University of Pittsburgh
School of Medicine Vascular Medicine Institute

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Nitrites, Skeletal Muscle Mitochondrial Bioenergetics, and Physical Activity in Old Age: The NO-Frail Study

PRINCIPAL INVESTIGATOR: **Daniel E. Forman, MD**
Professor of Medicine
Medicine-Geriatric Cardiology
3471 Fifth Avenue, Suite 500
Pittsburgh, PA 15213
412-864-2507

CO-INVESTIGATORS:

Frank Sciurba, MD
Professor
Department of Medicine

Anne Newman, MD, MPH
Professor
Department of Medicine

Kara Hughan, MD
Assistant Professor
Department of Medicine

Theodore Huppert, PhD
Associate Professor
Department of Radiology

Nancy Glynn, PhD Assistant Professor Department of Epidemiology

Sruti Shiva, PhD
Associate Professor
Department of Pharmacology and Chemical Biology

Simon Watkins, PhD
Director
Center for Biologic Imaging

STUDY COORDINATORS:

Tara Stakich, RN
Medicine-Geriatrics
3471 Fifth Ave, Suite 500
Pittsburgh, PA 15213
412-864-2082 or
412-720-0246

Alyssa Mathews, PA-C
Medicine-Geriatrics
3471 Fifth Ave, Suite 500
Pittsburgh, PA 15213
412-864-2082 or
412-720-0246

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KEY INFORMATION

Nitrate is something that people can eat in many vegetables. It breaks down into nitrite once it is in the body. Nitrite has been shown to help skeletal muscle cells work better with more energy and better action. Therefore, we are studying the benefit of nitrite capsules to help older adults who are not very physically active. This study will test whether taking nitrite capsules can improve muscle health and possibly help older adults to become more active.

This is research. It is separate from your usual care, which will go on as normal whether or not you are in the study. As part of research, you are asked to complete tests of your muscle and exercise capacity before and after 3 months of daily nitrite capsules (one capsule, 3 times a day). To test your muscle, we take a tiny piece of muscle from your thigh with a biopsy through a needle (after your leg is numb) and we also use a special imaging test (like an x-ray) called magnetic resonance spectroscopy. To test your activity we do special types of bicycle and walking exercise tests. This research allows us to see if nitrite increases the energy in your skeletal muscle and if that also relates to changes in your activity.

While nitrite relates directly to foods you might eat, we are giving it as a medication that is not now used regularly as part of medical care, and therefore it is considered an experimental drug. The nitrite capsule is not FDA-approved for use in older patients that are sedentary. However, the FDA does permit it to be used in experimental research studies like this, under strict regulations. Therefore, this study is monitored carefully by the Federal Drug Administration (FDA) to be certain that nitrite is safe. This study is funded by the National Institute of Health.

Research is entirely a choice. You do not have to do it, and if you start, you can still drop out at any time. The doctors and other personnel doing the study will do everything possible to keep you safe and to have a great experience.

Introduction

Older age is associated with loss of physical fitness, which means it is harder for older adults to be physically active. As older adults become less active it their risks of developing diseases, becoming weak, and having a worse quality of life.

We invite you to take part in a research study that is exploring a way to possibly increase energy in your muscle cells and seeing if that helps you to be more physically fit and active. The study involves taking a medication called nitrite as a capsule which you take 3 times a day for about 14 weeks (12 weeks of intervention and about 2 additional weeks for testing). Nitrite capsules are not related to your usual medical care. Your usual medical care will go on as normal whether you join the study or not.

Being in a research study is a choice. No one is required to do research. Before agreeing to be in this research study, or at any time if you join, you may discuss your care with another doctor who is not involved in the study. Please take your time to make your decision about taking part.

Why is this research being done?
Older adults are the fastest growing population group in the United States, and that is a big challenge to doctors and other medical caregivers since health problems usually increase as adults grow older.

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Who is being asked to take part in this research study?
We will complete study with a total of approximately 60 people who are all aged 70 years of age and older and who all do less than 1 hour of exercise or activity per week, here at the University of Pittsburgh.

How long will I be in this research study?
Your participation will last for about 4 months.

What procedures will be performed for research purposes?
If you decide to take part in this research study, you will be assigned by chance, like a flip of a coin, to receive the study drug, which are nitrite in capsules that you take 3 times daily, or you will receive a placebo, which is a capsule that looks just like the nitrite, but which has no effect. You will take one or the other for about 14 weeks. Neither you nor the research team will get to choose which one you will take or know which one you are on, but a separate pharmacist will be able to tell you and the PI if that becomes necessary. For the rest of this consent form, when we say study drug, we mean either the nitrite or the placebo capsules.

While nitrite relates to foods you might eat, the use of nitrite as a capsule is not now a regular part of medical care, and therefore it is not officially approved by the Federal Drug Administration (FDA) and it considered an experimental drug. Therefore, this study is monitored carefully the FDA to be certain that nitrite is safe.

You will visit the study clinic on scheduled dates, get tests, and tell the study doctor or study staff about any changes in your health or the way you feel. All research study tests, or procedures listed below, are not part of your routine care. You will make about 9 visits to the study clinic over 4 months. You will have telephone calls from the study staff while you are taking the study drug, including one call approximately a week after finishing your study capsules. You may also receive reminder calls or emails for appointments and such.

SCREENING PROCEDURES:
Procedures to determine if you are eligible to take part in a research study are called “screening” procedures.

We will review your medical history to see if it is safe and medically sensible for you to be in this study. We will talk with your doctor or other medical caregivers to be sure they agree that you can participate. We will check if you have had a recent blood test to make sure you are not anemic (a low blood count). We will also review your medical history to make sure you have no metal in your body in order to know if it’s safe for you to have the magnetic resonance spectroscopy test.

EXPERIMENTAL PROCEDURES:
If you qualify to take part in this research study, you will undergo a number of tests and procedures that evaluate how the study drug affects your body and your health. The study visits will take place at research labs at UPMC Montefiore, UPMC Kaufmann, and UPMC Presbyterian. For your convenience, a study staff member will meet you in the lobby of UPMC Montefiore hospital and bring you to the testing location for each visit.

Medical History
We will review your medical history, including the medications you take. We will ask about the history of heart disease and related diseases in your close relatives.

Physical Exam
A study clinician will complete a brief examination to make sure you are medically stable.

Vital Signs
We will measure your height, weight, temperature, blood pressure, oxygen level, breathing rate, heart rate, and oxygen saturation. Beginning at visit 4 we will also test methemoglobin levels with a device on your finger that is just like an oxygen saturation. The methemoglobin is to make sure the nitrite pill remains safe.

Blood Draw
The amount of blood to be drawn over the course of this investigation is an approximate maximum of 285 ml over approximately 16 weeks. This is equivalent to about 1.2 cups.

3 Day Food Record
We will provide you forms with instructions to record your daily diet for 3 days. You will be asked to record your diet before starting the study drug and again when you are taking the study drug. You will be asked to maintain a diet that is consistent throughout the study. Major diet changes during the 16-week study is discouraged.

Tests to assess your physical function

a. Cardiopulmonary Exercise Stress Test (CPET): this exercise test requires you to pedal on a stationary bicycle while breathing into a facemask or mouthpiece-like device on your face. The facemask or mouthpiece is attached by a small tube to a machine, in which there are special sensors to measure the oxygen and carbon dioxide in your breath as you exercise. Before you begin your exercise, there will be a brief 5-minute warm-up period to obtain resting data. Electrode patches are also placed on your chest to record your heart rate and electrocardiogram. We will place a blood pressure cuff on your arm in order to measure blood pressure during exercise. During the test, it will get harder to pedal a little at a time, until it becomes so hard that you are not able to continue. That is why this is also sometimes called a *maximal stress test*. During the exercise, we will ask you to rate (with a number) how hard you are working and how short of breath you are. As soon as you reach the point where it becomes too hard to continue, or if you experience significant pain or difficulty breathing, the exercise test will stop.

An exercise physiologist will perform the test supervised by a clinician (a doctor or other study clinician). The test might also be stopped if the physiologist or clinician determines that further exercise is unsafe, in which case the results will also be shared with your primary care giver and/or your cardiologist. If this test indicates you are too unstable to be in the study. The doctor or clinician would explain to you and your doctor why they were concerned. You may have to withdraw from the study if the clinician or your doctor felt it was unsafe.

b. A 400-meter corridor walk will also be performed. You will walk on a standard course. We will measure the time it takes for you to walk, and also to rate (with a number) how hard it felt to walk. During the 400 meter walk, you will wear a facemask that is similar to the one worn during the CPET, but in this case it will be connected directly to a small box that you wear on straps on your chest (it's a box about 5 inches by 2 by 2) that has sensors to directly measure the amount of oxygen and carbon dioxide you are breathing in and out as you walk around the track.

   During the CPET, you will also be asked to wear a near infrared spectroscopy (NIRS) device on your leg.
   - NIRS is a box that measures the oxygen in your muscles using just light through the skin. NIRS allows the researchers to measure oxygen in your muscles as well as blood flow. You will not feel anything when we do this measure.

c. Magnetic Resonance Spectroscopy (MRS) is a specialized test that uses magnetic waves to measure how your cells make energy. You will be brought to a special unit in the hospital where this machine is located. You will have to remove loose metal items (like watches and cell phones) and metal jewelry. During the scan you will be asked to do a small amount of exercise (about 30 seconds) that is similar to a kicking motion. This movement will be repeated several times while you are in scanner.

d. On a different day, you will return to the same stationary bicycle that you used for the maximal CPET, but you will be asked to pedal that has a fixed resistance (moderately hard) until you get too tired to continue. This is called a submaximal stress test, and it is a test of your endurance, or your staying capacity.

e. You will be asked to do a steady-state walking test. You will walk on the treadmill for 5 minutes at a fixed slow speed, only 1.5 mph. You will be asked to wear a facemask or mouthpiece as you do this. You will be asked to rate how hard you are working using a number system.

   During the steady-state walking test, you will be asked to wear a NIRS on your leg and an ActiGraph on your wrist. The ActiGraph is worn like a watch. This device measures your body movement. You will not feel anything from the NIRS or ActiGraph devices.

f. The same day you will also do a "Short Physical Performance Battery" which is actually a series of 3 short tests that are quickly completed together: 1) sitting and standing out of a chair; 2) walking over a 4 meter course (to measure walking

speed); 3) standing with your feet in different positions to measure your balance.

g. You will also be asked to complete a Handgrip Test. You will be asked to sit in a chair and squeeze a device as hard as you can with one hand at a time; then you will rest and switch to the other hand. We will ask you to do this three times on each hand.

h. Home Activity Monitoring
ActiGraph: We will ask you to wear an ActiGraph activity monitor at home like you wore for the steady-state walking test. This device measures your body movement and sleep. You will wear it at home for 7 days and bring it back at the next visit. You will wear it during all hours of the day except when you bathe or shower. We will give you directions on how to wear it and a log to fill out for the week to keep track of your activities/sleep.

Questionnaires

We will schedule rest breaks during the study visits that are designed to be sure you have time to rest and avoid getting too tired. During these sitting periods you will be asked to fill out questionnaires that ask about your sleep, mood, pain, other illnesses, quality of life, exercise, and test your thinking ability.

Muscle Biopsy

A study clinician will do muscle biopsies of your thigh muscle in your leg both before and after the 14 weeks of study drug. The purpose of the biopsies is to test how your muscles make energy both before and after the study drug. To do the biopsy, we will first apply numbing medicine (called lidocaine) several inches up from your knee. Lidocaine is similar to medicine used by dentists to numb your mouth. We then make a small cut in the skin (about a quarter of an inch). A biopsy needle is then be passed through that opening in the skin into the muscle in order to obtain a small piece of muscle (the size of a grain of rice, or about 150 milligrams). If the first pass of the biopsy needle does not get an adequate muscle sample (or if only fat is removed), additional passes of the needle may be performed (up to 5 passes). However, you can choose to say no to additional passes of the muscle biopsy needle if you do not want them. That will not affect your being in the study. A person will then push down on the biopsy spot on your leg for several minutes to ensure there is no bleeding. An ice pack will also be placed on the biopsy spot to reduce bleeding. We will then cover the biopsy with Steri-strips™ (or we may use a stitch in some rare instances, such as in people who are allergic to Steri-strips™) and a bandage. A pressure wrap is added, which you will wear for 4 hours.

We will do two biopsies at the beginning of the study (one on each leg), and two more about 14 weeks later when the study is about to finish. Two biopsies are important at each end of the study as one shows the long term effects of the nitrite on the muscle and the other shows the immediate effects of the nitrite in your muscle.

You will be given instructions about how to care for the biopsy sites and provided with the telephone numbers of study personnel to call if you have any problems.

Fasting
You will be asked not to drink or eat anything other than plain water for 8 hours prior to your arrival for Visits 4, 5, and 9. Once the biopsies and blood draws are completed on those days, we will give you a breakfast. If you have diabetes, a study physician will advise you on whether you will need any changes to your diabetes medicine on the day of visits 4, 5 and 9.

Withholding Certain Medications
Prior to certain visits, you may be asked to hold your anti-diabetic and/or anti-coagulation medications to keep you safe; if this applies to you, the study team will inform you prior to the visit.

Diabetic Participants

If you have diabetes, a study physician will advise you on whether you will need any changes to your diabetes medicine on the day of visits 4, 5 and 9. Participants with diabetes will be asked to bring their own glucometer (the machine that tests blood sugar levels) to assess glucose as needed. If a participant does not provide their own glucometer, a study glucometer will be available.

Encouragement of Daily Activity
Throughout the study, we will encourage you to begin or extend a daily walking routine, gradually increasing time and length as tolerated. Throughout the study, you will be asked general questions about activity level, exertion level, and any barriers to activity. These questions may be asked while you are attending a visit or during the weekly telephone calls discussed below.

Weekly Telephone Calls
After starting the study drug, the study staff will contact you by phone on a day and time that is good for you each week until 1 week following your final visit. Each call will last 5-10 minutes. We will ask you about how you are doing taking your study drug every day, if you missed any doses, any symptoms you have noticed, and any changes in your medications or medical history, such as emergency room visits or hospitalizations since your last study visit. We will ask you to use your drug diary card to report what you wrote down for the week to help you remember. During these calls, we will also ask about your walking activity.

In addition to these weekly calls, we would like you to contact the study staff or doctor anytime your health care team suggests a change in your medications or if you have any symptoms that cause you concern. There will be someone available from the study 24 hours/7 days a week for this purpose and we will give you numbers to always be able to reach study personnel who can help.

STUDY TIMETABLE

	Consent Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
					Study Drug Starts at Visit 4 and Continues through Visit 9					
Approximate Time between Study Visits		Same day As Consent Visit + 30 days	Same day as Visit 1 to 1 week later	Same day as Visit 2 to 1 week later	1 week	6 weeks	6 weeks	The Next day after Visit 6 to 1 week later. Than Visit 6	Same day as Visit 7 to 1 week later	Same day to 1 week later
Approximate Duration of each visit	1-2 hours	3-5 hours	3-4 hours	1-2 hours	3-4 hours	1-2 hours	3-4 hours	3-4 hours	1-2 hours	3-4 hours
Fasting Visit					X	X				X
Blood Draw		X			X	X				X
Consent	X									
Medical History	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X*	X	X	X	X	X*	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
					With extra vital signs for study drug safety monitoring					
Functional Assessments		Max exercise test 400Meter Walk	Sub-max exercise test Steady State Walk Short Physical Performance Battery Handgrip				Max exercise test 400Meter Walk	Sub-max exercise test Steady State Walk Short Physical Performance Battery Handgrip		
Activity monitor	X						X			
Questionnaires	X	X					X			
3 Day Food Record			X					X		
MRS				X					X	
Muscle Biopsies					X					X

__*If needed

What are the possible risks, side effects, and discomforts of this research study?
As with any research study, there may be adverse events or side effects that are currently unknown, and it is possible that certain of these unknown risks could be permanent, serious or life-threatening. You will be promptly notified if any new information develops during the conduct of this research study which may cause you to change your mind about continuing to participate.

Risks of nitrite medication:
The risks associated with the study drug, nitrite, are rare (happen in <1% of individuals and include nausea, belly pain, dry mouth, vomiting, flushing, increased heart rate or breathing rate, or low blood pressure. Nitrite can affect your blood hemoglobin. You can develop an abnormal amount of methemoglobin in the blood, which causes oxygen not to be released into your blood, and from this you may experience headache, dizziness, shortness of breath, a bluish color of the skin, seizure, or coma. Methemoglobin is a stable oxidized form of hemoglobin (in red blood cells) that can interfere with the normal function of blood to carry oxygen effectively. This is also rare (<1%). Your vital signs, including methemoglobin levels, are monitored closely throughout the study. There is no risk of taking the placebo, or fake capsule.

Risks of muscle biopsy:
The muscle biopsy is performed with a needle which may cause discomfort, bruising, scarring and soreness for several days (common), but to further reduce these risks, an elastic wrap and ice bag are applied to the leg post-biopsy to decrease the risk of these things. There is also the possibility of a vasovagal reaction (reaction of the nervous system due to anxiety) that may cause fainting. Bleeding and infection are rare. Additional unusual risks include allergic reactions to the elastic bandage wrap, leg numbness that would indicate the elastic bandage had been applied too tightly; and skin redness, irritation, and chafing from the Steri-strips™. An infrequent risk is that there is an allergic reaction to the Lidocaine used to numb the muscle and is given just before the biopsy. Lidocaine has risks which are described next. If you know you are allergic to Steri-strips™, you will require a stitch.

The numbing medicine Lidocaine (also call xylocaine) is used by the physician performing the muscle biopsy. This is a standard numbing medicine used regularly by dentists and physicians. Lidocaine, is injected in and below the skin for the skeletal muscle biopsy. If you have had prior difficulty with this common numbing medicine, the procedure will not be performed, and you will be excluded from the study. A very rare side-effect of Lidocaine is an allergic anaphylactic reaction that could result in symptoms such as shortness of breath, swelling of the throat, inflammation of the skin, skin rash, low blood pressure and death (rare). In order to prevent such an occurrence, you will be questioned before you enroll about prior experiences with Lidocaine.

Risks of exercise assessments: (stress test on treadmill and/or bicycle, 400-meter corridor walk, steady state walk on treadmill, handgrip strength and short physical performance battery):
These tests require people to apply effort. Although careful medical supervision will help to lessen the difficulty of doing these tests, some people might still find them unpleasant. The exercise test may cause muscle soreness or fatigue (common). Some people get anxious

while breathing through a facemask (common) or experience a fall (rare). Another risk is redness, skin chafing or irritation from the EKG electrodes used during exercise testing. If an abnormal rise in blood pressure or changes in the electrical pattern of your heart is noted, or if you develop chest pain, the exercise will be stopped immediately. Rarely, exercise may cause muscle sprains, muscle strains, or broken bones. Other risks include abnormal blood pressure (infrequent), fainting, dizziness (infrequent), disorders of heart rhythm (infrequent), and in very rare instances, heart attack, stroke, or even death (rare). In adults without a known history of heart disease, the risk of heart attack or death from maximal or sub-maximal exercise bouts is rare. A survey of more than 2,000 clinical exercise testing laboratories, in which more than 600,000 tests were performed, showed a death rate of approximately 0.5 per 10,000. Testing in this study may even be lower as we screen you carefully to best ensure safety before the test is started. A doctor or other study clinician will always be nearby.

The home walking program has similar risks as the hospital-based function and exercise tests, but since you will be tested first at the hospital with a maximal stress test under the direct watch of a study clinician where safety can be demonstrated, any walking that follows is also likely to be safe.

Risks of blood draw:
A risk of drawing blood is anemia, which is a lower blood count level because too much blood was taken. A common symptom of anemia is fatigue (feeling tired or weak). Therefore, the amount of blood to be taken over the course of this investigation will be carefully limited, and will be a maximum of about 1 cup, over about 16 weeks. Nonetheless, we encourage you not to donate blood just before enrolling or during the time you are in the study, and we will track any other blood tests that occur while you are participating.

To reduce any risks with actually drawing the blood, a licensed technician or registered nurse will complete the blood sampling. Common risks of blood sampling by venipuncture or intravenous line placement include temporary pain, bruising which may last for several days, redness, and swelling. Infrequent risks include feeling lightheaded or faint at the time the blood is drawn. This is usually due to nervousness (not due to the amount of blood), and it is not usually serious. Rare risks include infection and bleeding.

Risks of fasting

Fasting for blood work or for testing is common and carries little risk. Participants may feel tired, hungry or irritable until they are served the standardized breakfast upon arrival. Participants who are diabetic have relatively greater risks of hypoglycemia, but the study physicians/ medical providers/clinicians will guide these individuals, and possibly adjust their medications as needed to minimize these risks.

Risks of withholding anti-coagulant before muscle biopsy:
If you regularly take certain medications of these kind, (examples include aspirin, ibuprofen, Warfarin, Plavix) we will ask you to hold them for a specific number of days depending on the medication prior to visits when we do the muscle biopsies. This is to prevent excessive bleeding with the biopsy. The risk of holding these medications varies with your medical history. If the medications we asked you to hold are for arthritis pain, there is no health risk to

stopping these, but you may have more arthritis pain or swelling during the time they are held. You may use acetaminophen (also called Tylenol) and hot or cold packs on any joints for pain at this time. Any time a person with heart disease undergoes a change in anti-clotting medication there is a very small increase in risk of having a cardiac event. To decrease the risk, we will work with your primary care provider or cardiologist to be sure it is safe for you to hold the medication; we will have you hold the medications for the least number of days possible, and we will consult with your provider if any other intervention is needed. We will give you reminders to resume taking your usual regimen.

Risks of withholding anti-diabetic medications before exercise testing and muscle biopsy:
Certain kinds of medications for diabetes can cause a low blood sugar if you do not eat within a certain amount of time. If you have diabetes, we will review your medications and advise you if you are asked to fast prior to the study visits that include blood draws and muscle biopsies. The risk is that your blood sugar might increase over its usual level, but this will only be brief, and we will have you take your medicine as soon as possible.

Risks of Magnetic Resonance Spectroscopy:
The Magnetic Resonance Spectroscopy machine does not use radiation (such as with x-rays) and there are no direct risks of the magnetic waves it does use. The main safety concerns with MRI relates to keeping metal objects away from this magnetic device (as it might move metal objects). Therefore, you will be asked about metal objects or implants that could cause problems with the magnetic resonance spectroscopy. Many objects (like a cardiac stent) are very safe in the MRI, and we will determine if this test is safe for you.

It is also common for some people to feel claustrophobic (closed in) when in the tube-like magnetic resonance spectroscopy. Some also feel anxious or even discomfort due to the loud noises it makes. You are therefore required to wear earplugs to reduce this noise. Since you are asked to do a kicking exercise while undergoing this test (to analyze muscle energy use during and after the kicking), the kicking may feel tiring to your thigh muscles. Some people even feel “burning” of their muscles when kicking hard. However, this is a normal reaction to exercise of the muscle and does not indicate that the muscle has been hurt. This feeling will disappear very soon after the test is over. You may feel some mild soreness in your muscle for a day or two after the exercise if you are not used to using these muscles, and that usually disappears on its own.

Risk of questionnaires:
The questionnaires require people to answer questions about their daily activities and quality of life, and in some cases, be a source of emotional distress or annoying. You have the option to skip any question you do not feel comfortable answering.

Risks of collecting protected health information:
Although we are taking many steps to protect your information, there is always a chance that your information or identity could be disclosed. We will continue to review and improve the ways we keep your information private. To protect the research data, a code will be assigned and the information linking the code to your name and personal information will be stored in a separate document on a secure network with a password that only the PI and the study

coordinator know. Your research chart with your personal information is stored in a locked file in a locked office.

Risks of activity monitoring:
The activity monitor requires people to wear a watch like device with a Velcro wrist strap. This may be bothersome or annoying to those that do not typically wear a watch.

Risks of future genetic testing of stored samples:
The risks associated with gene studies include the potential for a breach of confidentiality, which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization.

In addition, there is a Federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Your research data/samples may be shared with investigators conducting other research; this information will be shared without identifiable information. These research data/samples may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

The data, samples, and genetic data generated from samples may be shared with other researchers and with federal repositories, in a de-identified manner (without identifiers).

Overall subject burden
Volunteering for this study includes you coming to UPMC in Oakland for approximately 9 visits spaced over about 4 months. It is possible that you will feel tired from doing the study tests or visits. All visits will be scheduled ahead of time on days and times that work best for you. We will be sure to give you plenty of rest periods in between tests at the visits. We want you to tell the study staff if you are feeling tired or have any concerns. If at any time, you need to stop a test or the visit, you should always tell the study staff. Here is another summary of the study visits so that you know how frequent they are and how long they last. We want to be sure you understand this so you can make a good decision about whether you should participate.

What are possible benefits from taking part in this study?
There is no guarantee that you will benefit from participating in this research study. Possible benefits to you from participating in this research study are obtaining a complete physical examination and laboratory blood tests, a positive feeling from contributing to research, as well as, you may feel more energy if you are assigned the sodium nitrite.

What other choices do I have if I do not take part in this research study?
You may continue to get regular care from your doctor.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study. If you think that you or your health insurance has been charged, please contact a member of the research team and the UPMC billing office that sent the bill.

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

Visit	Consent Visit & Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Amount	$50	$50	$50	$100	$50	$50	$50	$50	$100
VinCent card deposit				X	X				X

You will be compensated up to a total of $550 on a VinCent debit card. If for any reason, you have to be withdrawn from the study, you will be paid for the visits you completed. If you have to come in for an Interim Visit (including the separate Consent Visit if necessary), you may be compensated up to $40 at the discretion of the study personnel. You will also be provided a ticket for outpatient parking costs if needed.

All compensation is taxable income to the participant regardless of the amount. If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 28% of the payment be sent by the institution to the IRS for 'backup withholding'; thus you would only receive 72% of the expected payment.

Who will pay if I am injured as a result of taking part in this study?
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not give up any of your legal rights by signing this form.

How will my privacy be protected, and my information be kept confidential?
We will do our best to protect your privacy and the confidentiality of your research information by:

- Using a number code to label your samples and other information.
- Keeping your number code separate from your name, address, and other personal information. We will look at your information using the number code and not your personal information.
- Keeping your test results and other information in a secure computer database.
- Storing samples and other information in a secure place. We will limit and keep track of access to your samples to make sure they are safe.

In addition to the investigators listed and their research staff, the following individuals may have access to your information related to your participation in this research study:

- Authorized representatives of the study sponsor, Food and Drug Administration (FDA), and University of Pittsburgh Office of Research Protections may review your identifiable research information for purposes of monitoring the conduct of this research study.
- If investigators learn that you, or someone with whom you are involved is in serious danger or potential harm, they will need to inform the appropriate agencies, as required by Pennsylvania law.
- Information collected from this study may be shared with other investigators; however, this information will be shared in a de-identified manner (i.e., without identifiers).
- Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena. There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations. Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your

involvement in this research. It also does not prevent you from having access to your own information.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
Your de-identified research data will be maintained indefinitely, however, according to the University of Pittsburgh research record retention policy, all hard copy records must be maintained for a period of at least 7 years following final reporting or publication of a project. The results of this study could be published in an article but would not include any information that would let others know who you are.

Conflict of Interest
One or more of the investigators conducting this research has a financial interest related to the study as an inventor of intellectual property being evaluated/developed in this study, or through their ownership stake in a company with rights to that intellectual property or compensation from such a company. This means that the results of this study could lead to personal profit for the individual investigator(s) or the University of Pittsburgh. Any questions you might have about this will be answered fully by the Principal Investigator, who has no financial conflict of interest with this research, or by the Human Subject Protection Advocate of the University of Pittsburgh (866) 212-2668

Is my participation in this research study voluntary and may I withdraw, at a future date?
Your participation in this research study is completely voluntary and you may withdraw your consent at any time.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh, current or future medical care at a UPMC hospital or affiliated health care provider, or current or future relationship with a health care insurance provider.
If you choose to withdraw from this study, any identifiable research or medical information recorded from your participation in this research study prior to the date that you formally withdrew your participation may continue to be used and disclosed by the investigators for the purposes described above. Your biological samples stored for future research analyses will be kept unless you request for the sample to be destroyed.

Your doctor may be involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?
You may be removed from the study by the investigators in the event that the investigators feel

that the study may adversely influence your health; if you don't comply with study requirements; if a pregnancy test is positive; if you develop a severe, acute illness during the study period; or other situation as deemed by Dr. Forman's discretion. If you decide after the first biopsy, that you will not have the second, you will not continue any further in the study. Should any of these occur, your participation in the study will be terminated, and you will continue to receive appropriate care as necessary.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

HIPAA Authorization for Disclosure of Protected Health Information (PHI)
As part of this research study, we are requesting your authorization or permission to review your medical records to determine whether you qualify, based on study specific eligibility criteria, for study participation. This authorization is valid for an indefinite period of time. We will obtain the following information: your diagnosis, age, past medical history, diagnostic procedures, results of any clinical tests or blood tests, or relevant physical examination notes, that were already done as part of your standard medical care.

No information collected in this study will be placed in your medical record. If any information that is collected indicates there is a medical concern, the study doctor or a member of the study team (under the study doctor's direction) will notify your primary care provider.

This identifiable medical record information will be made available to members of the research team for an indefinite period of time.

Your medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the study sponsor, Food and Drug Administration, and the University of Pittsburgh Office of Research Protections, for the purpose of monitoring the study. Authorized representatives of UPMC or affiliated health care providers may also have access to this information to provide services and addressing billing and operational issues.

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

You can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up that point will continue to be used by the research team.

VOLUNTARY CONSENT
The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form, I agree to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date/Time

CERTIFICATION OF INFORMED CONSENT:
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date/Time