Permission to Take Part in a Human Research Study

Title of Research Study: Unacylated Ghrelin to Improve FuncTioning in PAD: The GIFT Trial: Phase II

Investigators: Mary McGrae McDermott, MD (Northwestern University), Tamar Polonsky, MD (University of Chicago)

Supported By: This research is supported by the National Institute on Aging.

Financial Interest Disclosure: If your doctor is also the person responsible for this research study, please note that she is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you have or may have peripheral artery disease (PAD). PAD is a condition in which blockages in the leg arteries prevent blood from getting down to the legs and feet during exercise.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

Few medical treatments are available to improve walking ability in patients with PAD. The research study will determine the effects of a medication called unacylated ghrelin on walking ability in people with blockages in their leg arteries. Unacylated ghrelin is an investigational drug that is not yet approved by the United States Food and Drug Administration (FDA) for treatment of PAD. Preliminary evidence suggests that unacylated ghrelin may improve blood flow to the extremities and promote improved skeletal muscle growth and energy use.

How long will the research last and what will I need to do?

We expect that you will be in this research study for approximately five months (baseline testing plus four months of study participation).

You will be asked to complete baseline testing, subcutaneously administer (inject under the skin) study drug daily for four months, and complete final follow-up testing.

More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

The study medication may cause side effects. You may experience mild facial swelling or dizziness from the unacylated ghrelin. It is possible that unacylated ghrelin may be associated with a heart arrhythmia, which consists of an irregular and potentially rapid heartbeat. An irregular and/or rapid heartbeat may be associated with low blood pressure or, infrequently, with stroke.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits to participants who receive unacylated ghrelin include improved walking ability. Taking part in this study may help scientists better understand ways to improve walking ability in people with peripheral artery disease.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled.

Instead of being in this research study, your choices may include discussing alternative treatment with your physician such as medication or supervised treadmill exercise or lower extremity revascularization (surgery or angioplasty), if you are a candidate for lower extremity revascularization. Medicare and some other medical insurance companies may cover 12 weeks of supervised treadmill exercise. If you are interested in any of these alternative treatment options you may discuss them with your physician. If you are interested in any of these alternative treatment options you may discuss them with your physician.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team. Dr. Mary McDermott is the person in charge of this research study (office: 312-503-6419; pager: 312-695-8733). You may also reach the study manager, Kathryn Domanchuk, at 312-503-6438. For problems arising on evenings or weekends, please call Dr. McDermott at 224-365-9974.

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?
We expect to enroll 30 people in this research study.

What happens if I say "Yes, I want to be in this research"?
If you are eligible for this study, you will complete baseline study testing, self-administer study injections daily for four months, and return for follow-up testing. More information is described below.

Baseline visits. For individuals who consent to the study at Northwestern, baseline visits will be performed at the Feinberg, Galter, or Olson Pavilions (251 E. Huron, 201 E. Huron St. and 710 N. Fairbanks) at Northwestern Memorial Hospital. For individuals who consent at the University of Chicago, visits will be performed at 5815 S. Maryland Ave. Both Northwestern and University of Chicago participants will have the MRI and biopsy (if performed) at Northwestern. Each visit will last approximately one to three hours.

The below measures will be performed over approximately three to four study visits:

- The blood pressure in your arms and legs will be measured (blood flow test). Depending on the results of the blood pressure in your legs, you may be asked to return for an additional test with Northwestern Medicine's vascular department, where pressures in your arms and legs will be repeated and will include a measurement of the blood pressure in your big toes using a small blood pressure cuff around the toe and a probe on your skin
- Questionnaires about your medical history, activities, and ability to walk
- A six-minute walk test (where you will walk back and forth down a hallway for six minutes), a four-meter (approximately 13 feet) walking test at usual and fastest pace, balance tests, and a test where you will be asked to stand up from a seated position in a chair
- Medication review
- Treadmill stress test, in which the distance that you can walk on a treadmill (slowly moving belt) will be measured
- A measurement of your height and weight will be taken
- Blood testing (see "Blood samples" below for more information)
- MRI. This study uses magnetic resonance imaging (MRI) to look at the arteries in your legs. MRI is a type of scan that uses magnetic fields and radio waves to make a picture of the blood flow in your legs. During the MRI, a blood pressure cuff will be placed on your thigh and inflated for approximately five minutes. The MRI will focus specifically on one of your legs and will not image your entire body.
- Optional muscle biopsy (see "Optional Muscle Biopsy" below for more information)

Study Drug Instructions. You will be taught to inject the medicine under your skin yourself. A study coordinator will deliver 7 syringes to your home or you will be asked to pick up the syringes. A thermometer will be given to you to monitor freezer temperature. You will be asked to self-inject the study drug for 7 days and will be asked to return to the medical center with the used syringes (deposited in a sharps container which will be provided) and thermometer. You will be asked to record whether or not you administered the study injections on a paper form during this period. If you do not self-administer at least 5 syringes in 7 days, you will not be eligible to participate in the study.

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Optional Muscle Biopsy. You will also be asked to undergo a calf muscle biopsy. The calf muscle biopsy is optional and is not required in order to participate in the study. If you agree to the calf muscle biopsy, the skin will be numbed with an injection of a medication (Lidocaine) under your skin, a small incision will be made in the skin, and a small piece of muscle (approximately the size of two eraser heads on a pencil) will be removed from the calf. Pieces of fat may also be removed during the biopsy. If you are on aspirin or another blood thinner, you may be asked to discontinue these medications, with permission from your own physician, for one week prior to the biopsy.

Randomization. If you are eligible for the study after completing baseline testing, you will be randomized to one of two groups: unacylated ghrelin injections or placebo injections. Placebo injections are identical in appearance to unacylated ghrelin but do not contain active medication. You will be asked to self-inject the study injections daily for four months. You will be asked to record whether or not you administered the study injection on a paper form each day.

The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. Approximately 60% of participants will get placebo and approximately 40% will receive unacylated ghrelin. Neither you nor the study doctor will know which treatment you are getting.

Study Drug Delivery or Pick Up. A study coordinator will deliver one-month supplies of study drug to your home and will ensure the drug is placed in your home freezer immediately upon delivery. The study drug is provided Mark Drugs. A temperature monitor will be left in your freezer and you will be asked to periodically check the monitor to ensure your freezer is at the proper temperature for storing the study drug. You will be asked to return this monitor at the end of the study. If your freezer temperature is not adequate for drug storage, then study drug will be delivered every two weeks or you will be asked to pick up the drug every two weeks and the drug may be stored in your refrigerator.

Four-month follow-up. After four months of administering study drug daily, you will be asked to return for follow-up testing over approximately two or three separate visit dates. Measures and tests conducted at baseline will be repeated and your study medication logs and syringes will be collected. If you agreed to a calf muscle biopsy at baseline, you will be asked to return for a separate visit for a calf muscle biopsy at four-month follow-up.

Blood samples. A sample of your blood will be taken at the baseline and four-month follow-up visits. At four-month follow-up, two blood draws will be performed (one prior to a ghrelin injection and again approximately one hour later). You will be asked to fast for 8 hours prior to the blood draw at four-month follow-up. The total amount taken is approximately 50 ml (3.5 tablespoons) at baseline and approximately 56 ml (4 tablespoons) at follow-up.

Kidney and liver functioning will be measured at baseline. Blood tests at baseline may need to be repeated depending on results. Additional blood samples may be taken over the course of the study as necessary for safety monitoring.

Some of your blood will be sent to the University of Virginia for ghrelin testing. Remaining blood will be stored and used for future research. Your blood may be analyzed for genetic factors as well as blood factors which may be associated with outcomes related to unacylated ghrelin (study drug) and peripheral artery disease. Genes are inherited molecules stored in cells that specify the proteins that your body makes. Many different genes and blood factors are important determinants of heart disease and stroke. However, relatively few of the important genes have

been identified and new blood factors are regularly being discovered which may be determinants of future heart disease and stroke. Therefore, it is not possible to list the specific genes or include all blood factors that might be eventually tested. Rather, the genes and blood factors we will study will be guided by ongoing research studies. In addition, genetic material obtained during the blood draw may be used in part to identify previously undiscovered genes that may be important determinants of future risk of heart disease and stroke. Results of your genetic and blood factor tests will remain confidential and will be used for medical research purposes only. Your blood will be labeled with a study identification number and stored without a link to your name. No names or initials will be used in any publication of the study results. Blood will be stored at Northwestern University Feinberg School of Medicine in Chicago. You will not receive any blood test results. You will not receive any payment for new biomarkers or other tests that may be developed as part of this research. Genetic testing is optional and you will have the opportunity to indicate whether you agree or disagree to storage of your blood for genetic testing at the end of this consent document.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to attend study visits and administer the study medication outside of the study visits as described above.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time; it will not be held against you.

If you decide to leave the research, contact the investigator, Dr. McDermott, at the telephone numbers listed above.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether you are willing to return for follow-up testing even if choose to stop taking the study pills.

Detailed Risks: Is there any way being in this study could be bad for me?

This research may hurt you in the following ways:

Risks associated with study medication. You may experience mild facial swelling or dizziness from the unacylated ghrelin. It is possible that unacylated ghrelin may be associated with a heart arrhythmia, which consists of an irregular and potentially rapid heartbeat. An irregular and/or rapid heartbeat may be associated with low blood pressure or, infrequently, with stroke.

Risks of baseline and follow-up data collection: When we measure the blood flow to your legs using blood pressure cuffs around your arms and ankles, some discomfort or pain in the arms or legs may occur. Loss of balance and falling may occur during the walking and balance tests. Falling may be associated with injuries to muscle or bone. However, the research assistant working with you has been trained to prevent falling during these tests. We will screen you for any active heart problems with an exercise treadmill stress test prior to enrolling you. These tests on the heart may lead to the need for procedures to improve the blood flow to your heart or hospitalization if the result on the exercise stress test shows a particularly worrisome

result. Testing may also be associated with an irregular heartbeat or a heart attack. chest pain, muscle fatigue or soreness, shortness of breath that does not go away with rest

Risks of drawing blood: The potential risks of drawing blood include a bruise at the site of vein puncture, inflammation of the vein, and infection. You may experience lightheadedness or dizziness or fainting after your blood is drawn. Care will be taken to avoid these complications.

Risks associated with MRI: The MRI scanner makes loud banging noises while doing a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise. The study staff will be in communication with you through an intercom system to tell you of the progress of the study. Some people might feel scared or anxious in small places (claustrophobic). The inflated blood pressure cuff may be associated with leg discomfort. The discomfort goes away after the cuff is deflated. Most of the MRI pictures taken in this study will not be in a form readable by either you or your doctor. Therefore a copy of the MRI pictures or the results of your individual study will not be given either to you or your doctor.

In order to make sure the MRI procedure will be safe, you will be asked to fill out a screening form before being in this study. It is important that you tell the study staff if you have any history of:

- Metal fragments or pieces in your eyes or face.
- Implantation of any electronic devices such as (but not limited to) cardiac pacemakers, cardiac defibrillators, cochlea implants or nerve stimulators.
- Surgery on the blood vessels of your brain or the valves of the heart.
- Claustrophobia (fear of enclosed places).
- Body piercings or tattoos.

Risks associated with questionnaires: There will be short surveys conducted during the study. There is a possibility that answering these questions might cause emotional distress.

Risks associated with muscle/fat biopsy: If you agree to the optional muscle/fat biopsy component of this study, risks include local infection and bleeding including a hematoma (a temporary pooling of blood under the skin) at the site of the incision. You will have some pain at the site of the biopsy during the procedure and for the first 1-2 days after the biopsy. The incision will leave a small scar in the skin where the biopsy was taken. The risk of infection or significant bleeding related to the muscle biopsy is less than 1/500. A skin numbing medication, Lidocaine 1% without epinephrine, will be given through an injection under your skin. Side effects of Lidocaine may include pain at the injection site, an allergic reaction, potential emotional excitement, or temporarily lowered heart rate and blood pressure. If you have a history of allergy to Lidocaine, you will not be allowed to undergo a muscle biopsy. Fewer than 1 in 2,000 people will have a side effect from Lidocaine.There is a rare risk of allergic reaction to the tape used to bandage the incision. If you are asked to go off of your aspirin or other blood thinner medication prior to the muscle biopsy, you may experience a stroke or heart attack while you are off the blood thinner. The risk of this happening is low. Study investigators will talk with your doctor to make sure that he/she feels that it is safe for you to go off of your blood thinner.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the

possibility of this happening. See the section below titled: **"What happens to the information collected for the research?".**

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you. You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay. This research study will pay for all tests performed as part of this research study.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of Northwestern University or the study sponsor.

Blood and muscle specimens that are not analyzed immediately will be prepared for long-term storage and will be kept in a freezer belonging to Dr. McDermott's research program at Northwestern University. Specimens will be stored for up to 70 years, after which they will be destroyed.

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. Because researchers are not able to look at study results until all participants have completed the study, you may not receive test results until all participants have completed the study.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), and the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include perceived risks to your health or safety. We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

If you become ill or are injured as a result of this study medication or procedures, you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The university and researchers will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

If you agree to take part in this research study, we will pay you $50 when study drug is delivered to your home and remaining syringes are picked up at 1-month, 2-month, and 3-month visits (for a total of $150) and $50 after you complete four-month follow-up testing for your time and effort. (Note: If study drug is delivered every two weeks instead of every month, you will receive $25 each time remaining syringes are picked up for the same total of $150.) If you participate in the optional muscle biopsy component of the study, we will pay you $100 after each completed muscle biopsy for your time and effort. Payments will be made in cash.

You will be given assistance and/or reimbursement for expenses related to travel such as parking, bus/train fare, taxi or Uber fare, and mileage, if requested. You will need to provide a receipt for taxi or Uber fare reimbursement. You will be provided up to $90 per visit for travel reimbursement. If you require the use of our taxi or Uber service, we will estimate your fare on www.taxifarefinder.com or www.uber.com. A one-way fare estimate must be below $45 (i.e. round trip of $90) in order for the study to provide taxi or Uber service.

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs
- Billing information
- Genetic health information (if you agree to genetic testing)

During this study, you may be coming to a Northwestern Memorial Healthcare Corporation entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH).

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

The following entities may receive your health information:

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.

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- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- The National Institute on Aging, who is sponsoring the study, and that company's contractors and partners.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- Others: The following individuals or organizations may also access, receive, or use your personal health information: Mark Drugs.

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

Also, Federal law/42 CFR Part 2 prohibits unauthorized disclosure of these records.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will not expire.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to: Mary McDermott MD, Northwestern University Department of Medicine, 750 N. Lake Shore Drive, 10th floor, Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

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Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	The researcher may perform genetic testing on my blood.
_____	_____	The researcher may contact me to schedule a muscle/fat biopsy at baseline and follow-up. I may decide not to undergo a muscle/fat biopsy at a later date. If I need to discontinue a blood thinner, I agree to have my physician contacted for permission to discontinue the blood thinner for one week prior to the biopsy.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent