best information from the scan, we must be sure that your blood sugar levels are as close to "normal" as possible before the scanning is done. In order to do this, you cannot eat or drink anything, other than water, for at lest 8 hours before this visit. We will place an IV (a hollow, plastic tube) into a vein in your arm. We will use this IV to take small blood samples to measure your blood sugar level every 5-7 minutes. You will also put your arm in a warming box set at 120 degrees F. You should tell the study doctor if the box becomes too warm.

We will also place an IV in a vein in your other arm. A pre-set amount on insulin will be given continuously through the second IV for at least 90 minutes before we can begin the scan. Based on the results of your blood sugar testing, we will also give you a sugar solution (glucose) through the same IV as the insulin. This is to keep your sugar levels in the normal range.

Once your blood sugar level is carefully controlled, we will take you to the PET scanning room. We will inject a small amount of radioactive glucose (FDG) through the same IV line as the insulin and sugar solution. The radioactive glucose is soaked up by muscle like normal glucose and can be seen by the PET scanner. Glucose without the added radioactivity cannot be seen by the PET scanner. When you have a PET scan, you will lie down on a bed. This bed will then slide into the PET camera. The PET camera looks like a large donut. Your legs will be in the center of the opening in the scanner and your head and arms will be outside the camera. We will take a PET scan of your calf muscles. This will take 60 minutes. It is important that you remain still during the PET scanning.

While the scanning is being done, we will draw 12 small blood samples from the IV in your warmed hand, to test radioactivity levels in your blood.

Before and during this test, we will measure the blood flow in your legs. This is done with an instrument that measures the size of a body part based on the amount of blood flow, using thin straps that are wrapped around your legs. Two blood pressure cuffs will be used during this procedure, one on the thigh and one on the ankle. The cuffs will be inflated and deflated at different times during the study. You will not feel any discomfort during this test. Each measurement takes no more than 10-20 minutes.

We will provide you with a meal at the end of this study visit.

Randomization

If you qualify for the study, we will assign you by chance (like the flip of a coin) to the Exercise training group or the Normal activity group for the next 3 months. You and the study doctor cannot choose your study group. You will have an equal chance of being assigned to each group.

Normal activity group:

If you are assigned to the Normal activity group, we will ask you to keep track of your daily activities at home. We will give you an activity log to fill out at home each day. Bring this activity log with you at each study visit, so we can track your progress.

Exercise training group:
If you are assigned to the Exercise training study group, you will come to the Research Center for 1-hour training sessions 3 times a week for 3 months. At these training sessions, you will walk on a treadmill. After a 5-minute warm-up period, we will ask you walk at 2 mph and at a 0% incline (flat surface). You will walk until your legs muscle hurt and then you can rest. Once your symptoms resolve, we will ask you to walk again. This is repeated until the exercise training session is complete. We will increase the speed of the treadmill and incline as you become more comfortable with each visit. You will also walk at home for at least 30 minutes 2 times a week. We will ask you to keep track of your exercise at home. We will give you an activity log to fill out at home each day. Bring this activity log with you at each study visit, so we can track your progress.

Study Visit 7 and 8-Repeat 6 Minute Walk and Treadmill Testing

Visit 7will take place about 4 weeks after Visit 6. Visit 8 will take place about 4 weeks after Visit **7**. Both visits will take about 1.5 hours. During these visits, we will perform the same tests as described under Study Visit 4.

Visit 9-Final Biopsy Visit

Visit 9 will take place about 4 weeks after Visit 8. This visit will take about 2 hours.

At this visit, we will:

- Ask you to complete 3 questionnaires about how you feel about your health and well being. You can skip any questions that you are not comfortable answering.
- Draw a blood sample
- Measure your ABI's
- Take a small muscle biopsy sample from your calf muscle.

Study Visit 10-Biopsy Check

Visit 10 will take about 15 minutes and will take place within 2-3 days after Visit 9.

At this visit, we will ask you to return so we can check where we did the biopsy. We want to make sure there is no sign of infection or other complications.

Study Visit 11-Final 6 Minute Walk Test and Treadmill Testing

Visit 10 will take place within 1 week of Visit 9. Visit 10 will take about 1.5 hours. During this visit we will perform the same tests and procedures as described under Study Visit 3.

Study Visit 12- Final PET Scan

Visit 11 will take place within 2 weeks of Visit 10. Visit 11 will take about 6 hours. During this visit you will have the same PET scan as described under Study Visit 6, including the blood pregnancy test if you are a female able to become pregnant.

We will draw a total of about 9 tablespoons of blood during the entire course of this research study.

Stopping early from the study:

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

- The study doctor and/or your treating physician do not feel it is safe for you to stop taking your aspirin and/or plavix
- You stop walking during the treadmill testing visit for reasons other than leg muscle pain (shortness of breath, back pain, joint pain)
- You develop rest pain or leg ulcers due to poor blood flow
- The study doctor finds abnormalities in your ECG during the treadmill testing that might be related to heart problems
- You become pregnant

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

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

Treadmill Testing and Exercise Training Risks:
Some subjects experience dizziness or lightheadedness when they first begin walking on the treadmill. This usually resolves after a few minutes of walking. You may also feel fatigue (tired), short of breath, of muscle tiredness. This is normal and will resolve shortly after completing the test. You should let the study staff know if these symptoms do not go away

after a few minutes of stopping the test.

ECG:
There may be some discomfort when the sticky pads used for the ECG are removed from your skin.

Risks of adjusting the blood sugar level:
The insulin may cause a drop in your blood sugar. We carefully monitor your blood sugar level throughout the visit and give you glucose to keep your sugar levels in the normal range. However, you may feel some symptoms of low blood sugar levels (hypoglycemia), which include dizziness, lightheadedness, shakiness, and sweating. This happens rarely. If this happens, we will give you an extra sugar solution through the IV. These symptoms usually resolve within minutes. Before you leave, we will check your blood sugar again to be sure it is safe for you to leave.

Warming Box Risks:
Very rarely people develop redness of the hand while it is in the warming box. This usually goes away once your hand is taken out of the warming box. The temperature can be adjusted if this happens.

PET Scan Risks:
The PET scan involves exposure to radiation, though the radiation will be out of your body within 24-48 hours. The radiation dose from each PET scan is about 9 mSv (an mSv is a unit of radiation dose). This is slightly less than 3 times the radiation amount received by the average person in the United States each year from natural source of radiation in the environment.

We are doing the PET scan in this study to answer research questions, not to give you medical care. The information created by this study will not become part of your hospital record. This PET scan is not the same as one that your own doctor would order. It may or may not show problems that would be found on a standard PET scan.

If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in scans of this sort) to review the results. If the radiologist thinks that there might be a problem, we will tell you and help you get follow up care.

If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Muscle Biopsy Risks:

We will take a small piece of muscle from your calf through a needle. This will likely cause bruising and may be tender for 1-2 days after it takes place. Other possible risks of the biopsy include bleeding, pain and infection.

Xylocaine is a medicine used to numb the area where the sample is taken. It may cause symptoms of an allergic reaction, like itching, hives, and swelling. You should tell the study staff if you have ever had an allergic reaction to xylocaine (which you may have had for other minor operations or dental work). It feels similar to a "bee sting" when it is injected. You may find this uncomfortable.

To prevent the risk of bleeding, you will need to stop your aspirin and/or other 'blood thinners' (such as clopidogrel, or plavix) five (5) days before the biopsy. If the study doctor and/or your own doctor do not think it is safe for you to stop aspirin and/or plavix, you will not be able to participate in the study. The risk of stopping aspirin and/or plavix is very low, but may include heart attack or stroke.

Genetic Testing Risks:

Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health, or have a negative impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. We will not place information about the study or the results of study tests in your medical record.

Pregnancy Risks:
If you are a woman of childbearing age, you will also have a blood test to make sure that you are not pregnant. If the test is positive, (pregnant) you will not be able to participate in the study. If

the test is negative, you must agree not to try to become pregnant during the study. You must use one of the following birth control methods:

- abstinence from sexual relations (no sexual intercourse)
- oral contraceptives (birth control pills)
- IUD or other barrier methods, such as cervical cap, or diaphragm with a gel that kills sperm
- condoms with a gel that kill sperm

If you suspect that you have become pregnant while participating in the study, you must contact Dr. Pande at once. You will have to withdraw from the study if you become pregnant, since the radiation you are exposed to during the PET scan could harm an unborn child.

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

You may or may not benefit from taking part in this research study. Previous studies have shown that structured exercise training can improve intermittent claudication symptoms.

Others with PAD and intermittent claudication symptoms may benefit in the future from what we learn in this research study.

What other treatments or procedures are available for my condition?

You do not have to take part in this research study to be treated for intermittent claudication. Other treatments that are available to treat claudication are:

- Cilostazol (Pletal)
- Pentoxifylline (Trental)
- Revascularization, a procedure that will "open" the blockages in the artery

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

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

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

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

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

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

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

We will pay you $300 if you complete the study. If you do not complete the study, we will pay you $50 for completing the biopsy and $100 for completing the PET scan. We will pay for the cost of your parking or public transportation up to $10. You will receive a check in the mail within 2 months of your completion in the study.

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

Our research study funds will pay for all research procedures done as part of this study. Costs for any ongoing or routine medical care you receive separate from this study would be billed to you or your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer for routine medical care.

What happens if I am injured as a result of taking part in this research study?

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

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

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

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

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

Reena Pande, MD is the person in charge of this research study. You can call her at 617-732-6320 during business hours. You can also page her at any time by calling the page operator at 617-732-6660 and asking for beeper # 37923.

If you have questions about the scheduling of appointments or study visits, call our research assistants at (617) 732-6320.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 617-424-4100.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

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

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

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards

- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside Partners, we cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

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

Your Privacy Rights

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

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

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

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

Informed Consent and Authorization

Statement of Study Doctor or Person Obtaining Consent

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

_____ _____

Study Doctor or Person Obtaining Consent Date/Time

Statement of Person Giving Informed Consent and Authorization

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

Signature of Subject:

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

Subject _____ Date/Time _____

Consent Form Version: June 2011