Document Coversheet

Study Title: Success of Long-acting Anti-inflammatories After Anterior Cruciate Ligament and Meniscal Injury

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	8/30/2024
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IRB6

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

For guidance, see:

- Which IRB?
- Which Protocol Process Type?
- "Getting Started"

Please contact the Office of Research Integrity (ORI) at 859-257-9428, IRBsubmission@uky.edu, or request a consult to resolve any questions prior to saving your selections.

Which IRB

(•) Medical ( ) NonMedical

Protocol Process Type

( ) Exemption
(•) Expedited (Must be risk level 1)
( ) Full

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

The Effect of Differing Strength Training Protocols in ACL Reconstructed Participants

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

BFRT

Anticipated Ending Date of Research Project: 9/30/2025

Maximum number of human subjects (or records/specimens to be reviewed) 55

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

Are you requesting that the UK IRB serve as the lead IRB for a multi-site study, **OR** that the UK IRB defer review to another IRB? [Click here for "IRB Reliance" help]
○ Yes ◉ No
If "Yes," before completing your IRB application, fill out the Reliance Request Form and submit it to irbreliance@uky.edu.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc.) 15 to 40

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

The subject population will consist of 60 individuals between the ages of 15-40 years old. The subjects may vary in ethnicity as it is not expected that this variable will affect the outcome of the study. Additionally, following previously published recommendations we will exclude people who report being pregnant, or have had a history of deep vein thrombosis, have a family history of deep vein thrombosis, or varicose veins. Following these subject recruitment recommendations has been shown to be safe within the age range and subject population to be studied [2, 6]. Lastly, the subjects must successfully pass the PARQ questionnaire with the exception of question 5 do you have a bone or joint problem as the subject group being studied has had a ACL tear, having the injury does not change the risk at all for the study participant. Subject enrollment will begin October 1, 2015 and end September 1, 2022.

The ACL injured study population will be:
Inclusion
1. Male or Female
2. Between 15-40 years of age
3. Having torn their ACL and no previous ACL reconstruction on either the involved or other limb

Exclusion:
1. Any other previous surgeries or conditions that might affect their gait
2. Any current condition other than ACL or meniscus injury which might affect their gait
3. Have a diminished capacity to provide informed consent
4. Are diabetic or have uncontrolled hypertension
5. Have recent inflammation, bleeding disorders, active bleeding or infection within the lower limbs.
6. Are allergic to Betadine or Xylocaine HCL.
7. Taking warfarin/Coumadin, clopidogrel/Plavix, Rivaroxabn/Xarelto, Dabigatran/Pradaxa, apixaban/Eliquis, edoxaban/Savaysa, betrixaban, or any other anti-coagulants that may cause excess bleeding.
8. Any implanted medical device
9. A history of deep vein thrombosis, have a family history of deep vein thrombosis, or varicose veins
10. Spinal fusion
11. Potential Subject reports that they will not be able to attend regular physical therapy or study visits
12. Subjects having a BMI of 35 or greater

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:	1	1		
Black/African American:	4	4		
Latinx:	3	3		
Native Hawaiian/Pacific Islander:				
White:	22	22		
American Arab/Middle Eastern/North African:				

Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☑ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☑ Students
- ☑ College of Medicine Students
- ☑ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☑ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

SUBJECT CHILDREN

0 unresolved comment(s)

SECTION 1. Risk Level

Complete this section and include it with your IRB application submission. *In Kentucky, a child is an individual less than 18 years of age unless the individual is legally emancipated.*

Note: the explanation(s) you are being asked to provide in Section 1 correlate(s) to the risk level you selected in the Risk Level section.

Minimal risk means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life *of a healthy child* or during the performance of routine physical or psychological exams or tests.

FOR FDA REGULATED RESEARCH: Based on the 2013 FDA final rule Subpart D, a placebo control arm of a clinical trial must be approved under either Risk Category 1, Risk Category 3], or Risk Category 4]. FDA does not consider administration of a placebo to offer a prospect of direct benefit to an individual subject under Subpart D, Risk Category 2 [21 CFR 50.52].

Not involve greater than minimal risk.

In the Risk Level section of the IRB Application you indicated your research does not involve greater than minimal risk.

A. Explain why your research does not involve greater than minimal risk:

The addition of the band to a standard treatment program does not increase the risk of any adverse events.

SECTION 2. Assessment and Evaluation of the Risks

For details, refer to the UK IRB's Policy on Children in Research.

A. Provide justification for the participation of children as research subjects in your study.

Children under the age of 18 are more susceptible to the condition being studied.

B. Has this research been conducted in adults? (•) Yes ( ) No

If yes, is there any indication that the proposed research would benefit, or at least not be harmful to children?

The training is typically done on all subjects, the use of the bands has been used in healthy populations both young and old without incident.

C. Indicate how many children you propose to enroll in the study: 15

Note: Whenever possible, involve the fewest number of children necessary to obtain statistically significant data which will contribute to a meaningful analysis relative to the purpose of the study.

Justify this number: At the onset, the study is open to all subjects ages 15-40. We except that only 10-15 subjects will fall under the age of 18.

D. Check all that apply:

☑ My research involves children 6 years of age or older.
☐ My research involves children under 6 years of age.

Indicate how assent will be solicited by selecting all that apply:

Assent will be solicited from: ◉ All Children ○ Sub-group of children ○ None of the children

I am requesting waiver of the requirement for assent from: ○ All Children ○ Sub-group of children ◉ N/A

Indicate justification for waiving assent for these children: (Check all that apply)

☐ 1. The intervention or prospect involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child/children and is available only in the context of the research.
☐ 2. The children are not capable of providing assent based on the age, maturity, or psychological state.
☐ 3. The capability of the children is so limited that they cannot reasonably be consulted
☐ 4. Other (explain)

** If you checked question 3, please explain:

** If you checked question 4, please explain:

E. Unless you are requesting a waiver of the requirement for assent for ALL children, you must answer "yes" to at least one of the following two statements.

Note: All assent forms or scripts must be attached to the "Informed Consent" section of this application. Be sure to save your responses in this section first.

For Children 6-11:
Assent will be obtained verbally. I have attached an assent script for obtaining verbal assent for IRB review.

○ Yes ◉ No

For Children 12-17:
The children will document assent by signing an assent form, or provide assent verbally if approved by the IRB, depending on the circumstances outlined in the application. I have attached an assent form or script for IRB review.

◉ Yes ○ No

F. Explain how study personnel will evaluate dissent (e.g., behaviors that would indicate the child does not want to participate such as moving away, certain facial expressions, head movements, etc.). If your study involves only children under 6 years of age, enter "N/A" below.

If the child does not seem to wan to participate, any form of negative body language or hesitation would be taken into consideration prior to having s/he sign any consent forms

G. Describe how parental permission will be obtained.

Parents will sign the consent form and the child will sign the assent form

I have attached a parental permission form for IRB review. ◉ Yes ○ No

Parental permission forms must be attached in the "Informed Consent" section of this application. Be sure to save your responses in this section first.

Note that for Risk Category 3 or Risk Category 4 where research involves more than minimal risk without the prospect of direct benefit to the individual child, the permissions of both parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available OR or only one parent has legal responsibility for the care and custody of the child.)

I am requesting

☐ The permission of both parents unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child. **(required for Risk Category 3 or Category 4 Research).**

☑ The permission of one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. **(permitted for Risk Category 1 or Category 2 Research).**

☐ Waiver of the requirement for signatures on parental permission forms. (Complete the "Request for Waiver of Signatures" questions in the in the Informed Consent/Assent Process/Waivers Section)

☐ Waiver of the requirement for parental permission.

Note: Parental/guardian permission cannot be waived for FDA regulated studies that are greater than minimal risk (Risk Categories 2-4).

Parental Permission Waiver Options

○ Complete the "Request for Waiver of Informed Consent Process" questions in the Informed Consent/Assent Process/Waivers Section.

○ Justify that the research study is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable request (e.g., abused children):

Justify:

H. Describe how study personnel will ensure that a parent is present when the child participates in any research activities.
Note: If the nature of the research is such that it is not appropriate to have a parent present (e.g., research into sensitive personal issues, physical examinations of teenagers, etc.), explain why.

The parent will be required to sign the forms to allow participation at the data collections, where the child will also sign the necessary forms to participate.

I. Describe the study personnel expertise for dealing with children at the ages included and whether they are knowledgeable and sensitive to the physical and psychological needs of the children and their families. Explain how the facility in which the research will be conducted is appropriate in relation to environment and/or equipment accommodating to children.

The PI is a clinician with a 15 year history of working with individuals, including children, who have had an ACL tear and reconstruction. The study personnel have experience in dealing with people of all ages. All needs of the child will be put as a priority in all situations of the process

J. If applicable, provide additional information that may support your request to involve children in research.

Children under the age of 18 are more susceptible to the condition being studied.

SECTION 3. Wards of the State

If you need to activate this section:

- go to the Subject Demographics section;
- select "Wards of State (Children)" in the categories of subjects and controls to be included in your study;
- save that section.

A. 45 CFR 46.409(a)

Please indicate which category describes your research proposal:

- ○ Research is related to subjects' status as ward of the state.
- ○ Research is conducted in schools, hospitals, or similar setting(s) in which the majority of children involved in the study are NOT wards.

B. 45 CFR 46.409(b)

Federal regulations state that an advocate must be appointed in circumstances where investigators enroll wards of the state for research studies which are greater than minimal risk **specifically risk category 3 or 4.** Please answer the following questions:

a) Will the advocate serve in addition to a guardian or in loco parents?

○ Yes ○ No

b) Check the applicable item:

- ○ Each child will have their own advocate.
- ○ One advocate will serve for all children enrolled in the study.
- ○ N/A

c) Explain why the advocate has the background and experience to serve as an advocate for the study.

d) Federal regulations state that an advocate cannot be associated with the study, investigator or organization. Please provide assurances that the advocate does not meet any of the criteria listed above.

SECTION 4. Children Located Outside the State of Kentucky

Does your study involve children outside the state of Kentucky? ○ Yes ◉ No

Provide information regarding the state definition of legally authorized representative, child, or guardian, as applicable to the research and to the federal definitions. [If the research is to be conducted in more than one state outside of Kentucky, provide this information for each state.]:

Guidance on Consent and/or Authorization by a Legally Authorized Representative

Consistent with Kentucky health care decision statutes for choosing a legally authorized representative for children, the following responsible parties in the order of priority listed shall be authorized to make research participation decisions on behalf of the child: (a) the judicially-appointed guardian of the person, if the guardian has been appointed and if the decisions to be made under the consent are within the scope of the guardianship; (b) the parent of the child.

Definitions

For definitions of "child/children", emancipated individuals, "legally authorized representative", "guardian", "assent", and "permission", see the ORI/IRB Informed Consent Standard Operating Procedures (SOP).

INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF.**
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☑ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

The informed consent will be read by the potential research study participant. All of the research study participant's questions will be answered and they will be given as much time as they require prior to making a decision to participate. Once any information consent is obtained, a copy of the signed consent form will be provided to the research study participant.
Complaints will be collected and reported to the IRB. Subjects will be asked to make a written record of the situation and complaint. Researchers will also provide a written account of the situation and return it to the IRB office at UK. To protect the subject's confidentiality, all forms and paperwork will be hand delivered to ORI. With the addition of the muscle biopsies we have added Dr. Darren Johnson who will serve as the physician 24-hour emergency contact and can be reached at 859-218-3131.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

☐ Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the ***Cover Letter Template*** *as a guide. There is an English and a Spanish version.*

○ **Option 1**

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

○ **Option 2**

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

○ **Option 3**

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Strength training has typically associated with exercises using up to 60-80% of a persons 1 repetition maximum (RM) to get improvements in muscle strength [1-3]. This training philosophy has been recently challenged by newer training methods that use as low as 20% of a 1 RM maximum [1, 2]. These types of training protocols typically have the person exercise at a higher volume of repetitions to gain similar strength improvements. Additionally, the use of compressive air bands (blood flow restriction training (BFRT)) to slow venous blood flow return to the leg muscles during exercise has been used extensively with low load strength training [1-3]. BFRT training has been used for 50 years, and has been shown to be a safe and reliable means of getting strength improvements without the need for a person to exercise their muscle at high levels. Further adverse events are exceedingly rare with a leading insurance provider reporting only 5 claims versus an estimated 80 million individual training sessions. This particular training program has proven to result in large strength gains that are maintained even after a period of detraining [1, 2]. Improvements in type 2 muscle hypertrophy have been reported, which are important for performance on many athletic tasks [1-3]. Further this type of training has shown the ability to be used in a wide range of populations from those recovering from surgery to the elderly [4, 5]. However, despite its wide use, how well the strength gains from this program transfer to other functional tasks such as jumping, hopping, and the ability to generate force quickly for athletic type movements is not fully known.

The rate of which a person can generate force, jump and hop are important metrics used to determine when a person is ready to return to sport again after surgery such as anterior cruciate ligament reconstruction surgery. These measures require the quadriceps to generate sufficient power quickly. Thus, significant improvements in strength as the result of using air bands during training may yield greater improvements in functional abilities than strength training alone. We aim in this study to show that training with air bands in healthy subjects improves performance in these important functional markers. Validating that this type of training improves functional measures in healthy individuals first will serve as justification of future studies focused in injured populations. Thus, we hypothesize that training with air bands (Kaastsu training) will result in significant gains in rate of toque development, as well as vertical and horizontal hop performance.
Anterior Cruciate Ligament (ACL) injuries are one of the most common knee injuries with an estimated 300,000 ACL injuries that occur annually in the United States.7 Many individuals elect to undergo ACL reconstruction surgery. Although this surgery typically has good short-term clinical outcomes, research has indicated ACL injuries and protracted quadriceps weakness can put individuals at risk for functional deficits and may increase the risk of knee osteoarthritis (OA).7,8ACL reconstruction typically produces good self-reported outcomes regarding knee function and return to sport.7,8 However, ACL reconstruction often falls short of its main goals of restoring knee function to pre-injury levels and preventing long-term joint degeneration.9 Functional deficits can persist even years out from surgery, and multiple lower extremity symmetry differences have been demonstrated 6 months after surgery, while quadriceps strength often never fully returns to pre-injury status.8 Additionally, whether performing this type of training prior to surgical reconstruction will help minimize muscle atrophy following surgery has yet to be assessed. Lastly, little is known of physiological response in the muscle to this type of training in those who have either torn or had their ACL reconstructed. Important changes in muscle fiber type, fibrosis, satellite cell number and muscle volume are unknown but important factors to assess if the treatment has been effective. Due to the ability to train at a low threshold, this type of treatment may prove to be very effective in conditions where individuals have either torn or had their ACL reconstructed.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

The objectives of this study are focused on subjects who have recently torn their ACL and plan on having it reconstructed:
1) Evaluate the effect of BFRT on quadriceps strength and knee biomechanics after an ACL reconstruction.
2). Identify alterations in quadriceps muscle morphology as the result of BFRT after an ACL reconstruction.
3) Determine the effect of BFRT on muscle fiber size and type, and the stem/progenitor cell composition after an ACL reconstruction.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

Laboratory-based, pre-post training study

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Male and females between the ages of 15-40 years old are potential candidates for this study. Subjects will be recruited from the University of Kentucky by word of mouth, personal request, and listserv postings. The listserv postings will be a simple message asking those interested in participating to contact the primary investigator. Internet and social media recruitment will follow the terms of use for each site utilized. Students in a course in which Brian Noehren is the instructor of record will not be recruited. Potential subjects will call or email the primary investigator for study details and, from information gathered from them, it will be determined if they qualify for the study. At this time, an available day and time will be decided upon for completion of testing. All study forms and subject information will be kept in a locked cabinet to ensure subject confidentiality. Using similar recruitment strategies as approved by IRB 11-0388 we will recruit subjects from University of Kentucky Healthcare orthopedics and sports medicine clinic patient populations who have torn their ACL but not yet had surgery. Potentially, interested subjects will be asked if a member of the research team may contact them to participate in the study. A member of the research team will then contact the potential subject to set up a time convenient for the potential subject to go over the informed consent document and receive their written informed consent.
None

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Informed consent will be obtained for all volunteer subjects if inclusion/exclusion criteria are met. The following will be completed depending on equipment availability, investigator judgment, and time available.

Questions regarding history of the subject will be investigated including following: age, sex, previous injuries, as well as the Sports Activity Scale will also be completed to determine the physical activity of the subject.

An online survey will be given to each participant in they will be prompted to complete a series of questionnaires at their visit to the Biomotion Lab. Self-reported data will be used to assess participant characteristics, knee outcomes, and variables contributing to knee outcomes. Surveys will be completed and managed via the web application Redcap, which is also used in currently approved research studies from the Biomotion laboratory (IRB #12-0492-P6H, IRB # 12-0490-P1H, and 14-0653-P2H). Redcap will be used to obtain patient demographics including height, weight, age, and gender. We also will administer a questionnaire to the subject to assess potential barriers to compliance and adherence of physical therapy and their belief in being able to complete the therapy (attached). We will administer this questionnaire at various points during rehabilitation including before starting physical therapy, before surgery, after surgery, and at the completion of the physical therapy.

Muscle strength testing will be performed in the following manner: We will use an electromechanical (isokinetic dynamometer) to record peak quadriceps strength isometrically, eccentrically and concentrically. Following a warm-up period, each subject will complete five maximum isometric contractions, followed by knee extension and flexion testing at various test speeds on both the uninvolved and involved limb. Subjects will be allowed 1-minute rest between sets and a 2-minute rest between limbs to prevent fatigue. Data analysis-data from the electromechanical dynamometer will be used to determine leg strength variables, such as rate of torque development and peak strength, for both the knee and the hip. Upon completion of these tests, the dynamometer will also flex and extend the knee at a slow speed to determine how stiff the muscle is. We will use a small electrode, placed on the quadriceps, to monitor that the muscle stays relaxed.

Muscle power testing: Subject will be in a seated position and a stabilizing strap will be placed around the thigh. A second strap will be placed around the bottom on the lower leg and attached to the isokinetic dynamometer. The subject will be assessed with the resistance set at one-third of the maximum strength. The subject will kick out up to 10 times against this resistance from which we will determine features of muscle power.

Subjects will be asked to rate their pain on a scale from 1-10 during a practice trail and during testing. If subjects rate their pain as a 3 or above, they will be given the option to use a pain reducing modality such as icing, taping, or e-stim. During their practice trail they will select which one they will use of the three. During the testing, the selected modality will be employed for the entirety of the strength testing protocol.

Assesment of hyperalgesia: A pressure algometer will be placed on the upper thigh of the subject and the pressure gradually increased until the point when the feeling of pressure first becomes that of pain. The subject will then press a trigger which will record that pressure value and end the test. The test will be repeated several times. These assessments will occur once before surgery and then during each physical therapy visit during the first two weeks of post operative care to determine the extent hyperalgesia in the acute phase after surgery.

Attachments

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Treatment program: The subjects will complete one of two programs. Both groups will receive the same training protocol with the only difference being one group will receive the use of the air bands that are inflated to a greater pressure. The use of the bands will follow

manufactures guidelines for use and is FDA approved. The groups will be randomized into the either of the two groups, through a computer assignment, The first group will use air bands inflated to provide restriction (40-60% occlusion). The other group will have the bands placed on their leg but they will be inflated a minimal amount (approximately 5% occlusion). Subjects will be instructed to be well hydrated prior to starting the training session. We will provide water and Gatorade to subjects if requested. These subjects will wear the BFRT air bands on their thighs only during the portion of the training designed to target their quadriceps muscle.

Their protocol will focus on quadriceps strengthening, and will be progressed per typical ACL protocols with exercises such as knee extension exercises, lunges, step downs, step ups, single leg squats, straight leg raises, and mini squats and wall sits performed as appropriate depending on the stage of rehabilitation. Subjects will also complete standard pre-operative and following surgery post opertavie physical therapy as part of their treatment session without the bands in the lab until they complete the study. This may include ice over the knee, range of motion exercises, hip strength exercise, neuromuscular re-education exercise and gait training exercises as needed and the subject's impairments dictate. Additionally, the program maybe extended 1-2 months depending on other surgical proceedures that may occure at the same time of surgery (ie meniscus repair) and/or subject vacation and holidays that may delay finishing the protocol.

Data collection for all subjects will be conducted in the BioMotion Laboratory the CCTS and the MRISC at the University of Kentucky. Testing sessions may last approximately 6 hours depending on scheduling of the MRISC and CCTS procedure room. Subjects will be requested to wear sports clothes (e.g. athletic shoes, shorts, and t-shirt). The first data collection will occur before they start the treatment program and will consist of all study proceedures except running and jumping. The second data collection will occur before surgery and will consist of measuring intake scales, quadriceps strength, and walking gait. Following surgery, subjects will be administered the intake questions at regular intervals to help the study staff assist them with attending their physical therapy visits. We will then administer all study interventions except running and jumping between 3-4 months after surgery. The last data collection will occur 6-7 months after surgyer and will include quadriceps strength assessment, walking and running gait, step down test performance and jumping. The timing of testing maybe delayed by upto 1-2 weeks if the subject is out of town for vacation or illness.

Research procedures for the muscle biopsy and MRI arm of the study will follow procedures already within another study focused on subjects with and ACL tear and reconstruction (11-0388):
Patients will be asked to stop taking aspirin 5 days and NSAIDS 3 days prior to starting the study. Study personnel will confirm that they have not taken aspirin or NSAIDS prior to the start of the muscle biopsy. Those who do not will be excluded from the additional analysis.

Muscle Biopsy: A muscle biopsy sample will be obtained from the vastus lateralis of both thighs in individuals before surgery and again when they have been cleared to practicing drills for their sport or are in a maintenance phase of physical therapy. The muscle biopsy procedure will proceed as follows for each subject taking approximately 15 minutes.

Subjects will report to the procedural room located in the outpatient unit of the CCTS or the UK HealthCare Orthopedics and Sports Medicine Center. Subjects will lie down and have a 1 inch by 1 inch portion of hair removed with a disposable razor on the outer surface of the thigh as necessary. The site will then be cleaned with alcohol followed by the application of Beta-dine. A local anesthetic (1% Xylocaine HCl, 3cc) will be used to numb an area the size of a quarter on the site of the outer thigh over the vastus lateralis muscle approximately a hand width above the knee using a 23-gauge, 1 inch needle, subcutaneously. Anesthetic will further be injected into the subcutaneous space of the numbed area from the muscle to the dermis. After 5-10 minutes, a sterile scalpel will be used to test for numbness before the procedure proceeds. In our experience, 5 minutes is adequate to sufficiently numb the area for the biopsy procedure. A ¼ inch wide incision will be made through the skin in the center of the anesthetized area with a sterile, single-use, #11 disposable scalpels. The incision needs to perforate the fascia of the vastus lateralis muscle sufficiently to allow for subsequent entry of the biopsy needle. The depth of the incision will be adjusted to accommodate estimated subcutaneous fat depth. A sterile 5mm Berkstrom biopsy needle (Pelomi Industries, Denmark) will be passed through the ¼ inch incision and a small piece (the size of a pencil eraser, equal to ~ 100-200 mg) of muscle will be removed. The angle of entry for the biopsy will be medial to lateral. This biopsy team will use the suction biopsy technique, whereby a small amount of suction with a Monoject 140cc syringe attached via sterile tubing to the end of the trocar will be applied to the needle prior to closing of the trocar, which enhances the investigators' ability to maximize the amount of muscle obtained. Manual pressure will be applied to the wound until bleeding stops. The muscle biopsy site will be cleaned with an alcohol preparation to clear all betadine and a band aid will be used to close the wound. The biopsied area will be covered with gauze and a pressure wrap applied. The muscle tissue obtained will be snap frozen in liquid nitrogen for further analysis. We will perform histo- and immunohistochemical analyses of the muscle biopsies. The analyses will result in the complete utilization of the collected tissue.
In addition, standard venipuncture methods will be used to collect one 7.5 mL tube of blood to be used for analysis at both biopsy colletion times and one week post surgery. Blood samples will be spun at 3500 RPM for 10 minutes and the serum will be frozen at -80°C. Samples will be stored and archived in the UK-Orthopaedics Serum repository for analysis. Samples can be destroyed if a subject requests this.
Diffusion Tensor imaging magnetic resonance imaging (DTI-MRI) routine turbo spin echo images for muscle volume, as well as T1 rho and T2 mapping sequences maybe run depending on time and investigator judgement on a 3T Siemens Magnetom Trio MRI scanner (Siemens Medical Solutions USA, Inc., Malvern, PA), at the University of Kentucky's Magnetic Resonance Imaging and Spectroscopy Center (MRISC). DIXON VIBE will be used to assess fat content of the thigh and vastus lateralis muscle, with CEST imaging to form an association with the degree of fibrosis of the muscle and ASL to estimate blood flow to the muscle. The patient will lay supine with a small bolster placed under their knee. Flexible coils will be placed along the leg and the Quadriceps will be imaged on the involved leg and as time allows the uninvolved leg. Hearing protection will be provided to increase the participants comfort. The DTI images will then be post processed with custom matlab code and muscle properties determined.

3 Day Food Record: We will ask subjects to complete 3 day food record (see attached) before starting the study, prior to and after surgery and then again at 4-5 months post surgery..

Gait Analysis: Small reflective markers will be attached to the subject's skin. Using Raptor cameras (Motion Analysis Corporation) a stationary trial will be collected to identify anatomical landmarks. Motion data at the hip, knee and ankle will be collected for 10 seconds every minute during both walking and running.

Treadmill Activity: The subject will be allowed to walk at their own self-selected pace for approximately 5 minutes to warm up. Following the warm up period each subject will be asked to walk 1.5 m/s for 2 minutes. The speed of the treadmill will then be increased gradually to a comfortable jog\run for the patient. They will then run at this pace for 2 minutes. The subject may also be asked to increase the jogging/running pace to 3.0 m/s and to jog/run at their self selected speed for 2 minutes. Following the run, the subject will be allowed to walk at a self-selected pace for as long as they need to cool down.

Jump analysis: Following standard previously published protocols we will have individuals perform jump landings. This will include drop vertical jump landings with the retroreflective markers on. The type of jump landing may vary between double limp to single limp landings. We will also have patients perform standard testing protocols for return to sport criteria that have been previously used for ACL research. This includes the triple hop, hop for distance and height tests[7-9].

Step test performance: Subjects will also perform step up and step down tests off of a step. The motion of their legs will be tracked as previously described under the gait analysis section. The task will simulate coming down and up from a step.

Data Analysis: The joint motion of the markers will be used to calculate ankle, knee and hip joint angles.

Attachments

Attach Type	File Name
DataCollection	Fear and concerns survery appendix C.docx
DataCollection	DC - CLEAN.pdf
DataCollection	BFRT Diet Record Instructions.pdf

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

The BioMotion Laboratory at the University of Kentucky provides this space and houses the equipment necessary for conducting this stuy. The laboratory is located within 500 meters of the University of Kentucky hospital and has an electromechanical dynamometer, the BFRT air bands and leg extension machine.

The Sports Medicine Research Institute at the University of Kentucky located in the Nutter Sports Complex provides additional space to muscle strength testing. The institute is located on campus and contains all the strength assessment equipment needed to complete the study. It is located next to a parking deck and participants parking will be validated who part there.

The Magnetic Resonance Imaging and Spectroscopy Center (MRISC) in the College of Medicine is a service center supporting basic and clinical research at the University of Kentucky. The Center includes an advanced 3T Siemens Magnetom Trio scanner with high performance gradients, echo-planar whole body imaging and multinuclear spectroscopic capabilities for both human and animal studies. There are also computing facilities, electronic and fabrication shops, and a multi-user laboratory available to support magnetic resonance and spectroscopy studies. Scientific and technical personnel are available to help in developing MR sequences and procedures as well as to help with image processing analysis.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.

- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Risks strength assessment and training are minimal and include muscle or joint soreness during and after the training session. The training program proposed has been shown to be safe within the population to be tested [2, 6]. Subjects will be closely monitored by the research team during data collections. The lab is only accessible with badge access and remains locked.

Muscle Biopsy. Potential risks involved within the study procedures include those during the muscle biopsy and exercise testing. With the muscle biopsy procedure, there is a risk of bleeding, bruising, pain, infection, and scarring of the skin. Bleeding could rarely result in development of a hematoma. Pain and soreness usually resolves within 24-48 hrs post-procedure. Numbness of the skin near the biopsy site may occur and is usually temporary, but this numbness may persist indefinitely. An allergic reaction to the anesthetic also may occur but is rarely seen.
Blood draws. There is a risk of local pain, soreness, bleeding, bruising and swelling, as well as lightheadedness, dizziness and rarely, fainting and/or a local infection.

MRI. The risks from MRI are minimal. The images taken will be of the quadriceps muscle and used to construct muscle fibers and determine muscle volume. They are used only for research and are not read for any clinical interpration.
Possible Risk/Side Effect from MR Scanning How often has it occurred? How serious is it? Can it be corrected?
Claustrophobia It occasionally occurs Can be treated Yes, volunteer is removed from the magnet
Loud noise It is expected to occur Not serious Yes, participants wear ear protection
Subjects will not receive any direct benefit from participating in this study. Risks to the subjects are minimal as strength is the primary outcomes being measured. If patients choose to participate in the study, the benefit to general knowledge may be great.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There is no alternative treatment to this study other than not participating in the study.

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Subjects in this study will undergo lower extremity joint strength testing of the knee done using an electromechanical dynamometer, jump height and hop distance will be recorded with a tape measure and stored electronically. For identification purposes, all subjects will be assigned a numerical identification code which cannot be traced back to them.
Patients will be assigned an identification number to protect their confidentiality. Hard copies of data will be stored in a locked filing cabinet in Wethington 419. Electronic data will be stored on a password-protected computer in Wethington 419. The names of the subjects will only be recorded on the informed consent forms, which will be stored under lock and key separate from the hard copies of data. Access to subject information will be limited to principal investigators and other team members. Collected data will be aggregated and presented without identifying information for individual subjects. Hard copies of the informed consent will be stored for six years following conclusion of the study at which time they will be shred and disposed of properly.
All muscle testing will be performed by trained individuals of the BioMotion Laboratory. The consent form will be administered to all subjects before testing, identifying all possible risks. Every effort will be made to protect from the risk of breach of confidentiality, and

consent forms will be stored under lock and key. The data collections will be staffed by at least two members of the research team.

All muscle biopsies will be performed by a study physician capable of performing biopsies. For the muscle biopsy samples, appropriate technique and all usual precautions including sterilization to help avoid any risk associated with these procedures will be taken. Patients will be asked to discontinue medications that may be associated with excessive bleeding, including aspirin and non-steroidal anti-inflammatory drugs prior to the procedure. Patients taking warfarin or clopidogrel will be excluded from the study. We will recommend that patients remain active following the procedure which may miligate against the pain and soreness/tightness post procedure. Post-procedure analgesics will be provided if requested and if medically appropriate. All participants will be given an instruction sheet for post-muscle biopsy care with phone contact numbers. The responsible study physician and an established method of contact for the study personnel to this study physician will be in place at the time of the biopsy. The research coordinator will follow up with the participant day 1 after the muscle biopsy. The physician will arrange a visit for evaluate the biopsy site if there are any concerns expressed by the participant or if there is any concern by study personnel.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

We will compensate each ACL subject $200 for completing the data collections, MRI, biopsy, and function\biomechanics. Subjects will be compensated $33 following the completion of the pre-operative training, $100 following completion of the study of the 4-5 month visit, and $67 following the completion of the 6-7 month follow up visit. In addition, we can reimburse subjects for up to a 15 mile round trip, for study visits, at .585 cents per mile reimbursement rate if they are coming from outside of Fayette County.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

There are no costs to the patient for participation in this study.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

Risk Assessment: A serious adverse event (AE) is defined as either fatal or life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is medically significant or requires intervention to prevent one or other of the outcomes listed above. This study is minimal risk.

Risk Assessment: A serious adverse event (AE) is defined as either fatal or life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is medically significant or requires intervention to prevent one or other of the outcomes listed above. This study is minimal risk.
Grading scale for AE intensity:

Mild: Discomfort noticed but no disruption of normal daily activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Incapacitating with inability to work or perform normal daily activity.
Attribution scale for AE reporting:

Probable: AE is related to the procedure (muscle biopsy), including pain, bleeding, infection, and death, if death resulted from one of the aforementioned complications.

Possible: AE follows the biopsy within a reasonable period (within 7 days), but may have been produced by other factors.

Remote: AE does not follow the biopsy within a reasonable period (more than 7 days) and could readily have been produced by other factors.

Unrelated: AE is judged to be clearly due to extraneous causes and does not meet the above criteria.
Monitoring Plan: Monitoring for adverse events will be conducted in real-time by the principal investigators and study coordinators. Risks involved with this study are considered greater than minimal risk. For this reason, we will utilize the standing independent Data Safety Monitoring Board (DSMB) as chartered by the University of Kentcuky Center for Clinical and translational Science (CCTS) to monitor the safety of this study. None of these individuals have any conflicts with this project, and therefore can serve the role of an impartial board who have expertise with these studies but who can oversee safety without bias. The DSMB will meet semiannually or as needed, and will review subject recruitment, AE's, side effects, laboratory results, withdrawals, protocol violations, and inclusion/exclusion criteria. More frequent meetings will take place if necessary or if side effects or other problems are prevalent.
AE Reporting Serious: AEs will be reported verbally to the IRB and CCTS OUTPATIENT UNIT within 24 hours and in writing within 48 hours of the event. Unanticipated events will be reported to the CCTS OUTPATIENT UNIT in real time and to the IRB no later than 48 hours after the event. Annual reporting of adverse events will be conducted with the IRB annual review/renewal according to their protocol. These reports will also be forwarded to the CCTS OUTPATIENT UNIT. The CCTS OUTPATIENT UNIT Administration will be informed within 15 days if for any reason the IRB or any other body temporarily or permanently suspends the study.
Data Accuracy and Protocol Compliance: All protocols involving human subjects will be directly supervised by the PI or his colleagues to assure compliance. All samples will be coded to eliminate bias. Detailed plans for maintaining subject confidentiality are described in the consent form.
Conflict of Interest: There is no conflict of interest. Investigators on this project have extensive experience with similar protocols and are well qualified to monitor progress and to determine what rate of unexpected AEs is acceptable. For these reasons, Dr. Noehren and his colleagues are capable of monitoring for safety objectively and without bias.

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

All biological specimens (blood, urine, muscle tissue, and/or synovial fluid), muscle strength, biomechanics data, demographics, patient reported outcomes, and information related to muscle adaptation may be used in future research endeavors, either by the research team or by secondary investigators should they request it. These samples are de-identified and will not contain PHI so participants will not be able to be readily identified. Participants consent to the indefinite storage of these specimens during the initial consent process and are notified that the samples no longer belong to them and breach of confidentiality would be the primary concern.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

Statistical Analysis:

Continuous participant demographic variables (e.g., age, body mass index (BMI), time since surgery) were summarized with descriptive statistics (e.g., sample size, mean, standard error). Categorical variables (e.g., sex assigned at birth) were summarized with descriptive statistics (e.g., counts and percentages). Summary statistics are also presented by treatment group. A chi-squared test was used to evaluate between-group differences in sex assigned at birth and two-sample *t*-tests were used to evaluate between-group differences in quantitative covariates.

All primary and secondary outcomes were continuous. For each outcome, change scores were calculated as: post-intervention (4-5 months post-surgery) – pre-intervention (baseline pre-surgery). Two-sample *t*-tests were then used to assess between-group differences in change scores. Distributional assumptions of two-sample *t*-tests were assessed using plots of each outcome. An analysis of blinding was performed for each of the participants, the data analysts, and the primary investigator of the study. Chi-square tests (or Fisher's exact tests in the case of small cell counts) were used to identify any association between guesses and treatment group for each of the blinded groups. All analyses were performed using R (R version 4.1.2, R Core Team, 2023) and p-vales ≤ 0.05 were considered statistically significant.