COVER PAGE

Protocol #: HSC20230594H

Study Title: Sex-specific determinants of early-phase recovery from skeletal muscle disuse

Approval Date: 12/09/2024

Concise Summary

Volunteers will undergo a 2-phase, randomized, clinical trial. It includes 7-days of single leg disuse and the use of an assistive device and an elastic leg band to limit weight bearing activities (Phase 1), immediately followed by 7-days of rehabilitation of both legs (Phase 2). In Phase 1, you will be asked to wear an elastic leg band that attach to your waist on your left leg and use an assistive device for a week. This will: i) dramatically reduce the amount of physical activity performed by your left leg (including regular standing and/or walking) and ii) result in a temporary loss of muscle mass and strength in your left leg. Muscle biopsies will be taken from your thighs to explore the effects of muscle disuse and characterize susceptibility to muscle loss.

In Phase 2, the elastic leg band and assistive device will be removed and you will complete a resistance-exercise rehabilitation protocol 3 times/week for 1 week. Muscle biopsies will be taken from your thighs to describe the molecular changes in muscle during recovery. Our goal is to determine if disused and healthy muscle in men and women respond similarly to physical activity. During all phases of the study we will closely monitor your general health, physical activity and diet.

Important Information
This information gives you an overview of the research. More information about these topics may be found in the pages that follow. You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled and will not affect your relationship with us.

1. What problem is this study trying to solve?
You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future**.**

The purpose of the study is to examine changes in the structure and function of skeletal muscle during periods of disuse (inactivity) and rehabilitation in middle-aged men and women. The negative health consequences of muscular inactivity in aging populations are well established, most notably the reduction in muscle mass and strength which can lead to the development of non-communicable diseases e.g., Sarcopenia. While descriptive, outcome data on disuse and recovery are abundant, key knowledge gaps limit our ability to implement evidence-based, rehabilitation strategies. Limiters include: i) an inability to identify individuals most susceptible to disuse, ii) insufficient information to differentiate between, and respond to, disuse atrophy in men and women, iii) limited insight into the mechanisms driving adaptation to early rehabilitative exercise, and iv) the assumption that disused and healthy skeletal muscle will have a similar, positive response to resistance exercise. This research study aims to address these knowledge gaps.

For more information, please see the *Why is this Study being Done* section below.

2. What will happen to me during the study and how is this different from continuing with usual care? What are all my options for treatment, including the pros and cons?

This study is being done in order to examine changes in the structure and function of skeletal muscle during periods of disuse (inactivity) and rehabilitation in middle-aged men and women.

If you qualify for the study, to implement skeletal muscle inactivity you will be asked wear an elastic band on your left leg to ensure non weight bearing on this leg and use an assistive device for 7 days. During this week, the amount of muscle and strength in your left leg will decrease. You will be monitored closely but may continue to live at home and participate in most of your regular daily activities. Immediately after the elastic band is removed, you will begin a 1-week exercise rehabilitation program (resistance exercise). You will complete 3 exercise sessions (e.g., Mon, Wed, Fri each week) each lasting approximately 30-60 minutes.

For more information, please see the ***What will be done if you decide to be in the research*** section below.

3. How much time will I spend on the study?

This study will last approximately 4 to 6 weeks and involves a total of 9 visits to UT Health San Antonio. During the study visits, if you chose to participate, you will be asked to:

- Complete 3 preliminary screening and familiarization sessions. Each session will last approximately 2-3 hours and will take place at UT Health San Antonio. These sessions will make sure you are eligible and ready to participate in the study.

- Wear an elastic band on your left leg and use an assistive device (e.g. crutches of a walker) for 7 days. During this week, you will be asked to visit the Barshop institute at UT Health San Antonio three times, once at the start for 2-3 hours, once 3 or 4 days later for 0.5-1 hour and once at the end of the week for 5-6 hours.

- Complete a 7-day exercise/rehabilitation protocol. Immediately after the elastic band is removed, you will begin a 1-week exercise rehabilitation program (resistance exercise). You will complete 3 exercise sessions (e.g., Mon, Wed, Fri each week) each lasting approximately 30-60 minutes. Sessions will take place in the UT Health San Antonio.

4. Could taking part in the study help me and are there risks?

The study will provide no direct benefit to you. However, we hope this study will improve our broader understanding of how to restore muscle health following disuse and ultimately direct the development of effective prevention and treatment strategies.

Potential risks associated with this research are mainly physical and include limb discomfort and blood clots from wearing an elastic leg band and using an assistive device, pain from muscle biopsies and blood tests and muscle soreness from exercise sessions.

For more information, please *see* ***How could you or others benefit from your taking part in this study*** section below. For details and a list of risks you should know about, please see the ***What are the risks of participation in the research*** section below.

5. What else should I consider before I make my decision?
This study will involve attending study visits at the Barshop Institute Clinical Research Unit (BICRU) 4939 Charles Katz Dr.

Please review the rest of this document for additional details about these topics and other information you should know before making a decision about participating in this research.

Consent to be part of a Research Study
To be conducted at
University of Texas Health Science Center at San Antonio (UT Health San Antonio),

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights, safety and welfare as a participant in the research. The PI for this study is Blake B. Rasmussen Ph.D. At the Sam and Ann Barshop Institute for Longevity and Aging Studies, University of Texas Health, San Antonio.

Funding

The National institute of Aging (NIH-NIA), a federal agency that promotes scientific research, is funding this study. This organization is providing money to UTHSA Sam and Ann Barshop Institute for Longevity and Aging Studies so that the researchers can conduct this study.

Purpose of this study – "Why is this study being done?"

The purpose of the study is to examine changes in the structure and function of skeletal muscle during periods of disuse (inactivity) and rehabilitation in middle-aged men and women.

You are asked to participate in this research study of the effect of physical inactivity on skeletal muscle (particularly leg muscles) mass and function and how physical rehabilitation (i.e. lifting weights), helps recover muscle mass and function after a short period of physical inactivity. The negative health consequences of muscular inactivity in aging populations are well established, most notably the reduction in muscle mass and strength which can lead to the development of non-communicable diseases e.g., Sarcopenia. While descriptive, outcome data on disuse and recovery are abundant (e.g. how inactivity affects muscle strength), key knowledge gaps limit our ability to implement evidence-based, rehabilitation strategies. Limiters include: i) an inability to identify individuals most susceptible to disuse, ii) insufficient information to differentiate between, and respond to, disuse atrophy in men and women, iii) limited insight into the mechanisms driving adaptation to early rehabilitative exercise, and iv) the assumption that disused and healthy skeletal muscle will have a similar, positive response to resistance exercise.

Disuse atrophy is rapid and debilitating. Strategies to restore muscle health following disuse are time sensitive and place a financial and human resource burden on our health care delivery system. The metabolic environment driving the recovery of skeletal muscle health following disuse is likely sex-specific and established during the early stages of rehabilitation. This project will provide a highly powered, detailed phenotypic characterization of the continuum of adults most and least susceptible to muscular disuse. Clinical outcomes will be supported by RNA deep sequencing and pathway analysis to establish a platform that: i) improves our ability to identify higher-risk individuals and ii) provides insight into time-sensitive, sex-specific and effective rehabilitation strategies. Our findings and reposed molecular data, may help identify future therapeutic targets and serve as an uncomplicated/comorbidity-free baseline for clinical trials in populations experiencing disuse atrophy.

The researchers hope to learn:

i) how middle-aged males and post-menopausal females may respond differently to physical inactivity.

ii) What processes inside the skeletal muscle cell (what molecular/genetic changes) cause or are related to the rebuilding of leg skeletal muscle mass and function after a short period of physical inactivity.

iii) Determine if disused (non-weight bearing) and healthy (normal weight bearing) muscle respond similarly to exercise.

This trial may be registered on www.ClinicalTrials.gov, a publicly available registry of clinical trials. 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.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you are a healthy male or post-menopausal female between the ages of 50-65 years old who has expressed interest in this project.

How many people are expected to take part in this study?
This study will enroll approximately 140 study participants (70 men and 70 women).

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend approximately 9 visits, over approximately 4 to 6 weeks, with the researchers or study staff. You will spend between 0.5 and 6 hours at each visit, depending on the procedures being done. It will be necessary for you to return to clinic every week during the study. All in-person visits will occur at Barshop Institute for Longevity and Aging Studies.

Study Procedures - as a participant, you will undergo the following procedures:

Visit 1, Screening and Baseline Testing, Research only

This visit will take approximately 2 hours and will occur at the Barshop Institute. You will be asked to arrive fasting to the research unit for this visit. After the consent is signed, you will undergo screening and baseline testing procedures as outlined below. The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you. If screening lab test results are abnormal, the investigator will make a clinical decision whether to repeat the tests and when that should occur.

Outline of visit

- Informed Consent- We will review all details of the research program in private. You will be provided with adequate time to have your questions answered, concerns addressed or clarified, and for you to consider whether or not you wish to participate. You will be given a copy of the informed consent to keep.
- Medical history & physical exam/assessment
  o Routine vital signs like blood pressure, heart rate, height, weight, etc will be obtained.
  o Detailed medical history including illnesses, surgeries, social habits, medications and allergies will be obtained.
  o Physical exam similar to one at your primary physician's office will performed.

- **Screening labs-** a blood draw, approximately 2 tablespoons, will be drawn and used to assess your general health status. The following blood tests will be performed:

- blood cell count - liver enzymes - - electrolytes - blood clotting factors - cholesterol - estrogen/testosterone - thyroid hormone - urine analysis - heavy water enrichment (may also do this test at Familiarization or Pretesting visit)

Please note that all test results will be confidential and given only to members of the research team working on this project. However, some of these results will become part of your medical record at UT Health San Antonio. You should be aware that the testing may reveal medical conditions you may not want to know about or wish to disclose. You should not volunteer for this study if you do not want to know the results of the screening tests.

The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you.

Study Procedures (visit 2 to 9) - as a participant, you will undergo the following procedures:

Familiarization (visit 2):

- If the results of medical screening are satisfactory, you will be asked to return to UT Health San Antonio approximately one to two weeks later, for a familiarization visit. This visit will take about 1 to 1.5 hours to complete and will include:

- A fitting to ensure the elastic leg bands are the correct size and comfortable.
- Familiarization, instruction and practice using an assistive device (e.g. crutches or a walker).
- Introduction and familiarization to the exercise tests used in the study.

Pre-testing visit (Visit 3):

- This visit will be scheduled about a week before you start the disuse phase. During this visit, you will:
- Receive further instruction and practice using an assistive device.
- We will also test your muscle strength and endurance using a standard leg extension machine.
- We will also ask you questions and collect information about your diet and foods you regularly consume.
- To help us measure your physical activity levels, you will be provided with a small watch-like device to wear the entire duration of the study (about 1 month). This activity monitor does not track or record your location, it only tells us how many steps you take each day.
- To help us measure how your muscle metabolism, you may consume up to 250 ml (~ 1 cup) of deuterated or "heavy" water. We will provide small tubes to collect small amounts of saliva every 1-2 days, which can be stored in your fridge or freezer and then bring them back for Study Visit 1.
- If you pass all the screening tests and decide to participate in the study, you will be complete 7 days of wearing an elastic leg band and using an assistive device.

Study Phase 1: Start of 1 week of disuse (Visit 4):

- Eligible participants asked to arrive fasting to the Barshop Institute research unit to undergo the following:
- Vital signs – typical assessments like blood pressure, heart rate, respiration rate, and temperature
- Blood draw – Similar to blood draw at Visit 1. Approximately 2 tablespoons will be drawn for research-only to analyze blood markers that are thought to be related to aging.
- 24 hour diet recall - We will also ask you questions and collect information about your diet and foods you regularly consume.
- DXA scan– we will measure the total amount of fat and muscle in your body by a technique called Dual Energy X-ray Absorptiometry. During this procedure, which will last about 10 minutes, you will lie on an imaging table while an x-ray camera passes over your body from head to foot. The distance between the camera and your body will be about two feet. During the DXA study, you will have to lie flat on your back. You will receive a small amount of radiation during the test.
- Muscle biopsy - We will take 2 small samples (one from the left leg and one from the right leg) of your thigh muscle using a special needle. These are called muscle biopsies.
    - To do this, we will clean your thigh and inject a local anesthetic (numbing medicine like your dentist uses) to numb a small area of your skin. We may have to shave a small area for the incision. We will clean the area with a special antiseptic solution. Next, we will make a small cut in your skin (about ¼ inch). The biopsy needle will then be passed through this cut into the muscle and a piece of muscle tissue about the size of a pea will be obtained. At the time the muscle is obtained, many people feel pressure and a thumping sensation. About a third of people feel cramping or pressure. The pain is mild to moderate and lasts 30 seconds. The pain stops when the needle is removed but your muscle may be sore for a few days.
    - In the areas where the biopsies were done, we will apply strips of adhesive tape (Steri-strips®) that will help the skin to close. The adhesive tape will come off on its own, and you do not need to peel it off. If you know you are allergic to adhesives used in these types of devices, we can suture your skin and have you return to remove the stitches.

- Application of leg sling and assistive device – Study personnel will put the bands on your leg during Study Visit 1 and you will be given the assistive device you practiced with during the run-in phase. The elastic band will help keep your left knee slightly bent /flexed and must be worn for the entire 7-day disuse period. They can be removed while you are sleeping or bathing.

NOTE: You will still be able to drive a car with an automatic transmission, and perform regular daily activities while wearing the elastic band/leg sling.

- Activity monitoring - You will also be given an additional small-watch like activity monitor to wear on your ankle while you have the bands.
- Drinking heavy water - During your visit you may consume up to 100 ml (~ ½ cup) of deuterated or “heavy” water to measure muscle metabolism during disuse. You will consume the deuterated water in small amounts (up to 50 ml or ~ 3.5 TBSP) over one hour.
- Saliva sampling - We will provide small tubes to collect small amounts of saliva every 1-2 days, which can be stored in your fridge or freezer and then bring them back for Study Visit 3.

Study Phase 1: Visit 5

- You will be asked to return the Barshop Institute for a brief (~30-60 minute) study visit on day 3 or 4 of this phase (i.e., 3 or 4 days after starting the 1 week of wearing the leg sling and using the assistive device) so we can take a blood sample to make check your risk for blood clots as well as check the fit and comfort of your leg band.

Study Phase 2: Visit 6

- You will be asked to arrive fasting to the Barshop Institute research unit, during this visit we will transition from Phase 1 of the study, muscle disuse (i.e. wearing the leg sling and using crutches, this will end and we will begin the physical rehabilitation) to undergo the following:
- Vital signs – typical assessments like blood pressure, heart rate, respiration rate, and temperature.
- Blood draw – Similar to blood draw at Visit 1. Approximately 2 tablespoons will be drawn for research-only to analyze blood markers that are thought to be related to aging. There will be 2 blood draws during this visit.
- DXA scan– we will measure the total amount of fat and muscle in your body by a technique called Dual Energy X-ray Absorptiometry. During this procedure, which will last about 10 minutes, you will lie on an imaging table while an x-ray camera passes over your body from head to foot. The distance between the camera and your body will be about two feet. During the DXA study, you will have to lie flat on your back. You will receive a small amount of radiation during the test.
- Muscle biopsy - We will take 4 small samples of your thigh muscle (2 from the left leg, and 2 from the right leg) using a special needle. These are called muscle biopsies. To do this, we will clean your thigh and inject a local anesthetic (numbing medicine like your dentist uses) to numb a small area of your skin. We may have to shave a small area for the incision. We will clean the area with a special antiseptic solution. Next, we will make a small cut in your skin (about ¼ inch). The biopsy needle will then be passed through this cut into the muscle and a piece of muscle tissue about the size of a pea will be obtained. At the time the muscle is obtained, many people feel pressure and a thumping sensation. About a third of people feel cramping or pressure. The pain is mild to moderate and lasts 30 seconds. The pain stops when the needle is removed but your muscle may be sore for a few days. o In the areas where the biopsies were done, we will apply strips of adhesive tape (Steri-strips®) that will help the skin to close. The adhesive tape will come off on its own, and you do not need to peel it off. If you know you are allergic to adhesives used in these types of devices, we can suture your skin and have you return to remove the stitches.
- Consume heavy water - you may consume up to 100 ml (~ ½ cup) of deuterated or “heavy” water to measure muscle metabolism during disuse. You will consume the deuterated water in small amounts (up to 50 ml or ~ 3.5 TBSP) over one hour.
- Collect saliva samples - We will provide small tubes to collect small amounts of saliva every 1-2 days, which can be stored in your fridge or freezer and then bring them back for Study Visit 9.
- Measure leg strength - We will also test your muscle strength and endurance using a standard leg extension machine and biodex.
- 24 hour diet recall - We will also ask you questions and collect information about your diet and foods you regularly consume.
- Start exercise rehabilitation - For your resistance exercise rehabilitation, you will complete a series of individual leg extension exercises and leg curls (e.g. 10 reps, 4 sets).

Study Phase 2: Visit 7

- During the rehabilitation phase, you will be asked to visit the Barshop institute three times (e.g., Mon, Wed, Fri) over one week to complete bouts of exercise.
- For your resistance exercise rehabilitation, you will complete a series of individual leg extension exercises and leg curls (e.g. 10 reps, 4 sets).

Study Phase 2: Visit 8

- During the rehabilitation phase, you will be asked to visit the Barshop institute three times (e.g., Mon, Wed, Fri) over one week to complete bouts of exercise.
- For your resistance exercise rehabilitation, you will complete a series of individual leg extension exercises and leg curls (e.g. 10 reps, 4 sets).

Study Phase 2: Visit 9

- For the last study visit, you will be asked to arrive fasting to the Barshop Institute research unit, this will mark the end of the 1 week of exercise rehabilitation and the end of the study. During this visit you will:
- Vital signs – typical assessments like blood pressure, heart rate, respiration rate, and temperature.
- Blood draw – Similar to blood draw at Visit 1. Approximately 2 tablespoons will be drawn for research-only to analyze blood markers that are thought to be related to aging. There will be 1 blood draw during this visit.
- DXA scan– we will measure the total amount of fat and muscle in your body by a technique called Dual Energy X-ray Absorptiometry. During this procedure, which will last about 10 minutes, you will lie on an imaging table while an x-ray camera passes over your body from head to foot. The distance between the camera and your body will be about two feet. During the DXA study, you will have to lie flat on your back. You will receive a small amount of radiation during the test.
- Muscle biopsy - We will take 1 small sample of your thigh muscle (1 from the left leg only) using a special needle. These are called muscle biopsies. To do this, we will clean your thigh and inject a local anesthetic (numbing medicine like your dentist uses) to numb a small area of your skin. We may have to shave a small area for the incision. We will clean the area with a special antiseptic solution. Next, we will make a small cut in your skin (about ¼ inch). The biopsy needle will then be passed through this cut into the muscle and a piece of muscle tissue about the size of a pea will be obtained. At the time the muscle is obtained, many people feel pressure and a thumping sensation. About a third of people feel cramping or pressure. The pain is mild to moderate and lasts 30 seconds. The pain stops when the needle is removed but your muscle may be sore for a few days. In the areas where the biopsies were done, we will apply strips of adhesive tape (Steri-strips®) that will help the skin to close. The adhesive tape will come off on its own, and you do not need to peel it off. If you know you are allergic to adhesives used in these types of devices, we can suture your skin and have you return to remove the stitches.
- Return saliva samples – return the saliva samples that you collected throughout the previous week.
- Measure leg strength - We will also test your muscle strength and endurance using a standard leg extension machine and biodex.
- 24 hour diet recall - We will also ask you questions and collect information about your diet and foods you regularly consume.
- Finish exercise rehabilitation - For your resistance exercise rehabilitation, you will complete a series of individual leg extension exercises and leg curls (e.g. 10 reps, 4 sets).

Future Use of Your Information or Biospecimens Collected as Part of Your Participation

Identifiers may be removed and the de-identified information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

Your biospecimens, even if identifiers are removed, may be used for commercial profit and you would not share in this commercial profit.

Research involving your biospecimens will include whole genome sequencing. Whole genome sequencing is the process of determining the complete DNA sequence of a person or other organism’s genome at a single

time. DNA is short for deoxyribonucleic acid. DNA contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child.

Return of Research Test Results for Genetic Tests to Subjects

It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician.

Information about Optional Procedures – "What are other research activities that may be done but are not required for your participation?"

Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is stopped.

Risks – "What are the risks of participation in the research?"

Risks from the specific research procedures (drug(s), interventions, or procedures)

There are risks to taking part in this research study. One risk is that you may have side effects while on the study.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The following section will describe the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

Risks and side effects related to the include those which are:

Risks from Crutches and Elastic Leg Bands:
Likely, and may not be serious (5-30 subjects out of 100):

- It is likely that you will experience a loss of muscle mass and strength in your inactive left leg. We expect your muscle mass and strength to return after the period of rehabilitation.
- You may also experience some upper body muscle soreness in muscles and joints due to the use of crutches/assistive device.

Less likely, and may or may not be serious (1-5 subjects in 100):

- There also may be an increased risk of tripping and falling. You will also experience an impaired ability to perform some of your regular activities of daily living. We will try to minimize these risks by providing you with detailed instruction and several familiarization and practice sessions.

Rare, and may or may not be serious (less than 1 in 100 needlestick procedures):

- There is a very slight risk of developing blood clots (DVT: deep vein thrombosis) due to the disuse/reduced leg movement. A DVT is a blood clot in a vein in your legs. The possibility of a DVT occurring is thought to be minimal and is unlikely to occur in healthy individuals. However, if clotting was to occur, it could result in decreased blood flow to a region of your body (e.g. your leg) or result in a blood clot traveling to your lungs. This could be a very serious health concern, and could cause death or require emergency medical treatment. You should not participate in this study if you have ever experienced a blood clotting disorder. The risk of DVT will be lowered by the use compression stockings and instruction on how to avoid blood pooling in your leg.

Risks from exercise:

Likely, and may not be serious (5-30 subjects out of 100):

- There is very little risk associated with resistance exercise. Some individuals may feel fatigue or experience muscle soreness during or following exercise bouts.

Rare, and may or may not be serious (less than 1 in 100 needlestick procedures):

- There may be a very small chance of a muscle strain or tear from resistance exercise, this will be prevented by conducting a warm up and stretching before lifting any weights.

Risk from heavy water:

Less likely, and may or may not be serious (1-5 subjects in 100):

- You may experience some nausea or dizziness from consuming heavy water. To minimize this risk, we will have you consume small amounts over several hours. Study staff will also monitor you during the first few doses to make sure you do not have any side effects.

Needlestick blood draw:

Likely, and may not be serious (5-30 subjects out of 100):

• Some people experience bleeding, bruising or swelling at the site of the needle entry. Fainting or lightheadedness may also occur. A qualified phlebotomist will perform your blood draw to reduce the risk of this happening.

Less likely, and may or may not be serious (1-5 subjects in 100):

• Bleeding may occur outside of the blood vessels (hematoma/bruise).

Rare, and may or may not be serious (less than 1 in 100 needlestick procedures):

• There is a small risk of infection and nerve damage at the needle entry site

Muscle biopsy:

Less likely and not serious (1-2 subjects in 100):

• At the time the muscle is obtained, most people feel a pressure sensation, and some people feel a thumping sensation.

• People might feel cramping, pain or soreness. In the people who feel cramping, pain or soreness, this will usually be mild to moderate in severity and will last approximately 30 seconds. The pain stops when the needle is removed, but your muscle may be sore for a few days.

• Bleeding from a muscle biopsy may occur and will be seen as bruising at the place on your leg where we take the muscle. The swelling or bruising usually goes away with rest within 2-3 days, although sometimes it may take a week. The bruising is reduced by using hot packs.

Rare and Serious (less than 1 in 500 of these procedures):
• Rarely, bleeding from a muscle biopsy may be severe enough to require hospitalization.
Rare and Serious (less than 1 in 1,000):
• Very rarely, some subjects may experience numbness or tingling at the biopsy site. This usually is temporary and goes away in a few days. There is the possibility that nerve damage could be permanent.
Rare and Serious (less than 1 in 100):
• There is a small risk of infection at the site of the muscle biopsy. Symptoms of an infection would include pain, redness, swelling, and yellow-greenish (pus-looking) discharge in the biopsy site, and is usually accompanied by fever. Because multiple biopsies of the muscle may be performed, the risk of infection and pain in the leg may increase. Infections can be usually treated effectively with antibiotics taken by mouth. In very rare occasions, hospitalization is required to give antibiotics through the vein, and an operation could be needed to clean the infected area.
• Allergic reactions to the local anesthetic we use for the muscle biopsy are extremely rare, but could include a skin sore, swelling, or hives.
There is the possibility that a future biopsy may not be done at the discretion of the PI in case the subject did not tolerate well a prior biopsy.

Radiation exposure for body composition (DXA)
Participation in this research study involves exposure to radiation from medical imaging (ex: Fluoroscopy, CT, PET, Nuclear Medicine scan). Every member of the general public receives approximately 310 mrem (a unit of radiation exposure) every year from natural sources, including cosmic radiation and radiation naturally found in our environment. Current evidence and research suggest that the risks of medical imaging at radiation doses below 10,000 mrem are too low to be detectable and may be nonexistent (American Association of Physicists in Medicine Policy PP 25, Health Physics Society Position Statement PS010-4). The total amount of radiation exposure that you are anticipated to receive from the procedures associated with your participation in this research study is 0.3 mrem, which is less than the amount of radiation exposure a member of the general public receives from natural sources per year on average.
If you have had prior radiation therapy (such as for cancer), or have any questions regarding radiation and its risks, please reach out to the Radiation Safety Office who can put you in touch with someone who can help address your concerns

For more information about risks and side effects, ask one of the researchers or study staff.

We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

Genetic Informational risks related to the study

This study will/may include genetic testing. Human tissue contains genes that determine many of a person's physical characteristics, such as the color of eyes and hair. In some cases, genetic testing of tissues can be used to indicate a risk for the development of certain diseases. Genetic information is unique to each individual and could potentially be used to discover possible changes in a person's future health status or life expectancy, or that of his/her children and family members. Even if your tissues are used for this type of research, the results will not be put in your health records. Releasing this information to you could cause psychological distress, anxiety or family problems.

Releasing this information to others, such as including it in your medical record, may pose a possible risk of discrimination, or increase difficulty in obtaining or maintaining disability, long-term care, or life insurance.

These risks would occur if your information is released by mistake. The measures being taken to protect your privacy are discussed below and make this possibility unlikely.

Even though the results of genetic testing may not be linked to you, it is possible that people of your ethnic background may be found to be at more risk for certain diseases based on future genetic research and this information might harm you in the future as a member of the group. Also, there may be unknown risks of genetic testing in the future.

Are there Risks related to withdrawing from the study?

If you decide to withdraw from this study early, please discuss your decision with the principal investigator. The researcher may ask you to complete study withdrawal procedures at a final study visit. This visit may include some aspects of visit 3 e.g., return of assistive device equipment. There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time, may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

What if a research-related injury occurs?

The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – "How could you or others benefit from your taking part in this study?"

You may not receive any personal benefits from being in this study.

We hope the information learned from this study will benefit other people with similar conditions in the future.

Payments – Will there be any payments for participation?

The researchers will provide you with a MasterCard®. Compensation will be automatically credited after completion of each phase of the study (e.g. after the pre-study phase [visit 1-3], after phase 1, i.e. after completing the week of disuse [visit 4-6], and after phase 2, i.e. after the 1 week of rehabilitation [visit 7-9]). Your name, address, date of birth, and social security number will be shared with a third-party solely for the purposes of compensation processing. This information will only be used for the administration of the compensation (ClinCard) and will be kept strictly confidential.

Study Visit	Compensation Amount
Initial medical screening (Visit 1)	$40
Familiarization visit (Visit 2)	$60

Pre-testing visit (Visit 3)	$100
Elastic band & assistive device (Visit 4-6)	$250 ($50/day, no biopsies)
Leg check visit (Visit 5)	$100
Rehabilitation visits (Visit 6-9)	$200 ($100/day, no biopsies)
Study visits with biopsy (Visit 4, 6 and 9)	$600 ($200 per visit)

The total you may receive if you complete all the study visits is up to $1350. Compensation will be paid after the completion of each phase of the study. following completion of all of the screening visits/familiarization (up to $200), after competition of the leg band and crutches study visits ($750) and following completion of all rehabilitation study visits ($400). If you are withdrawn or decide to drop out prior to the end of the study, you will be reimbursed for the portion you have completed.

If you are paid, the money you receive may be taxable. When the total payment is $600 or more in one calendar year, the institution must report the amount to the IRS. The IRS considers it earned income and treats it like any other income.

Costs – Will taking part in this study cost anything?

The sponsor will provide all the equipment used during this study free of charge. At the end of your participation, you must return all devices/equipment to the researcher.

Ask the researchers if you have any questions about what it will cost you to take part in this study (for example bills, fees, or other costs related to the research).

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the Federal Government. With this Certificate, the researchers cannot be forced to disclose, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings or any other person not connected to the research, your (or your family member's) name or any of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under certain circumstances. Circumstances that warrant the release of your information without your permission include:

abuse and/or neglect, intention to harm yourself or others, or certain communicable diseases, or other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research. Should you require medical treatment as it relates to the information, document, or biospecimen pertains, additional consent will be obtained.

Limits of Confidentiality
Even without your consent, suspected or known abuse or neglect of a child, disabled, or elder abuse, threatened violence to self or others or other local health reporting requirements will be reported to appropriate authorities.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out whose it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include: medical history, blood work, information gathered from your medical record if available, treatments prior to the study, information you provide during participation in the study, results of blood tests, and demographic information like your age, marital status, and race or ethnicity.
We will get this information by asking you, asking your doctor, and/or by looking at your medical record if one is available through the UT Health San Antonio System.

How will your PHI be shared?
Because this is a research study, we will be unable keep your PHI completely confidential. We may share your health information with people and groups involved in overseeing this research study including:

- The sponsor of the study, National Institutes of Health (NIH), and the National institute of Aging (NIA) who is funding the study.
- The UT Health San Antonio Claude D. Pepper Older Americans Center, where the study is being conducted.
- University approved texting platform
- The members of the local research team
- The Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out.
- The Research offices at UT Health San Antonio
- The UT Health San Antonio Data and Safety monitoring board the committee that checks the study data on an ongoing basis, to determine if the study should be stopped for any reason.
- the members of the local research team.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group 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 when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the UT Health San Antonio for review or testing. We will use appropriate information security safeguards that meet applicable state and/or federal laws, rules, regulations designed to protect your data when it is being collected, stored and transmitted.

If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you need to say this in writing and send your letter to:

Blake B. Rasmussen PhD
4939 Charles Katz Dr.
San Antonio, TX 78229

If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.

You will only have access to your PHI until 6 months after the study end date.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of the study. This permission to use your personal health information expires when the research ends and all required study monitoring is over.

How you may be contacted throughout the Study.

E-mail Authorization Agreement

The research team would like to communicate with you regarding your research visits via email, which uses an "encrypted" method for secure transmission. When one of the research team sends you an email, you will receive an email that says "[SECURE MESSAGE]" from a research team member with a link to open the message. When you click on the link it will take you to a secure website where you can read the message and reply after successful authentication. If you are not able to receive email, you may not be eligible to participate in the study.

Texting

The research team would like to communicate with you regarding your participation via text message. These messages may include information related to your participation in the study and payment information, if applicable. In order to do this, we will share your name and phone number with *UT Health San Antonio's secure texting platforms*. Standard text messaging rates will apply if you do choose to receive the text messages.

If you are not able to receive texts, you may not be eligible to participate in the study.

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?

If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact:

Primary contact:
Sean Kilroe PhD can be reached at 409-443-8020

If primary is not available, contact
Blake Rasmussen PhD can be reached at 210-450-7491

The UT Health San Antonio committee that reviews research on human subjects (Institutional Review Board) will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the IRB by calling 210-567-8250, or by mail to IRB, UT Health San Antonio, Mail Code 7830, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900.

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read and understand the above information.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.

Adult Signature Section

- You have voluntarily decided to take part in this research study.
- You authorize the collection, use and sharing of your protected health information as described in this form.

Printed Name of Subject	Signature of Subject	Date	Time AM PM
Printed Name of Person Obtaining Consent and Authorization	Signature of Person Obtaining Consent and Authorization	Date	Time AM PM

☐ Consent and authorization were obtained from this individual who is unable to read and/or write but can otherwise communicate and/or comprehend English. The method used for communication with the subject was: _____.

The specific means by which the subject communicated agreement to participate was: _____