Official Title: MiACLR: Michigan Initiative for Anterior Cruciate Ligament Rehabilitation

NCT Number: NCT03626857

Document Date: March 23, 2023

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: MiACLR: Michigan Initiative for Anterior Cruciate Ligament Rehabilitation

Company or agency sponsoring the study: National Institutes of Health

Principal Investigator: Riann Palmieri-Smith, PhD, ATC, School of Kinesiology and Department of Orthopaedic Surgery, University of Michigan

1.1 Key Study Information

You, or your child, may be eligible to take part in a research study. (Parents or legal guardians who are giving permission for a child, please note: in the sections that follow the word 'you' refers to 'your child.')

This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

2. PURPOSE OF THIS STUDY

2.1 Study purpose: Thigh muscle weakness and activation deficits (i.e., inability to fully contract the muscles) are common after anterior cruciate ligament (ACL) injury. Loss of thigh muscle strength reduces its ability to serve as a shock absorber during physical activity. This can lead to increased loads on the knee and deterioration of the joint (such as osteoarthritis). This research study is being done to determine if we can improve rehabilitation following ACL surgery using neuromuscular electrical stimulation (NMES) and exercise.

3. WHO MAY PARCITICPATE IN THE STUDY

Taking part in this study is completely **voluntary**. 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 otherwise entitled.

3.1 Who can take part in this study?

People between the ages of 14-45 who are scheduled to undergo ACL-reconstruction surgery can participate. If interested, you need to be willing to participate in testing and training sessions as outlined in this document.

However, you may NOT be in the study if you:
1) have suffered a previous ACL injury;
2) have undergone previous major surgery to either knee;
3) have a history of recent significant knee injury (other than ACL) or lower-extremity fracture;
4) are pregnant or plan to become pregnant;

Before you sign this consent form and we bring you in for testing, we will ask you a series of questions that helps us to determine whether you meet these criteria. We will also check your medical record to ensure you meet some of these criteria.

3.2 How many people (subjects) are expected to take part in this study?

We expect approximately 195 total subjects to take part in this research study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

In this study we are looking at two different physical therapy interventions, NMES and exercise, to see if they can help improve muscle strength and contractility after ACL reconstruction. Both of these therapies may be used in standard of care physical therapy programs, alone or together, at the discretion of the physical therapist. However there has not been a great deal of research on how best to use these interventions. This study will be looking at how well each of these therapies work together, compared to what might be done in standard of care.

If you are interested in participating, you will be randomly assigned (i.e. like a flip of a coin) to one of two study groups by a computer program. You will not be able to choose your study group. The two study groups are shown below:

NMES and Exercise Focus with Standard of Care	Standard of Care

No matter what group you are assigned to you will receive standard of care physical therapy at a minimum. You are not giving up any standard physical therapy care, which you would normally expect to receive outside of the study. By participating in the study you will also receive NMES and Exercise at varying levels depending on the group that you are assigned to. The standard of care group may sometimes be referred to as the control or placebo group. However, even the standard of care or placebo group will receive some level of NMES and exercise, so you will not be able to tell which group you are in.

This is a blinded study, which means you will not be told which group you are placed in. For some research studies, such as the one you are being asked to join, it is important that you do not learn which group you are placed in. Whether you intend it or not, sometimes learning this information may make you change your actions and behaviors in ways that could impact the outcome of the study. We will not reveal your group assignment to you until the end of the overall study, which may be some years down the road.

Regardless of the group you are in you will be asked to report to MedSport to have the study interventions/placebos delivered 2 times per week for 16 weeks (8 weeks of NMES followed by 8 weeks of Exercise) beginning shortly after you have your ACL reconstruction. We will make every attempt to schedule the interventions alongside your normal physical therapy so you can have the interventions delivered while you are reporting for your already scheduled care. In addition to the study interventions, you will be required to report for testing in up to 5 time points: 1) prior to your ACL reconstruction; 2) about 6-10 weeks after your ACLR; 3) about 14-16 weeks after your ACLR; 3) approximately 9 months post-ACL reconstruction; 3) and 18 months after your ACL reconstruction. We will take a variety of measurements at these testing sessions, which we will describe below. Some people will opt to break up the testing sessions so they aren't as long, which could result in you reporting for testing more than 5 times. In between your last two research office visits, at 12 months and 15 months, we will email you a brief survey to be completed at home.

Study Interventions

NMES

You will receive NMES twice a week at your regularly scheduled physical therapy visits. NMES will begin approximately 7-14 days after your ACL surgery and will continue for approximately 8 weeks.. You may also choose to have the NMES done at a time separate from your physical therapy appointment.
For NMES, you will sit in a device that measures muscle strength with two sticker-like pads (electrodes) applied to your thigh muscle. While relaxed, an electrical stimulation will be delivered to your thigh muscle, causing it to contract. The level of stimulus will depend on which group you are placed in. We will deliver this stimulus to your muscle 15 times at each session and the stimulus will stay on for 10 seconds at a time and will then shut off. You will have approximately 1 minute of rest in between each stimulus. The total NMES time will be 15-20 minutes.

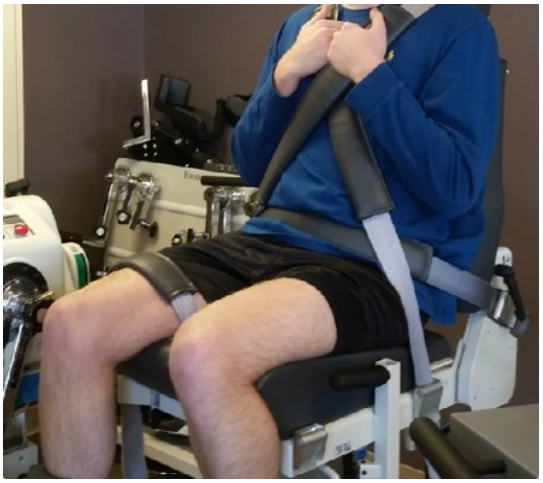
Exercise
At around 8-12 weeks after ACL surgery, you will begin to do motorized leg-press exercises twice a week at your regularly scheduled physical therapy visits. You may also choose to complete the exercise at another time that is convenient for you.

For Exercise, you will be seated in a specialized leg press machine that will apply a weight to your thigh muscles. You will be asked to perform a total of five sets (one set is a warm-up) of the muscle contractions with two minutes of rest between each set. The intensity of the exercise intervention will be based on the strength of your leg muscles at the beginning of each week and the group you are placed in. This exercise session will last between 15 – 20 minutes each visit. We may place electromyographic (EMG) electrodes (small stickers) on the skin over your thigh, leg, and butt muscles during this intervention. The electrodes are similar to EKG sensors that doctors use for heart exams. You will not feel the electrodes working. They will measure the activity of your muscles.

Study Testing Sessions
Study-related measurements may be performed at the 5 testing time points. Not all measures will be recorded at each time point. Table 1 below will show you when each measurement will be taken.

Muscle Strength and Activation Testing

- First, if you would like to warm-up your muscles, you will be provided with an opportunity to do some light exercise (e.g. exercise bike or stretching).
- After which, we will clean your skin with alcohol wipes and may place electromyographic (EMG) electrodes (small stickers) on the skin over your thigh and leg muscles. The electrodes are similar to EKG sensors that doctors use for heart exams. You will not feel the electrodes working. They will measure the activity of your muscles.
- You will sit on a chair attached to a system that measures the strength of your leg muscles (Picture 1).Your leg will be attached to the system through a series of straps.
- We will place additional electrodes on the top and bottom of your thigh muscles. These electrodes will send electrical pulses into your muscles, causing them to contract. We will send only as much electricity as necessary to result in a complete muscle contraction.
- You will then practice kicking/pulling against the device at 50-100% of your perceived maximum effort.
- You will rest for one or two minutes, and then you will kick/pull your leg muscles as hard as you can several times.
- We will send electrical pulses into your muscles during and directly after each kick. Throughout the testing, we will regularly ask about your comfort, please let us know if you are having any issues.



Picture 1. Person set up for muscle strength testing

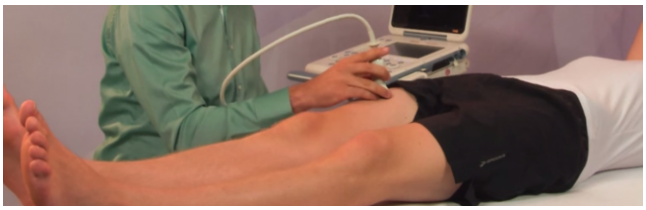
- We will make these measurements at each of the 3 testing time points.

Hop and Walking Testing

- Your hopping and walking pattern will be assessed using motion capture. Motion capture allows us to understand the forces that are applied across your knee as well as the position of the knee while you move.
- Prior to testing, round balls will be placed on the skin overtop of bones and muscles located on the lower half of your body. The balls will be held on your skin with double-sided tape and stretchy tape. The balls will allow cameras located in the laboratory to track the position of your body during testing.
- Now you will be asked to complete a series of single-leg hop tests for each leg individually. These tests will have you jump forward on a single leg and jump to the side on a single leg. You will also be asked to walk so we can track you knee while you move too. We will explain each test to you and you will be allowed to practice until you feel comfortable.
- Walking measurements will be collected at all 3 testing time points.
- Hopping measurements will be collected approximately 9 months after your ACL reconstruction and possibly again at 18 months after your ACL reconstruction.

Muscle Ultrasound

- We will do a muscle ultrasound on the front of both of your thighs and over both of your knees. Muscle ultrasound uses a wand (Picture 2) which produces sounds waves to generate pictures of your muscles, tendons, cartilage and ligaments.
- We will place gel on your thigh and your knee and then move the wand around to take pictures of your thigh muscle and knee cartilage. You will not feel any sensation through the wand.
- We will complete this at all 3 testing time points.



Picture 2. Thigh Muscle Ultrasound

X-rays

- We will take knee x-rays before your ACL reconstruction and 18 months after your ACL reconstruction. These X-rays allow us to take pictures of the bones in your knees.
- Prior to each knee X-ray all females will be required to take a urine pregnancy test

MRI measures

- We will take an MRI of your knee and thigh muscles.
- The MRI machine uses a strong magnet and radiowaves to make images of the body interior. The scanning procedure is very much like an x-ray or a CT scan. You will be asked to lie on a long narrow couch for 30 minutes to 1 hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a magnetic field. Your will not feel anything during the test. Your will, however, hear repetitive knocking noises that arise from the MR scanner. We will provide headphones or earplugs to you to diminish the sounds. The space within the large magnet in which you will lie is somewhat confined. If you feel discomfort at any time, notify the operator and you can discontinue the exam at any time.
- If an injury or potentially significant health condition happens to be identified by one of the investigators during the MRI examination, both you and your treating physician will be notified. Please note that the MRIs are for research only and will not be read by your clinical provider(s). The persons reading the MRI scans for our study are scientists and not clinicians and have no medical training in reading MRI scans to diagnose conditions.
- If you have already undergone an MRI as a part of your clinical care you will still need to have an additional MRI for research purposes only.

- We will only take an MRI at 18 months after your ACL reconstruction

Muscle Biopsy: Before your surgery, a member of the study team (Dr. Haus) may take a small muscle biopsy from one or both of your thighs at the MedSport clinic. We may also ask you to have biopsies taken on both thigha up to two additional times after your surgery. We will perform all the biopsies under sterile conditions. Each biopsy can take up to 30 minutes.

The muscle biopsy procedure involves numbing a nickel-sized portion of the skin of your thigh with a local anesthetic, making a small incision (1/4 inch), and removing a small piece of muscle (approximately the size of 2-3 grains of rice). The incision will then be closed with a piece of sterile tape.

You do not have to take part in the muscle biopsies to participate in other parts of this study.

Questionnaires

- We will provide you with a series of questions about how your knee feels and how you feel about performing activities. We will allow you to fill these out on your own while in the laboratory or we can read them to you and you can answer the questions verbally.
- We will ask you to complete these questions at all 3 testing time points.
- A survey will also be sent to you at home at 12 months and 15 months to ask about your recent physical activities.

Table 1. Measures that will be recorded at each testing visit

Before ACL Reconstruction (ACLR)	During the ACLR	6-10 weeks after ACLR	14-18 weeks after ACLR	9 months after ACLR	18 months after ACLR
1. Knee X-ray 2. Questionnaires 3. Strength 4. Muscle Ultrasound 5. Walking	1. Muscle Biopsy (optional)	1. Strength 2. Questionnaires 3. Muscle Ultrasound	1. Strength 2. Questionnaires 3. Muscle Ultrasound 4. Muscle biopsy (optional)	1. Strength 2.Questionnaires 3.Muscle Ultrasound 4. Hop testing/Walking	1. Strength 2. Questionnaires 3. Muscle Ultrasound 4. Hop testing/Walking 5. Knee X-ray 6. Knee MRI 7. Muscle biopsy (optional)

Photographs or Video

We may take photographs or video of you while you are participating in study interventions or study testing sessions. These photographs or videos may be used in research papers or presentations, but your head/face would be blurred. You can take part in the study even if you choose not to let us take your pictures or video.

4.2 How much of my time will be needed to take part in this study? Your participation in this study will last for approximately 18 months to 2 years and will require your participation in up to 32 intervention/placebo sessions and will involve a minimum of 5 testing visits (maximum of 8 testing visits if some of the testing is divided up). Each training session will last 20 minutes or less and the testing sessions could last between 1-4 hours.

4.3 When will my participation in the study be over? Your participation in the study will be over after the last testing session. You may stop participating at any time if you wish to do so.

4.4 What will happen with my information used in this study? Your collected information may be shared with the National Institutes of Health. With appropriate permissions, your collected information may also be shared with other researchers, here, around the world, and with companies. Your identifiable private

information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

4.5 What are my responsibilities in the study?
As a participant in this research study, you have certain responsibilities that may apply to this study, such as coming to all scheduled appointments and reporting any new health problems you may have during the study.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks? The known or expected risks and the procedures that the researchers will use to minimize these risks are stated below:

- **Discomfort from electrical pulses (Common):** You may feel some discomfort from the electrical pulses we send into your muscles for the NMES or for the muscle activation testing. These electrical pulses are similar to those that patients experience during rehabilitation. A researcher will be present during all study procedures, so you can tell us if you're feeling any discomfort. We will stop the electrical pulses or other procedures any time you ask us to.
- **Allergic reactions (Infrequent):** You may experience allergic reactions from the application of electrode paste and adhesive tapes necessary for attaching electrodes or markers. Similarly you could have a reaction to the ultrasound gel. We will use hypoallergenic tapes to minimize allergic reactions. If redness or excessive itching occurs, the area will be monitored closely by study staff and testing will be ended at their discretion or in accordance with your wishes.
- **Skin irritation (infrequent):** You may experience some skin irritation from the tapes and sensors attached to your body, especially when removing them. This should be temporary and should usually go away by applying skin lotion. You may decide to shave your legs before the study visit.
- **Muscle or Joint Discomfort and Swelling (Infrequent):** During or following the experiment, you may feel temporary or persistent muscle aching or joint pain, swelling, or general fatigue. We will provide appropriate rest breaks during the experiment. The level of soreness should not be greater than what would be experienced following a regular exercise session.
- **Knee looseness (Rare):** It is possible that exercising could increase knee looseness or laxity. Prior research indicates that high-intensity exercise training is safe for individuals with ACLR. However, there is a very small risk that knee looseness/laxity could be increased.
- **Muscle Strain, Ligament Sprain, or patellar fracture (Rare):** There is a small risk of injury during repeated muscle contractions, electrical stimulation, or hopping. Current literature indicates that there is a rare chance of patellar fracture in ACL-reconstructed individuals with patellar-tendon graft during activation testing. However, we are only aware of a single-case and this person had been experiencing pain in the kneecap and didn't inform the researchers. Please let us know if you experience unusual pain in your kneecap during testing.
- **MRI risks - Burns, metal attraction (Rare):** The magnet that is a part of the MRI may attract metals that are implanted within your body. Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other device in or on your body, it is very important that you tell the operator/investigator immediately and the scan may not be performed. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches, credit cards, and phones should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments or if you have ever worked in a metal

shop you should notify the operator/investigator. Failure to tell investigators/operators about metal objects in or on your person may result in burns to your skin.

- **Radiation exposure from X-rays (Common):** During the course of this study, as a result of procedures to be carried out for research reasons, you will be exposed to radiation in the form of X-rays. The biological effect of radiation is measured in terms of Roentgen equivalents in man, or "rem", which is a unit of uniform whole body exposure. The radiation you will be exposed to in this study will amount to approximately 0.0004 rems. The effects on your body of this radiation exposure will be added to your overall life-time radiation risk. Your life-time radiation risk includes the background radiation you are exposed to naturally like everyone else living on this planet, which is on the average 0.3 rem per year; the radiation you will be exposed to in this study is about 1-thousendth the yearly background radiation. In terms of radiation a person may get exposed to during medical care, the amount you will receive in this study will be about 4% of the amount of radiation received in routine dental x-rays or chest x-ray, which is 0.01 rem. Federal Government requires that the amount of radiation exposure of radiation workers does not exceed 5 rems per year; the radiation you will be exposed to in this study is 800-thousandths that amount. The risk from radiation exposure of this amount is too small to estimate. Your life-time radiation risk also includes any radiation you may have received in the past for diagnosis or treatment, and any such radiation you may be exposed to in the future. Please tell us if you have had any major radiation exposure in the past, particularly in the past two years, such as treatment with x-rays or radioactivity, or diagnostic x-rays, CT-scans or nuclear medicine scans. All female subjects will have a urine pregnancy test prior to undergoing X-rays. If this test were to come back positive, X-rays would not be taken due to risk to the unborn fetus.
- **Muscle Biopsy:** You will likely feel pain, cramping, or bleeding where the sample is taken. Infection is very rare as your skin is cleansed with alcohol and the needle used is sterile. It is very rare, but you could have an allergic reaction to the numbing agent that is used to numb your skin. Tell the research team if you are allergic to any drugs in the "-caine" family (for example, lidocaine, bupivacaine). Activity is good for your muscle after the biopsy. Walking is required after the biopsy procedure to help prevent additional stiffness and blood clot formation. The development of a blood clot is related to inactivity and may occur in less than 1% of biopsy procedures. There may be additional pain at the biopsy site during or after exercise and there is also a possible risk of scarring.
- **Breach of Confidentiality (Rare):** Confidentiality refers to the researchers' agreement to handle, store, and share research data to ensure information about you is not improperly revealed. We will only share data among the study team members. All data that is associated with you will be identified with a study ID number and only the study team will have the file that links you with your study ID. Once the study is complete, we will destroy the file that links you to your data. All data will be transferred and stored on secure devices and servers.
- **For women of child-bearing potential:** If you are pregnant, the unborn baby may be affected if you have an MRI scan, x-ray or undergo electrical stimulation. Currently, the effects of MRI on a fetus are unknown and international safety standards recommend that MRI is utilized cautiously for pregnant women. Therefore if you are pregnant, you are ineligible to be in the study. If at any time during the course of the study you become or suspect that you may be pregnant, please notify the PI so you can be removed from the investigation. You will be asked during screening whether you are pregnant or are trying to become pregnant; you should not take part in this study if you are. Sexually-active women of child-bearing potential are asked to use a reliable birth control method for the duration of this study.
- **Unforeseeable Risks:** As with any research study, there may be additional risks that are unknown or unexpected. If you have any questions or are unsure about anything outlined below please do not hesitate to ask the study team.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section

10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks 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 involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study. Some subjects may realize improved muscle strength and function as well as improved motion for their knee and lower body. It is possible these benefits could improve the long-term health of the knee and its cartilage.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVE TO PARTICIPATING IN THIS STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You do not have to participate in this research study. You will still receive standard physical therapy after your surgery whether you are in the study or not. You may also receive NMES or exercise as a part of that physical therapy. There may also be other ways of treating your condition, including other experimental therapies. Your doctor or surgeon can tell you more about these other treatments, their risks and their possible benefits. You should have this discussion about the risks and benefits or other alternatives prior to making your decision about whether or not you wish to take part in this research study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished? No harm will come to you if you decide to leave the study early.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples 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 suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $25 per week for the training sessions (16 weeks x $25/week = $400) and $10/hour for each testing session in which you participate. If you opt to participate in the biopsies, you will receive $50 for each biopsy performed. You will receive payment from the testing/biopsy sessions after each testing/biopsy session you complete and you will receive payment for the training sessions once ALL of the training sessions are complete. If you withdraw from the study before completing all training sessions you will be compensated for the sessions you completed.

If you receive payment of greater than $100 for taking part in this study, the University of Michigan accounting department will collect your name, address, social security number, payment amount, and related information. The information collected will be used for tax reporting purposes if you participate in additional studies and the total amount of study payment exceeds $600 in a calendar year. In this situation the University of Michigan accounting department is required for tax reporting purposes to submit this information to the Internal Revenue Service (IRS).

8.3 Who could profit or financially benefit from the study results?

No person or organization has a financial interest in the outcome of the study. Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my information?

- In any publications that result from this research report, neither your name, nor any information from which you may be identified will be published without your consent.
- Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you.
- Personal identifiers will be removed from the data before we share any of this information with anyone else.
- Only the research investigators of this study will have access to the list that connects identifying information with your information. This will be kept in a locked cabinet in the PIs' offices or labs.

This research will be covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is funding this project 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 from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996

(HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Demographic information
- Personal information
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

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. If your name and identifiable pictures will be used in any publications or presentations, the researchers will ask for your separate written permission.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of

Michigan “Notice of Privacy Practices”. This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researcher listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Riann Palmieri-Smith, PhD, ATC
Mailing Address: 401 Washtenaw Avenue, Ann Arbor, MI 48109
Telephone: 734-615-3154

You may also express a concern about a study by contacting the Institutional Review Board listed below.
University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111. *When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.*

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?
Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- You will receive a copy of the signed and dated informed consent

12. SIGNATURES

Consent/Assent to Participate in the Research Study (not including biopsy)

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with research staff member listed below. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

-- BELOW TO BE COMPLETED BY STUDY TEAM MEMBER --

Date of Birth (mm/dd/yy): _____

Consent/Assent to Participate in the Muscle Biopsies that are Part of the Research Study

I understand the information about the muscle biopsies printed on this form. I have discussed this biopsies, its risks and potential benefits, and my other choices with research staff member listed below. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Legally Authorized Representative or Parent Permission

Participant Name:

_____

Parent/Legally Authorized Representative:

Printed Legal Name:

_____

Signature: _____

Address: _____

Date of Signature (mm/dd/yy): _____

Relationship to subject: Parent Spouse Child Sibling Legal guardian Other

If "Other," explain: _____

Reason subject is unable to consent: _____

If this consent is for a child who is a ward of the state (for example, a foster child), please tell the study team immediately. The researchers may need to contact IRBMED.

Consent/Assent to video/ photography for purposes of this research

This study involves video and/or photography. If you do not agree to be videoed or photographed, you can still take part in the study. Photographs/videos may be used in presentations or publications, including medical journals, textbooks, and electronic publications. I understand that the image may be seen by members of the general public, in addition to scientists and medical researchers that regularly use these publications in their professional education. These photographs or videos may also be used for teaching purposes.

_____ Yes, I agree to allow myself/my child to be video/ photographed.

_____ No, I do not agree to allow myself/my child to be video/photographed.

Print Legal Name: _____

Signature: _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____