Title: The Impact of Free Fatty Acid Reduction on Vascular Function in the Metabolic Syndrome

NCT00759291

Document Date: February 28, 2008

STUDY PROCEDURES AND PROTOCOL

This study uses a randomized, placebo-controlled crossover design.

After providing informed consent, both groups will undergo an initial screening visit in the Vascular Medicine Research Center. This visit will include a comprehensive health history and physical exam and anthropomorphic data collection (height, weight, body mass index (BMI) and waist-hip ratio). Screening blood tests will be drawn to assess fasting glucose, blood count, lipid profile, glycosylated hemoglobin, and assessment of renal and hepatic function. Baseline serum insulin and nonesterified free fatty acid levels will also be drawn at this visit. An ECG will be performed.

We hypothesize that acipimox, by decreasing plasma FFA concentrations, will augment endothelium-dependent vasodilation in conduit vessels and insulin-mediated vasodilation in forearm resistance arterioles *in vivo*, whole-body insulin sensitivity, and AKT and eNOS phosphorylation in skin biopsy specimens *ex vivo,* when compared with placebo.

Subjects will be studied at 2 separate visits, 4 weeks apart, in a randomized, double-blind crossover design. Subjects will receive either acipimox 250 mg tablets orally every 6 hours, or matching placebo, for 7 days prior to and at 7 am on the morning of the study visit. Each visit will include vascular function testing and a forearm skin biopsy. Forearm blood flow will be measured in the basal state, and with insulin infusion.

*Evaluation of vascular function in conduit vessel*s:

Vascular function of the brachial artery will be measured in all subjects as reported previously by the applicants and recommended by a recent task force (56-58) (also see Preliminary Results Section). To assess endothelium-dependent vasodilation, measurements of brachial artery diameter will be made under basal conditions and during reactive hyperemia following five minutes of an ischemic stimulus. Forearm ischemia will be induced by inflating a blood pressure cuff on the upper part of the arm to suprasystolic pressures for 5 minutes. This results in vasodilation of the downstream resistance vessels. Following release of the cuff, there is a 6 to 10-fold increase in flow through the brachial artery, i.e., reactive hyperemia. Flow is a physiologic stimulus that releases nitric oxide from the endothelium. We have found that the maximal increase in brachial artery diameter occurs at one minute of reactive hyperemia and that this dilation is mediated by nitric oxide (56, 57). Endothelium-independent vasodilation will be assessed by measuring brachial artery diameter under basal conditions and 3 minutes following the administration of sublingual nitroglycerin (0.4 mg) (58). Maximal brachial artery dilation occurs 3 to 4 minutes after the administration of sublingual nitroglycerin.

The diameter of the brachial artery will be measured using high resolution B-mode ultrasonography. An ultrasound scanner (Toshiba model Powervision 8000) equipped with a high resolution linear array transducer (7.5 mHz) is used to image the artery and thus enable measurement of its diameter and cross-sectional area. A longitudinal image (parallel to the artery) is acquired just proximal to the antecubital fossa. The transducer is then positioned at 90 degrees to the vessel to acquire an image through the center of the vessel so that the near and far wall interfaces will be clearly discernible. A simultaneous electrocardiographic signal is recorded. The video output and electrocardiographic

signal of the ultrasound machine is connected to a computer equipped with a Data Translation frame grabber videocard. The R wave on the electrocardiogram is used as a trigger to acquire (digitize) frames. Digitized images at baseline and after intervention (e.g., reactive hyperemia, nitroglycerin) are stored on the hard drive and backed up on removable media. Acquisition and analysis of the stored images is performed using software designed for this purpose by Medical Imaging Applications. The vessel wall lumen interface is determined by derivative based edge detection following identification of the region of the anterior and posterior walls by the investigator. The maximum diameter of the vessel is then determined (59). We have found that this technique yields an interobserver variability of 0.05±0.16% and intraobserver variability of 0.01±0.15%.

Evaluation of vascular function in forearm resistance vessels:

Each subject will be studied in the post-absorptive state, in a quiet, temperature-controlled (23°C) room. Alcohol and caffeine will be withheld for 12 hours prior to the study. In order to evaluate insulin-mediated vasodilator function in forearm resistance vessels, resistance arteriole flow will be determined before and during euglycemic, hyperinsulinemic clamp. Measurement of insulin-mediated vasodilation will be made in each study condition (placebo & drug) before and during hyperinsulinemic clamp. Forearm blood flow will be determined by venous-occlusion strain-gauge plethysmography, as described previously by this laboratory (60, 61). Forearm blood flow (FBF) will be derived from the rate of change in forearm circumference during venous occlusion and will be expressed at ml/100 ml tissue/minute. Each determination of forearm blood flow will comprise at least five separate measurements. FBF measurements will be recorded on a Hokanson AI6 physiologic recorder.

Hyperinsulinemic Clamp

A whole-body hyperinsulinemic- euglycemic clamp will be created via an intravenous infusion of insulin. A primed constant insulin infusion of 80mU/m^2/min is started and continued for 120 minutes. This dose has been demonstrated to attain typical postprandial insulin concentrations, facilitating evaluation of both initial-phase and steady-state insulin-mediated vasodilation (65). Contralateral cubital vein glucose will be measured every 5 minutes to ensure a constant glucose concentration of 5.1 mmol (90 mg/dL). Adjusted dextrose 20% solution will be infused intravenously to maintain this concentration. Systemic glucose and insulin concentrations will be determined from the control arm cubital vein. Whole body insulin sensitivity will be quantified by determining M, (metabolized glucose) during the final 5 steady-state measurements. M will be calculated as the glucose infusion rate, adjusted according the method described by DeFronzo and colleagues (66).

Tissue Acquisition

Abnormalities in endothelium-dependent vasodilation have been demonstrated in humans in peripheral and coronary conduit arteries, peripheral and coronary resistance arterioles, and in skin microvessels of patients with diabetes (67-70). Therefore, we will biopsy easily accessible arm skin microvessels to determine the effects of each intervention on endothelial insulin signaling. The skin will be cleansed with betadyne and draped to create a sterile field. Lidocaine 2% will be used to anesthetize a 1.2 cm ring in the arm around the biopsy site. A 6 mm bioptome will be used to obtain a

skin sample. The skin biopsy is marked for orientation and immediately frozen in liquid nitrogen and stored at –80 C for subsequent protein extraction for Western blot.

Tissue Analysis
The analyses of biopsy specimens will be performed in the laboratory of Dr. Thomas Michel.

Western blotting: The analyses of the skin and muscle biopsy specimens will be performed under the direction of Dr. Thomas Michel (consultant). Skin biopsy specimens are immediately frozen in liquid nitrogen. Frozen tissues are homogenized using a Polytron homogenizer in lysis buffer (71). After 30 min of incubation on ice, samples are centrifuged for 20 min at 14,000 g at 4°C to yield a solubilized preparation. Protein concentration is measured by using a protein assay (Bio-Rad; Richmond, CA). Equal quantities of protein from each sample (10 μg) are resolved by SDS-PAGE on 9% gels and electroblotted onto nitrocellulose. After incubation overnight with 5% bovine albumin -Tris-buffered saline with 0.1% Tween 20 (TBST), membranes are incubated for 1 h with the specified primary antibody [(monoclonal anti-eNOS or anti-Akt antibodies at 1:10,000 dilution, Transduction Laboratories) or (polyclonal phospho-eNOS Ser1179 or phospho-Akt antibodies at 1:5,000 dilution; Cell Signaling)]. After several washes, the membranes are incubated for 1 h with a horseradish peroxidase-labeled goat anti-rabbit (for phospho-Akt or phospho-eNOS Ser1179) or anti-mouse (for total Akt or total eNOS) immunoglobulin secondary antibody (Pierce Chemical). After being washed 10–15 additional times, the membranes are incubated with a chemiluminescent reagent according to the manufacturer's protocols (SuperSignal West Femto; Pierce Chemical) and exposed to X-ray film.

Immunodetection: Serial 4 uM sections of skin biopsy sections are deparaffinized, hydrated, and serially incubated in citrate buffer, H_2O_2, blocking solution, primary antibody, and appropriate secondary antibody, with intervening washes. The ABC biotin/avidin method with Nova Red substrate is utilized for immunodetection (Vector Labs). Primary antibodies include: total Akt (Cell Signaling), phospho-specific Akt (Ser 473, Cell Signaling), total eNOS (Transduction Labs), and phospho-specific eNOS (Ser 1177, Cell Signaling). When available, blocking peptide is incubated with primary antibody in a separate section to ensure specificity of staining. If blocking peptide is not available, additional sections are incubated without primary antibody. To ensure localization of identified signal in vascular cells, additional sections will be processed for immunofluorescence and colocalization with primary antibodies directed against the endothelium-specific von Willebrand factor (Santa Cruz Biotechnology). Images will be viewed using an AX70 Olympus Microscope with Phase 3 Imaging System (Image Pro 4.0 software) or the Zeiss LSM-410 Invert Laser Scan confocal microscope with imaging software (Matrox Image-Series Utilities).

Assays for markers of inflammation, insulin, free fatty acids

Plasma samples from insulin resistant and healthy subjects will be assayed for high sensitivity CRP (hsCRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) using the respective ELISA kits (Sigma; Endogen, Woburn, MA; BenderMedSystems; Vienna, Austria). Plasma insulin concentration will be measured using an Immunoenzymatic Sandwich Assay (Beckman Coulter, Inc.). Acrylodan-labeled Intestinal Fatty Acid Binding Protein (ADIFAB), a fluorescent molecule, will be used to assay the concentration of free fatty acids. The assay is accurate to about 1nM (72). All assays will be performed in duplicate by investigators blinded to the status of the subject (metabolic syndrome or control) and treatment.

BIOSTATISTICAL ANALYSIS

Statistical Analysis

Sample size calculation: All specified protocols employ a randomized, placebo-control cross-over design. Given the paired-design, the sample sizes have been calculated using estimates of the difference in flow-mediated, endothelium-dependent vasodilation after placebo and active treatment.

Table 2: Calculated Power For a Given Effect Size and Standard Deviation

Treatment Effect \ Standard Deviation	3.5%	4.0%	4.5%
2.5%	.97	.91	.84
3.0%	.99	.98	.94
3.5%	1.0	.99	.98

Based on previous studies, we expect to find an absolute difference in flow-mediated, endothelium-dependent vasodilation of the brachial artery between the test agent and placebo of 3% with an estimated standard deviation of 4% (68). With a 2-sided alpha error of 0.05 and a power of 90%, 30 subjects in each group of each protocol should find at least this difference in the primary endpoint (Table 2).

Statistical methods: All descriptive data will be expressed as means ± standard deviation. The primary endpoint of change in flow-mediated, endothelium-dependent vasodilation (i.e., the change in brachial artery vasodilation) between active therapy and placebo, will be assessed using repeated measures ANOVA (73). All analyses will employ the intention-to-treat principle. The treatment "order effect" will be explored by examining the interaction between treatment group (e.g. acipimox vs. placebo) and sequence of treatment (placebo first vs. active therapy first).

Baseline characteristics of treatment and control patients will be compared using Student's t-test or non-parametric tests, depending on the distribution of the data. To examine whether the active therapy has similar effects on flow-mediated vasodilation between healthy subjects and those with the metabolic syndrome, we will test the interaction between treatment group and the metabolic syndrome (yes/no). In secondary analyses, we will assess the effects of active therapy on eNOS phosphorylation, insulin sensitivity, and plasma inflammatory markers such as CRP, IL-6, and TNF-α. We will assess the relationship between the change in eNOS phosphorylation and changes in endothelium-dependent vasodilation using linear regression analyses, controlling for age, and gender. Likewise, we will examine the relationship between changes in insulin-mediated vasodilation and insulin-sensitivity associated with active treatment. Multiple analysis of variance (MANOVA) will be used to examine the main and interaction effects of categorical variables on multiple dependent variables, and multiple analysis of covariance (MANCOVA) for continuous independents. Thus, in the analyses, we can include vascular function and other outcomes simultaneously as dependent variables in the models. If the dependent variables are uncorrelated with each other, repeated measure ANOVA for each dependent variable will be employed.

Data interpretation: Vascular function will be determined after each intervention. Each intervention will be studied individually. If flow-mediated vasodilation is restored after an intervention (acipimox) compared with placebo, it will be interpreted that FFA impairs endothelial insulin signaling and decreases endothelium-dependent vasodilation. This interpretation will be confirmed by cutaneous tissue testing. If eNOS serine$_{1177}$ phosphorylation is increased after an intervention compared to placebo, it will be interpreted that improved activation of the PI3-kinase

pathway increases eNOS phosphorylation and resultant NO production. This interpretation will be supported if multivariate linear regression analysis defines a significant positive relationship between changes in eNOS phosphorylation and vascular and/or skeletal muscle metabolic function. If endothelium-dependent (flow-mediated) or insulin-mediated vasodilation remains similar despite an intervention (acipimox), it will be interpreted as a lack of effect of the agent on endothelial-insulin signaling and vascular function. If any intervention increases vasodilation to nitroglycerin, it will be interpreted that the intervention has improved vascular smooth muscle function. If the intervention improves vascular function in both subjects with the metabolic syndrome and healthy subjects, this will be interpreted as a generalized effect, independent of the metabolic syndrome.

Partners HealthCare System
Research Consent Form

Subject Identification

Template Version Date: June 2005

Protocol Title: The Impact of Free Fatty Acid Reduction on Vascular Function in the Metabolic Syndrome

Principal Investigator: Joshua A. Beckman, MD

Site Principal Investigator:

Description of Subject Population: Adults with Metabolic Syndrome & Healthy Adults

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form. If you have any questions about the research or about this form, please ask us. 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 copy of this form to keep.

Why is this research study being done?

We would like permission to enroll you as a participant in a research study. The purpose of the study is to test the effect reducing the release of free fatty acids from fat cells with acipimox. Free fatty acids are fats in the blood used to provide energy to cells that are not attached to other small particles. We want to see if acipimox improves the ability of cells to use blood sugar for energy and improves the way blood vessels expand. We will be comparing acipimox to an inactive medicine (placebo). You will receive both acipimox and placebo at different times during the study.

Acipimox is approved for use in humans in Europe, and is used as a cholesterol lowering medicine. Acipimox has not been approved by the U.S. Food and Drug Administration (FDA) and is not available in the United States. Therefore, this is considered an investigational research study.

Thirty (30) adults with Metabolic Syndrome and 30 healthy adult volunteers will be enrolled in this study at Brigham & Women's Hospital (BWH). You are being asked to participate because you are a non-smoker with Metabolic Syndrome, or you are a non-smoking healthy adult. Studying healthy volunteers helps us to understand whether the results we get are different in people with diabetes.

How long will I take part in this research study?

It will take you about 6-10 weeks to complete the study. During this time, you will be asked to make 5 study visits.

What will happen in this research study?

This study will test blood vessel function during treatment with acipimox and a placebo. The order of medications that you will receive is random and neither you nor the study doctors know what you are receiving until the end of the study. Should your medical condition require it, we can find out the name of the medication as needed.

Visit 1: Screening Visit (about 1 hour)

If you agree to participate in this study, you will be asked to sign this consent form, and a copy will be given to you. At the first study visit, a doctor or nurse will ask you questions about your health history. You will also have a complete physical examination, including an electrocardiogram (ECG). An ECG is a tracing of the electrical activity in your heart. Your height, weight, and waist/hip measurements will also be recorded. You will also have blood drawn (about 3 tablespoons) to test for:

- the number of red and white blood cells
- liver function
- kidney function
- cholesterol

The tests described above are done to be sure it is safe for you to take part in the study.

The levels of insulin (a hormone produced by your pancreas that regulates the level of sugar in your blood) and fatty acids will also be measured.

If you are a woman of childbearing age, you will also have a urine 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 gels that kill sperm

If you suspect that you have become pregnant while participating in the study, you must contact Dr. Beckman at once. You will have to withdraw from the study if you become pregnant, since we don't know if salsalate would harm an unborn child.

Visit 2 (about 20 minutes)

If the test results from the screening visit show that you can continue in the study, you will be asked to come to the Vascular Medicine Research Center. This is Visit 2, when we will give you the study medicine to take home. You will be asked to return one week later for Visit 3.

At Visit 2 you will either receive the active study medicine, acipimox, or a placebo. (You will receive both acipimox and placebo during this study.) The medicine you receive first will be determined like the flip of a coin. Neither you nor the study staff will know which medicine you receive first. You will be asked to take one tablet four times a day for one week, and report to the Vascular Laboratory on the morning of Visit 3. The dose of acipimox in this study will be 250 mg tablets every 6 hours. The acipimox and placebo tablets look exactly alike.

Visit 3: (5 hours)

You should have nothing to eat or drink, other than water, after midnight. You should take the study medicine as instructed. At this visit we will test the function of your blood vessels and take a small piece of skin (punch biopsy) from the inside of your forearm. The blood vessel testing and the punch biopsy are explained below:

During the blood vessel testing, you will be lying quietly on your back on a portable bed, and the lights in the room will be dimmed. First, a picture of the artery in your forearm, called

the brachial artery, will be taken using an ultrasound machine. We will put a cool gel on your arm and move a probe back and forth over the artery. The probe looks like a microphone. Pictures of the artery will be taken before and after inflating a blood pressure cuff on the upper part of your arm. The cuff will remain inflated for 5 minutes. Next, you will be given a small dose of nitroglycerin under your tongue. This causes the blood vessels in your arm to relax. Ultrasound pictures of the artery will be taken again to find out the effect of the nitroglycerin. This testing gives us information that future ultrasound tests can be compared to.

After the ultrasound test, the blood flow in your forearm will be measured using a method called plethysmography. Very thin, flexible tubes (catheters-also called an I.V. for "intravenous") will also be inserted into a vein in each forearm. One of these IV's will be inserted after warming one of your hands in a warming box. A warming box is a clear plastic box that you rest your hand in. The temperature inside this box is 150 degrees F. This IV will be used to take tiny blood samples (several drops each) for measurement of blood sugar every 5-7 minutes during the test. A constant amount of insulin will be given - through the catheter in your other arm for up to two hours. Also, glucose (sugar solution) will be infused (given over time slowly) through the same catheter. The amount of glucose infused will be adjusted to keep blood sugar levels within the normal range.

During the testing of your blood vessels, you will be quietly lying on your back on a stretcher and the lights in the room will be dimmed. The blood flow will be measured 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 forearms. Two blood pressure cuffs will be used during this procedure, one on the wrist and one on the upper part of the arm. The cuffs will be inflated and deflated at different times during the study. You will not feel pressure from the increase in blood flow.

At this visit you will also have a punch biopsy. We will use a special instrument to remove (punch) 3/16th inch (5 mm) circular piece of skin from the inner side of one forearm. You may choose which arm the sample is taken from. The sample will be about the size of a pencil eraser. The area will be washed with betadine, a brown soap that kills germs on the skin. Xylocaine (numbing medicine) is injected through a small needle into the skin surrounding the biopsy site to decrease pain. The wound will be closed with a bandage that you can take off after 3-4 days.

Once all of the tests are finished, you can have something to eat.

Visit 4: (about 20 minutes)

Four weeks after Visit 3, you will be asked to come to the Vascular Medicine Research Center for Visit 4. At that time, you will be given study medicine again. You will be asked to return one week later for Visit 5. You will be asked to take one tablet of the medicine with food or milk at 7:00 p.m. that evening, one tablet with water at 1:00 a.m. on the morning of Visit 5 and one tablet with water at 7:00 a.m. on the morning of Visit 5.

Visit 5: (about 6 hours)

You should have nothing to eat or drink, other than water, after midnight. You should take the study medication as instructed before this visit. All of the procedures explained under Visit 3 above will be repeated.

Up to 9 tablespoons (a little more than 4 ounces) of blood will be drawn during the entire study.

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

Acipimox, the active drug in this study, has been used by thousands of people and is generally well tolerated. In people who took acipimox (250 mg 3 times a day) for 1 month or longer, the most common side effects were (the most common are listed first):

- flushing, itching, and/or a feeling of heat in the skin. (more common in women than men)
- upset stomach
- headache
- vomiting (throwing up)
- low blood pressure
- heartburn
- loose stools (bowel movements)
- skin blisters

Rarely, (slightly more than 1 in 1000 people) allergic-like reactions have occurred after one dose. You should seek medical attention and contact the study staff immediately if you develop allergic reactions after taking the study medicine, such as:

- hives

- swelling of the eyelids, lips, tongue or face
- difficulty breathing

During the ultrasound test, a blood pressure cuff on your upper arm will be inflated to a high pressure for 5 minutes. This may cause temporary discomfort or aching. There are no known risks. The ultrasound test itself is non-invasive, that is, no needles are used and testing is done on the surface of the skin only.

Nitroglycerin is taken under the tongue during the vascular function ultrasound tests. Nitroglycerin may cause a temporary headache. Less than 1 in 100 people may develop low blood pressure or a fall in heart rate with low blood pressure. Blood pressure and heart rate are checked regularly during the study, and a member of the study staff is with you at all times. If the top number of your blood pressure at rest is lower than 100 mm Hg, you will not be given nitroglycerin.

As with all blood drawing or tube insertion, there is usually some pain at the site of the needle stick. Bruising (turning black and blue) may also occur. Rarely, lightheadedness or fainting can occur. As with any arterial tube, clotting, inflammation (redness, swelling) or infection may occur.

Once you leave the hospital after the study, you should contact the study doctor right away if you have:

- bleeding from the needle site(s) that does not stop after putting pressure on the area for 10 minutes.
- redness or swelling in the area of the needle site(s) or develop a fever.

You may have an ache or discomfort after the biopsy procedure. Rarely, there may be some bleeding requiring 1-2 stitches, or an infection. These will be treated if they occur. You may develop a small scar at the site of the biopsy.

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

You will not receive any direct health benefit from taking part in this study. We hope that the knowledge we gain from this study will help us better understand how blood vessels work in people with atherosclerosis.

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.

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.

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?

You will be paid for your time spent in participating, and will receive $100 for each vascular function test visit (Visits 3 and 5). You will receive up to $200 for completing the study. Payments will be issued within a few weeks of completing the study. In addition, parking costs will be validated at the time of each study visit. Costs for public transportation will be reimbursed at the end of the study.

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

There will be no cost to you or to your health insurer to participate in this study. All costs associated with this study will be paid for by the research funds of the investigator. Cost for routine medical care, not associated with this study, will be charged to you or to your health insurer.

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.

Giving you care does not mean that Partners hospitals or researchers are at fault, or that there was any wrongdoing. There are no plans for Partners to pay you or give you other compensation for the injury. 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, who 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.

Joshua A. Beckman, MD is the person in charge of this research study. You can call him/her at 617-525-7052 Monday-Friday 9-5.

If you have questions about the scheduling of appointments or study visits, call the 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?

Federal law requires Partners (Partners HealthCare System and its hospitals, health care providers and researchers) to protect the privacy of health information that identifies you. This information is called Protected Health Information. In the rest of this section, we refer to this simply as "health information."

If you decide to take part in this research study, your health information may be used within Partners and may be shared with others outside of Partners, as explained below.

We have marked with a ☒ how we plan to use and share your health information. If a box is not checked ☐, it means that type of use or sharing is not planned for in this research study.

We will also give you the **Partners Notice for Use and Sharing of Protected Health Information.** The Notice gives more details about how we use and share your health information.

- **Health Information About You That Might be Used or Shared During This Research**

  ☒ Information from your hospital or office health records within Partners or elsewhere, that may be reasonably related to the conduct and oversight of the research study. If health information is needed from your doctors or hospitals outside Partners, you will be asked to give permission for these records to be sent to researchers within Partners.

  ☒ New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study

- **Why Health Information About You Might be Used or Shared with Others**

  The reasons we might use or share your health information are:

  - To do the research described above
  - To make sure we do the research according to certain standards - standards set by ethics and law, and by quality groups
  - For public health and safety - for example, if we learn new health information that could mean harm to you or others, we may need to report this to a public health or a public safety authority

- For treatment, payment, or health care operations

- **People and Groups That May Use or Share Your Health Information**

1. People or groups within Partners

☒ Researchers and the staff involved in this research study

☒ The Partners review board that oversees the research

☒ Staff within Partners who need the information to do their jobs (such as billing, or for overseeing quality of care or research)

2. People or groups outside Partners

☒ People or groups that we hire to do certain work for us, such as data storage companies, our insurers, or our lawyers

☒ Federal and state agencies (such as the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections) and other U.S. or foreign government bodies, if required by law or involved in overseeing the research

☒ Organizations that make sure hospital standards are met

☐ The sponsor(s) of the research study, and people or groups it hires to help perform this research study

☐ Other researchers and medical centers that are part of this research study

☐ A group that oversees the data (study information) and safety of this research study

☐ 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.

- **Time Period During Which Your Health Information Might be Used or Shared With Others**

- 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.

- **Your Privacy Rights**
  - You have the right **not** to sign this form permitting us to use and share your health information for research. If you don't sign this form, you can't take part in this research study. This is because we need to use the health information of everyone who takes 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.

    If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. This includes information used or shared to carry out the research study or to be sure the research is safe and of high quality.

    If you withdraw your permission, you cannot continue to take part in this research study.
  - 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.

    In this research study, you may only get such health information after the research is finished.

- **If Research Results Are Published or Used to Teach Others**

  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.

Consent to take part in this research study, and authorization to use or share your health information for research

Statement of Subject or Person Giving Consent

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other options for treatments or procedures, and other important things about the study.

- I have had the opportunity to ask questions.

If you understand the information we have given you, and would like to take part in this research study, and also agree to allow your health information to be used and shared as described above, then please sign below:

Signature of Subject:

Subject _____ Date/Time _____

OR

If you understand the information we have given you, and would like to give your permission for the person you are authorized to represent to take part in this research study, and also agree to allow his/her health information to be used and shared as described above, then please sign below:

Signature of Parent(s)/Guardian or Authorized Representative:

Parent(s)/Guardian of Minor _____ Date/Time _____

OR

Court-appointed Guardian or Health Care Proxy _____ Date/Time _____

OR

Family Member/Next-of-Kin Date/Time

Relationship to Subject:

Signature of a Witness (when required by the PHRC or by the Sponsor):

Witness (when required) Date/Time

Statement of Study Doctor or Person Obtaining Consent

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

Study Doctor or Person Obtaining Consent Date/Time

In certain situations, the Partners Human Research Committee (PHRC) will require that a subject advocate also be involved in the consent process. The subject advocate is a person who looks out for the interests of the study subject. This person is not directly involved in carrying out the research. By signing below, the subject advocate represents (or "says") that the subject has given meaningful consent to take part in the research study.

Statement of Subject Advocate Witnessing the Consent Process

- I represent that the subject, parent(s), or legally authorized individual signing above has given meaningful consent.

Subject Advocate (if required by the PHRC or sponsor for this study) Date/Time

Consent Form Version Date: February 2008