PennState

HRP-591 - Protocol for
Human Subject Research

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Neuromuscular Electrical Stimulation for Achilles Tendon Rupture Rehabilitation

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Version Date:

Provide the date of this submission. This date must be updated each time the submission is provided to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

07/14/2023

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual, When do I have to register my project at ClinicalTrials.gov?" for more information.

NCT03340545

Important Instructions for Using This Protocol Template:

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. **GENERAL INSTRUCTIONS:**
   - Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
   - Do not change the protocol template version date located in the footer of this document.
   - Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
   - **GRAY INSTRUCTIONAL BOXES:**
     - Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
     - **Penn State College of Medicine/Penn State Health researchers**: Delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu).
     - **Penn State researchers at all other campuses**: Do NOT delete the instructional boxes from the final version of the protocol.
   - Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.
2. **CATS IRB LIBRARY:**
   - Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3. **PROTOCOL REVISIONS:**
    - When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.
    - Update the Version Date on page 1 each time revisions are made.
4. **PROTOCOL AMENDMENT HISTORY LOG**:
    - 4/26/2022: Changes requested by NCR/NIH. Modification made by DHC.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Penn State Health:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

Achilles Tendon Ruptures (ATR) are common and permanently affect the function of the lower leg. Regardless of the treatment approach, most patients develop long-term functional deficits, including decreased plantar flexion strength, lower heel-rise height, and altered gait patterns. It is believed that tendon lengthening and calf muscle atrophy, which develop during the first few weeks of recovery, contribute to these functional deficits. The initial development of atrophy is likely caused by reduced loading and muscle activity of the affected leg. However, long-term atrophy may be related to tendon elongation. On the other hand, tendon elongation initially rises during the first few weeks of unloading and slowly reduces, but not wholly, when loading is resumed. However, atrophied calf muscles may need to provide more loading for optimal tendon recovery. Therefore, there seems to be a vicious spiral between tendon elongation and muscle atrophy.

This study aims to evaluate a neuromuscular electrical stimulation (NMES) rehabilitation protocol for Achilles tendon ruptures. Our preliminary data has shown that force applied to the tendon can be modulated using electrical intensity and pad placement. Therefore, NMES can produce significant contraction in the calf muscles and induce controllable, low-magnitude, cyclic loading to the tendon, which cannot be achieved with voluntary muscle contractions. This approach can potentially overcome the limitations of the current rehabilitation protocols.

The results of this study will allow the development and demonstration of the initial feasibility of an NMES protocol for patients recovering from ATR. This protocol may improve lower-leg strength and tendon and muscle properties of patients recovering from an ATR, which can result in improved functional outcomes. NMES technology is widely available in physical therapy and rehabilitation centers. Consequently, NMES can be quickly adopted and incorporated as part of routine care for ATR.

This is the second phase of a three phase study.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

The primary outcome of this study is to measure the ability of participants to perform a heel rise at week 12, which is a strong predictor of long-term outcomes.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Muscle volume, Achilles tendon length and area, steps, and self-reported outcomes VAS (pain), ATRS, FAOS, PAS, adverse events, and compliance to the proposed treatment.

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the study procedure is available to patient without taking part in the study.

Achilles tendon rupture (ATR) is a common injury that affects active individuals and has increased 10-fold in the past few decades [1]–[6]. Approximately one out of five patients are unable to return to previous activity levels [7], and two out of three have continued functional deficits seven years after injury [8]. Lower-leg functional deficits include decreased heel-rise height, heel-rise work, concentric strength power, reduced plantar flexion strength [9], and decreased ability of the ankle to absorb load and generate power [10]. These deficits persist beyond 14 years after injury [11]. Poor functional outcomes resulted in 30-40% of athletes not returning to the professional level and those who do have up to a 50% reduction in performance levels [12], [13]. Structural changes in the tendon-muscle unit after ATR are strongly related to deficits in plantarflexion function and altered running and jumping biomechanics 1-6 years after injury [14]. Specifically, ATR results in long-term tendon elongation [15], increased tendon area [16], [17], altered mechanical properties [18], [19], and reduced calf muscle volume [16]. These structural changes rapidly develop over the first weeks of recovery, continue for a few months after injury and change very little after that [20]. Therefore, recent improvements in rehabilitation protocols have focused on including early mobilization and weight-bearing [21]. Although these protocols result in better outcomes [22], patients still develop functional deficits [22]–[26].

Standard Rehabilitation Protocol: Participants will receive the current standard rehabilitation protocol given at Hershey medical center or any other suggested medical center suggested by their surgeon. Briefly, no weight bearing for the first 2 weeks, followed by partial weight bearing in a cam boot with heel wedges for weeks 3 and 4. Gradual reduction of heel wedges during weeks 5 to 6. After 7 weeks, participants will discontinue the use of a cam boot and progressively transition to full weight bearing.

2.2 Previous Data

Describe any relevant preliminary data.

A recent double-blind study (clinicaltrials.gov NCT01833936) that applied **a one-time session** of NMES (at the moment of surgery) to patients undergoing ATR repair reported trends towards improvement of muscle volume [27]. It is extremely encouraging that a one-time application of NMES resulted in 'trends' towards maintaining muscle volume and this provides support that a daily structured NMES protocol would enhance those results. Additionally, the proposed study will evaluate not only muscle volume, but also early structure (tendon length, area and mechanical properties) as functional parameters (heel rise) that have been shown to be predictive of longer term functional outcomes [28], [29].

Relationship between NMES pad position, intensity and force: Pad placement plays an important role in the amount of force generated during NMES. Four placements are considered in this study (Fig. 2). Placements I to III covered small regions of the calf: medial gastrocnemius, lateral gastrocnemius, and soleus, respectively. Placement IV covered all calf muscles. The NMES parameters used are shown in Table 1. 20 healthy subjects (age range 20 to 53) were recruited for this pilot study. Plantar flexion angle had a minor effect on force for placement IV. For the other pad placements, the effect was negligible. The force produced by each placement increased as a function of intensity until it plateaus (Fig. 3). As expected, pad placement covering small regions of the calf muscle (placements I, II, and III) produced lower forces compared to stimulating all calf muscles (placement IV). Interestingly, placement IV had a sharp increase of force and plateaued at lower intensities compared to the other pad placements. This indicates that it will be easier to tune and produce smaller forces when stimulating smaller regions of the calf muscles. In later stages of healing, pad placement IV can provide larger forces.

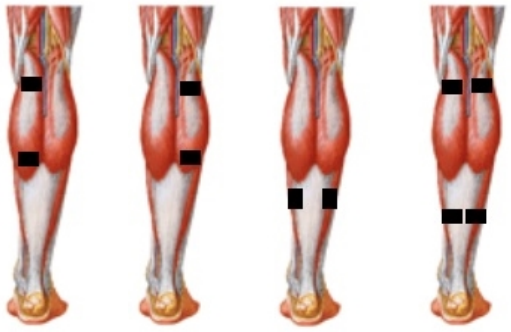

Figure 2. Pad placements: I) medial gastroc, II) lateral gastroc, III) soleus, IV) full calf.

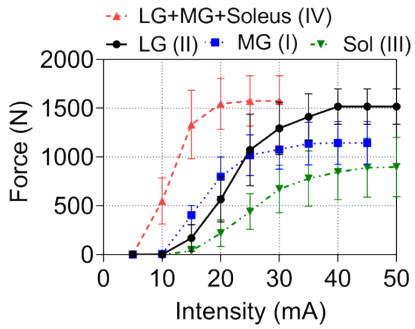

Figure 3. Force produced by different pad placements as function of intensity.

Table 1. NMES parameters for patients recovering from ATR.

Hz	PW (μs)	Plantar Flexion
50	300	0º, 10º, 20º, 30º

2.3 Study Rationale

Provide the scientific rationale for the research.

The cause of long-term functional deficits remains unclear and is thought to be multifactorial. Changes in tendon length, area and mechanical properties, as well as muscle atrophy, are likely to play a role in the long-term deficits [30]–[32]. Significant changes in muscle pennation angle and fascicle length have been observed during the first 4 weeks post-injury [33]. Muscle atrophy rapidly develops within the first 6 weeks following ATR and does not significantly improve over time [16], [34]. Short-term atrophy is likely caused by reduced activity of the calf muscle, but long-term atrophy might be associated with tendon elongation [15]. Tendon elongation develops within the first 6 weeks following ATR and remains relatively constant after this point [35]–[37]. The timing of the adverse changes in the muscles and tendon coincides with the periods without weight bearing or partial weight bearing of current rehabilitation protocols [38]. In clinical practice the majority of rehabilitation protocols recommend no weight bearing for 2 weeks after repair, partial weight bearing starting from week 4, and full weight bearing at week 6 [39]. In studies using early functional rehabilitation, full weight-bearing is allowed during the first 2 weeks [21], however the patients report loading around 25% of bodyweight onto the injured side [40]. Additionally, weight-bearing does not guarantee muscles activation or tendon loading [41]. We propose to use neuromuscular electrical stimulation (NMES) to provide muscle activity and mechanical stimulus to the tendon during the weeks of reduced leg activity.

NMES can positively impact several of the factors affecting the recovery from ATR and has been successfully applied as part of rehabilitation protocols for knee surgery to preserve muscle volume and

strength [42]–[45]. Therefore, NMES can attenuate muscle atrophy during the first weeks of recovery after ATR repair surgery. Abundant work in animal studies has shown that controlled loading immediately after rupture or repair enhances up-regulation of repair genes [46], increases the diameter of newly organized collagen [47], decreases occurrence of sensory neuropeptides in the tendon proper [47], and improves tendon strength [48]. In humans, early controlled loading improves mechanical properties of the Achilles tendon after rupture [36]. Consequently, NMES can also provide controlled tendon loading during the first weeks of recovery, likely improving the structural and mechanical properties of the healing tendon. Additionally, NMES significantly reduces the risk of deep vein thrombosis [49], a possible complication during recovery from ATR [50]–[52].

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

[Do not type here]

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

Subjects: 50 participants will be recruited.

1. male and female participants,
2. Age 18-65,
3. Having a diagnosis of an acute complete Achilles tendon rupture and undergoing surgical repair.

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

The exclusion criteria include:

1. Those unable to understand spoken English.
2. Participants treated non-operatively
3. Augmented surgical repair (i.e., use of additional tissue at the repair site)
4. Tendon ruptures associated with the use of fluoroquinolones (Examples include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin))
5. Allergy to ultrasound gel
6. Any other condition affecting the ability of the participant to walk or jump
7. Any other health conditions known to impair normal healing:
    a. Diabetes
    b. Cardiovascular conditions decreasing blood supply to the leg
8. Those unable to consent

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Subject participation will be discontinued by recommendation of the team physician (Dr. Bader) if the subject experiences excessive pain during stimulation (>5/10), excessive tendon elongation (>3 cm), gapping at the repair site (>5 mm) or other AEs. Participants will also be removed if the outcomes from the repair surgery require patients to deviate for the standard rehabilitation protocol. An additional criteria include failure of the subject to adhere to the protocol and subject consent withdrawal.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Data collected up to the time of withdrawal may be used in the study. Subjects will recruited until the desired number of participants with complete data points is reached. Subjects who experience AEs that are potentially related to the intervention will be followed via phone call or email to obtain information on how the AE resolves.
Participants who experience any of the above mentioned AEs will be followed up with until resolved or stabilized.
Subject will be asked for consent to be contacted for possible future studies. Withdrawn subjects will be contact if new information is available concerning to the methods and techniques used in the study.
The subjects who withdraw from the study will not be replaced.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (**Error! Hyperlink reference not valid.**). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (**Error! Hyperlink reference not valid.**) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.

- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (**Error! Hyperlink reference not valid.**).

[Do not type here]

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (**Error! Hyperlink reference not valid.**) for recruitment purposes, include this method in this section.
- Information provided in this protocol needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (**Error! Hyperlink reference not valid.**). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Potential subjects will be identified when they become eligible for tendon rupture repair after a complete rupture.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

[Do not type here]

4.2.1 How potential subjects will be recruited.

Clinicians who agree to collaborate in the study will hand a flyer to participants diagnosed a mid-portion Achilles tendon rupture and ask them if they want to be contacted to know more about the study. Those expressing interest will be contacted by a member of the research team.

4.2.2 Where potential subjects will be recruited.

4.2.3 Recruitment will occur in the Bone and Joint clinic in a private room within the clinic When potential subjects will be recruited.

Participants meeting eligibility requirements will be approached in the Bone and Joint Outpatient Clinic and presented with the study opportunity prior or shortly (within a week) to their planned surgery date.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their

eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Eligibility and screening questions will be asked after obtaining verbal consent. Those questions have been included in the document "Eligibility and screening questions" submitted with application

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (**Error! Hyperlink reference not valid.**). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **<u>Exempt Research at all Locations Except Penn State Health and the College of Medicine</u>: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312- Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):**

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the ds that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Participants will be approached about potential participation in the study as soon as feasible following determination of eligibility and getting initial verbal consent to introduce the study to the participants. Participants could be approached prior to or shortly after (within a week) of surgery. This will occur at the Sports Medicine Clinic in State College or the Bone and Joint Clinic at the Hershey Medical Center. Subjects will be considered "enrolled" in the study after signing the informed consent. The consent form will be signed by the participants and the consenter. The signed consent form will be uploaded in REDCap. The participants will receive a copy of signed consent form via emails, mails or during in-person visit.

- In a case that in-person meeting is not possible, the consent process will be done remotely. The research staff will obtain verbal permission from the participant before sending study information via email.
- The telephone consent process follows the PSU IRB guidelines. The potential subject who is an adult and cognitively healthy person will receive a blank copy of the consent form, flyer, and a link to the introductory video. This information is provided as an email or as a hard copy prior to phone call or video conference session.

- After one or two days, a member of the study team will contact a potential participant via telephone, or video call meeting and will start the procedure of consenting, a witness will be also present with the study team member during the telephone consent discussion.

- The procedures of the study will be reviewed with the participant to ensure that the participant understands all aspects of the study. All questions and concerns will be answered prior to the end of the discussion. Time will be given for the potential participant to respond to the consent process, and give a positive response, or decline to enroll in the study. Then the subject is asked if he/she would like to participate. If yes, If the participant decides to enroll in the study the subject signature line on the consent document will be signed, dated

with time at the remote session and returned to the study team. The participant will return the signed consent form to the research staff in person or via email, fax or mail. The participant will be warned about the confidentiality risks associated with returning the signed consent form by email. The consenter and witness involved in the consent discussion will be documented in the research records.

- The consenter will add their signature to the consent form when it is received from the participant. Study activities will begin after the consent is signed by both the participant and the person obtaining consent.
- A copy of the fully executed consent form will be sent to the participant by email, mail or fax.
- The phone consent procedure should be included in the note to file used to document the informed consent process in the research record or medical record.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Participants will be approached by a member of the research team and presented with the study opportunity. Participants will be given ample time to read and review the consent form on their own. All questions the participant may have will be answered, and written consent will be obtained. Consent will be obtained in accordance of principles of GCP and ICH guidelines.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

[Type protocol text here]

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

Flyer and verbal script.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

N/A

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

N/A

5.4.3 Describe why the research involves no more than minimal risk to subjects.

N/A

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

N/A

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

Subjects who do not understand spoken English will not be enrolled in the study. Members of the study team involved in the recruitment may not be fluent in other languages to interact with patients who do not understand spoken English.

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

The linking list will be destroyed upon completion of the study. Additionally, any PHI will be destroyed or deleted upon completion of the study.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Information about type of repair and medication is needed for screening purposes.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

The study team would be unable to identify the appropriate participants to be included in this research study.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations. The research team will collect only information essential to the study and in accord with the "Minimum Necessary" standard (information reasonably necessary to accomplish the objective of the research) per federal regulations. Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (**Error! Hyperlink reference not valid.**). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

[Do not type here]

7.1 Study Design

Describe and explain the study design.

This is a randomized clinical trial with two groups: control and stimulation. Participants will be randomly assigned to a NMES (active) treatment or control group in a 1:1 ratio. No stratification factors will be considered in the randomization process based on covariates such as gender, activity, and age. In the stimulation group, subjects will receive standard rehabilitation and NMES will be applied to calf muscles 6 weeks after repair surgery. The pad placement and stimulation parameters will updated in a weekly basis for the stimulation group. The control group will follow standard rehabilitation and will not receive NMES. For both groups, ultrasound evaluation will be performed at week 6 and 12 weeks after surgery. The primary outcome (heel-rise) will be measured at week 12 after repair. Other outcomes (activity level, pain) will be measured daily for the first 6 weeks after repair.

7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

All participants participating will receive a standard rehabilitation protocol. All participants will be randomly assigned to NMES or control (standard of care) for the first 6 weeks after surgery. For the randomization process, a master list with patient codes will prepopulated with randomly assigned treatments (NMES vs control). As recruitment is performed, patients will be assigned a code with the corresponding intervention. The randomization will be performed at a 1:1 ratio between control and stimulation group. The research teams conducting the rehabilitation protocol at the Hershey Medical Center will instruct and evaluate all participants on how they place the electrodes, operate the NMES device (intensity combo II. This is a commercially available, FDA-approved device), and select the parameters to be used (Table 2 and Figure 2). The intensity will be set to the maximum comfortable intensity by the patient. Additionally, the research team will ensure the participants perform the procedure correctly at each weekly visit. The NMES device has an adherence meter to evaluate adherence to the protocol. Self-applied NMES intervention has been successfully used in several studies targeting muscle weakness after major knee surgeries [53], [54].

Table 2. Proposed NMES protocol

Week	Pad Placement	Time (min) x times per day
1	I, II, III	10 x 1
2-3	I, II, III	10 x 2
4-6	IV	20 x 2

<u>*Ultrasound evaluation:*</u> *Cross-sectional area of the Gastrocnemius muscle and the Soleus muscle will be obtained in axial and Sagittal planes(both legs). The fat thickness and the skin thickness are being measured in both healthy and injured leg.* Achilles tendon length will be measured using panoramic imaging sliding the probe from the calcaneus to the medial gastrocnemius. Cross-sectional area at the point of injury will be evaluated using regular ultrasound imaging. Elastic properties of the Achilles tendon will be measured using shear wave elastography. Shear wave elastography is a method available in some clinical ultrasound scanners that consists on generating shear waves in the tissue by sending high intensity ultrasound pulses. The speed of wave propagation is recorded by the scanner. The mechanical properties of the tissues are estimated from the values of the wave speed. For the area of lateral and medial gastrocnemius, the ultrasound probe is placed distally at a point 25% of tibial length from the medial tibial plateau. For the soleus, the ultrasound probe is placed proximally at a point 30% of tibial length from the medial malleolus. Extended field of view images are taken in short axis [55]. This ultrasound evaluation is not part of the standard of care for Achilles tendon rupture. The ultrasound evaluation will take place at the radiology suite at 30 hope drive (Hershey), the Biomechanics and imaging lab at 342 Leonhard Building (State College), or Motion Analysis Lab (University of Delaware).

<u>*Self-reported diary and outcomes*</u>: To evaluate frequency of loading, from the day after surgery, participants will complete a diary (paper or electronic survey via REDCAP) on estimated daily weightbearing load, number of steps/days with a pedometer placed at the hip, and pain on a visual analogue scale (VAS). Although standard of care prescribes no weight-bearing during the first two weeks after repair, patients are active during that period of time. The level of activity (steps), even though does not involve the use of the injured limb, can help explain potential differences in self-reported outcomes, especially kinesiophobia scores. These measurements are not part of the standard of care. Self-reported outcomes will be also collected at weeks 6 and 12: the Achilles tendon Total Rupture Score (ATRS) [56], the Physical Activity Scale (PAS) [57], the Foot and Ankle Outcome Score (FAOS) Quality of Life subscale [58], and the Tampa Scale of Kinesiophobia (TSK) [59], [60]. Patient reported outcomes (ATRS, PAS and FAOS) are part of the standard of care for Achilles tendon rupture.

Single heel-rise tests: The ability of performing a single heel-rise will be evaluated at week 12. The participants will stand on a flat box with the ankle in neutral position and will be asked to perform a single heel-rise. The participants will be classified as being able to perform a one-legged heel-rise if they were able to lift the heel at least 2 cm once while keeping the knee straight [60]. MuscleLab® (Ergotest Technology, Oslo, Norway) measurement system will be used for the evaluations as previously described in our previous study [29]. This will be performed in the physical therapy clinic at 30 Hope Drive. This test is not part of the standard of care for Achilles tendon rupture.

Table 3. Study Procedures for Stimulation and control groups

Week	Procedure
1	Consenting, Randomization, Distribution of diary and activity monitor, Demonstration of NMES (stimulation group only), (in-person visit)
2, 4	Adjustment of NMES (stimulation group only), collection of steps, and diary data. (Visit 2 can be done virtually with a video call, visit four should be done in person.)
6	Ultrasound Imaging, Questionnaires (ATRS, PAS, FAOS, TSK), collection of steps and diary data, Discontinue use of NMES (stimulation group only). (In-person visit)
12	Ultrasound Imaging, Heel-rise test, Questionnaires (ATRS, PAS, FAOS, TSK) (In person visit)

7.2.1 Visit 1 (Week 1).

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

This visit will be scheduled in first week after the surgery. The research team or clinician of the research team will demonstrate the NMES procedure to the participants. The research team will verify that the procedure is applied properly and follows with the protocol. An explanation of the information needed for the diary will also be provided. Participants will take the NMES device (for the treatment group)and the diary home and perform the procedure by themselves. Randomization will be communicated to the patient at this visit. Participants are provided the pedometer at this visit, and instructions on how to use it. The study team will not collect AEs at this visit. The total duration of this visit is estimated to be 45 minutes.

7.2.2 Visit 2 (week 2)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

This will occur during week 2 after surgery (with a window of 3 working days before or after depending on the patient schedule). Research team will evaluate healing progress of the participant and will report any AE. Research team will collect the diary and pedometer data. Research team will explain and demonstrate the new pad placement for the electrodes and the new settings of the electrical stimulation device (intervention group only). This should take about 10 minutes. This visit can be done via video call.

7.2.3 Visit 3 (week 4)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

This will occur week 4 after surgery(with a window of 3 working days before or after depending on the patient schedule). Research team will evaluate healing progress of the participant and will report any AE. Research team will collect the diary and pedometer data. Research team will explain and demonstrate the new pad placement for the electrodes and the new settings of the electrical stimulation device (treatment group only). This should take about 10 minutes. The Pedometer and the NMES device (if applicable) of the participant will received and changes to the new device. This procedure will be done to check the memory of the devices with the values entered in the REDCap.)

7.2.4 Visit 4 (week 6)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

This will occur at week 6 after surgery (with a window of 7 working days after surgery depending on the patient schedule). Research team will evaluate healing progress of the participant and will report any AE. Research team will collect the diary and pedometer data. Participants will be instructed to discontinue the use of the NMES device. Subjects will fill out questionnaires and receive final an ultrasound imaging section. Participants must return both the NMES device and pedometer (activity monitor) at this visit. This should take about 1 hour.

7.2.5 Visit 5 (week 12)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

This will occur at a visit at week 12 after surgery (with a window of 3 working days before or after depending on the patient schedule). This is NOT part of the standard of care. Research team will evaluate healing progress of the participant and will report any AE. Research team will perform a heel-rise test. Subjects will fill out questionnaires and receive final an ultrasound imaging section. This should take about 1 hour.

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

12 Weeks.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use

and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

Medical Device to be used in the Proposed Study (Provided by Manufacturer): The InTENSity Select Combo II stimulator is a portable electrotherapy device featuring four therapeutic modes: Transcutaneous Electrical Nerve Stimulator (TENS), Neuromuscular Electrical Stimulation (NMES), Interferential (IF) and Russian which are used for pain relief. The stimulator sends gentle electrical current to underlying nerves and muscle group via electrodes applied on the skin. The parameters of device are controlled by the buttons on the front panel. The intensity level is adjustable according to the needs of patients.

Approval status with the Food and Drug Administration (FDA): 510(k) approved

Indications for NMES (provided by manufacturer)
Select Combo II Stimulator may be used for the following conditions:
1) Symptomatic relief of chronic intractable pain.
2) Post traumatic pain.
3) Post surgical pain.
4) Relaxation of muscle spasm.
5) Increase of blood flow circulation.
6) Prevention of disuse atrophy.
7) Muscle re-education.
8) Maintaining or increasing range of motion.
9) Immediate post-surgical stimulation of lower leg muscles to prevent venous thrombosis.

Proposed use of the device
This device will be used within the indications provided by the manufacturer. Specifically, 'prevention or retardation of disuse atrophy' of calf muscles after Achilles tendon repair surgery. However, although this device is intended to prevent atrophy, NMES has not been applied as part of the rehabilitation strategy for patients undergoing Achilles tendon repair surgery. Therefore, this study plans to evaluate the effect of applying NMES to calf muscles on functional outcomes used to evaluate recovery from Achilles tendon rupture. In the NMES will be applied in addition to standard therapy.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

The stimulation group will follow the NMES protocol proposed in table 2 and Figure 2. The intensity will range between 15 and 30 mA.

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

A master list with patient codes will be prepopulated with randomly assigned treatments. As recruitment is performed, patients will be assigned a code with the corresponding intervention. The randomization will be performed at a 1:1 ratio between control and stimulation group.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

The stimulation device provides an activity log that will be used to monitor compliance. Additionally, entries to the pain and activity diary will be also use to evaluate compliance.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

N/A

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

The device will be purchased from manufacturer. The device in case that includes cables, pads, batteries and a user manual.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

Device cases will be labeled with “Do not use if you are not part of the Neuromuscular Electrical Stimulation for Achilles Tendon Rupture Rehabilitation Study”

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

The research team or clinician of the research team will demonstrate the NMES procedure to the participants. The research team will verify that the procedure is applied properly and corrects any problems with the protocol.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

At the week-6 visit, patients will return the stimulation device to a member of the study team.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Patients can follow standard rehabilitation while using the stimulation device.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

50 Participants will be enrolled.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

Two independent sample proportion comparison test was to compute the sample size using G* Power 3.1. A power analysis was performed based on the proportion of participants able to perform a heel rise at week 12, which is a strong predictor of long-term outcomes. With current rehabilitation strategies, 50% of participants are able to perform a single heel-rise at week 12. A clinically-significant improvement that would justify the application of the proposed treatment would be that 85% of participants would perform a heel-rise. A minimum of 22 subjects should be recruited in each group to achieve 80% power, with 5% significant level, equal allocation, to detect a significant difference between the two groups. Assuming an attrition rate similar to our previous studies of 10%, the total number of subjects in the NMES group should be 25.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

We will recruit 25 participants to participate in the NMES intervention and 25 for standard rehabilitation (control). Summary statistics for variables of interest including recruitment, retention, adherence, and reported pain will be calculated. To test the difference between groups (NMES and control), we will quantify the odds ratio and the 95% confidence in of performing a single heel-rise test. If the bottom end of the confidence interval is higher than 1.0, the improvement will be significant. Chi-square goodness of fit will be used to study the associations between groups and covariates such as gender, activity, and age. Cochran-Mantel-Haenszel test will be used to evaluate the consistency of such associations.
Protocol deviations, such as missing visits, or lost to follow up (within the 10% already considered in the power analysis) will have a negligible effect on the statistical analysis since the proposed analysis can have unbalanced groups. The planned interim safety analyses will quantify the odds ratio between adverse events in the intervention group and standard of care. If the bottom end of the confidence interval is higher than 1.0, the incidence of AEs in the intervention group will be significant higher than that of standard care.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

The research team will monitor the recovery of the participant during standard-of-care visits and determine the occurrence of possible adverse related to Achilles tendon healing (re-rupture, deep vein thrombosis, deep and superficial infection) or the use of NMES (skin irritation and excessive pain. Research team will capture and report all AEs at every visit. These AEs will be evaluated by a physician study team member (Dr. Bader) for their relatedness and severity. If the team member physician (Dr. Bader) prescribes a modification in the rehabilitation protocol or additional interventions (surgery), the patient will be removed from the study. Cumulative data will be evaluated every 2 months to determine if incidence of adverse events is higher than the normal (standard of care). The normal (standard of care) incidence of re-ruptures is 5% [4], [25], deep vein thrombosis is 48% [61], infection 2.8% [62], skin irritation 33% [63].

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Achilles tendon healing:
- re-rupture
- deep vein thrombosis
- deep and superficial infection

NMES:
- skin irritation
- excessive pain

Benefits/efficacy:
- self-reported outcomes (questionnaires)
- daily step count
- ability to perform a heel-rise

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Data about tendon healing will be taken during study visits.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Data about tendon healing will be collected at 6, and 12 weeks. Pain, weight bearing, and step count will be recorded daily for the first 6 weeks. Heel-rise evaluation will be performed at week 12.

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The treating research team will monitor the subject's healing progress. If concerns are found, participants will be asked to see out team physician (Dr. Bader) who will determine the proper course of action, i.e., removal from the study, modification of the rehab protocol and/or additional interventions. A NIAMS-appointed Safety Officer (SO) will review the study data on a routine basis.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Cumulative data will be reviewed every two months.

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

For testing the difference groups and standard treatment, we will quantify the odds ratio and the 95% confidence of AEs or SAEs. If the bottom end of the confidence interval is higher than 1.0, the improvement will be significant.

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

If the odds ratio of AEs related to the intervention and/or SAEs of the intervention reaches statistical significant levels compared to standard treatment, the study will be suspended immediately.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

Risk of Randomization: You will be assigned to a treatment program by chance. The treatment you receive may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.

Heel-rise test: The heel-rise testing may cause local tendon pain. The subjects will be informed that if they have a pain level above a 5/10 they should inform the evaluator, stop the test, and avoid strong physical activity for 1 or 2 days.

NMES usage: The device used for this test is FDA approved. There is a minimal risk of infection. Discomfort during and muscle soreness after usage lasting a few days after the test may be experienced. Skin irritation caused by the adhesive pads may also occur. Excessive pain might occur during stimulation, even at the recommended settings. Subjects will be instructed to gradually increase the stimulation intensity up to the recommended level by PT. Subjects will be instructed to contact the research team if the excessive pain occurs at or below the recommended intensity.

Tendon healing: Re-injury of the tendon is also a potential risk. The rate of tendon re-rupture in standard therapy is estimated between 2% and 5% [64]. Gapping or non-healing of the tendon have also been observed in regular therapy. These adverse events may be observed in the participants participating in the study. Statistical analysis will be performed to determine if the risk of these adverse events is higher in the intervention group compared to standard therapy.

Additional Risks

Loss of confidentiality is another risk of participating in this study. To minimize this risk. Identifiable information will be kept locked in the lab. Only the PI and the research personal participating in the study will have access of the key. Identifiable information will be destroyed according to the plan in section 9.0.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 13.0.

Participants in the active stimulation arm may see less atrophy of calf muscles, better biomechanical properties of the healing tendon, and better function of the lower leg

11.2 Potential Benefits to Others

Include benefits to society or others.

The results of this research may benefit future patients undergoing tendon repair

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Incidental findings from ultrasound imaging or research team evaluations will be communicated to the participant and to the treating physician (surgeon).

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Subjects will be compensated $100/visit for the visits in weeks 2, 4, 6 and 12. A total compensation of up to $400 for their time and effort in participating in the study.
Participants will be compensated using the Greenphire Clincard.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

No additional costs to the participant are expected.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is

available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Recruitment will happen at the bone and joint clinic (Hershey and State College). Ultrasound imaging will occur at 30 Hope Drive, Hershey or the Biomechanics and Imaging Lab at 342 Leonhard, State College.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

An i2b2 cohort assessment was conducted utilizing data within the Hershey Medical Center system. 45 unique individuals who meet the inclusion criteria above, from 01/01/2018 to 01/01/2019, were identified. It is expected that similar number will be available during the duration of the study.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

The PI (Cortes) will devote 25% of his time to this study.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Resources of Penn State Hershey Medical Center are available

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

Training of therapists and participants on applying the NMES protocol
NMES applied at home by the participants themselves are common clinical practice. Research team are trained to provide and monitor such interventions. Typically, research teams demonstrate the procedure to the participants, participants will perform the procedure by themselves, and the research team verifies that the procedure is applied properly and corrects any problems with the protocol. The research team will verify and adjust the protocol during subsequent visits scheduled as part of regular physical therapy visit.

Ultrasound Imaging.
Dr. Cortes and Dr. French will agree on the protocols for ultrasound data collection according to the stablished protocols that have been used in previous studies [65]–[70].

Other data collection instruments
Members of the team will be will be trained on using REDCap which will be used to record other data collection instruments such as questionnaires and to store data from imaging session and functional tests.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

[Type protocol text here or indicate as not applicable]

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer participants, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

University of Delaware

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Dr. Cortes and Dr. Silbernagel will have a monthly zoom meeting during the course of the study. Otherwise, issues requiring more immediate attention will be communicated through email or phone calls.

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

The data collection and submission will be done through RedCap. The same protocol will be used for both locations for a seamless data flow between sites.

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Clinicians collaborating in the study will identify patients at the moment of diagnosis with a complete Achilles rupture and undergoing an Achilles repair surgery at the sports medicine clinic. Clinicians will hand out the study flier and briefly mention to the patient that they may be eligible for a research study. The flier will include a QR code that will direct patients to a YouTube video were more information about the study is provided. If the participant is interested, the PI and/or a member of the team will provide an electronic copy the informed consent for the patient to read. At the post-surgery appointment, a member of the team will discuss any details of study with the participant and will answer any questions they may have. Then the screening questions will be asked, and participants will sign the informed consent if eligible to participate.

Participants will be randomly assigned to a NMES treatment or control group in a 1:1 ratio. The Statistician will be responsible for generating a master list for each site with patient codes will prepopulated with randomly assigned treatments (NMES vs control). As recruitment is performed, patients will be assigned a code with the corresponding intervention. The randomization will be performed at a 1:1 ratio between control and stimulation group.

Method:
1. The Statistician will generate one mutual master list (for State College and for the University of Delaware).
2. The master list will be shared with the team members in charge of recruitment through REDCap.
3. Once a subject is recruited (screened and consented), the next available code from the list will be assigned.
4. The patient will be then notified of the type of treatment they will get.

The master list will be stored and available in REDCap.

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Dr. Silbernagel will report AEs, SAEs, Ups and protocol deviations to IRB and Dr. Cortes as soon as feasible. Reports to the SO and the NIAMS will be performed as outlined in section 18.

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Kelly Nye, Data Management Specialist, Department of Public Health Sciences, will perform audits to ensure data collection instruments and procedures are performed according to the good clinical practice guidelines.

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

In the response, incorporate the following as written:
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

Research subjects will be routinely evaluated by research team (part of the study team) during visits of the standard rehabilitation protocol.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention
- The test finding is considered an adverse event by the investigator.

18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study device(s)", the adverse event will be classified as associated with the use of the study device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Not applicable

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Not applicable

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Reporting AEs, SAEs and UPs to the NIAMS and the SO

- AEs will be reported in aggregate in the biannual report to the safety officer.
- The PIs will report SAEs to IRB, the Safety Officer and the NIAMS, through the NIAMS Executive Secretary, within 48 hours of becoming known by the PI.
- The PI will notify all Ups to the PSU IRB, the SO, and the NIAMS within 48 hours of the initial notification.

- Protocol deviations impacting participant safety should be reported to the NIAMS and the SO (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event; all other deviations that do not impact participant safety should be reported as part of the routine DSM report

18.7 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

Not applicable

18.8 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

The study will be interrupted if AEs (re-rupture, deep venous thrombosis, infections, and skin irritation) occur at a rate higher than that reported for standard of care.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (**Error! Hyperlink reference not valid.**).

Describe how you will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

The research team will collaborate with the Department of Public Health Sciences (DPHS), within Penn State College of Medicine (PSCOM), who will serve as the data monitoring entity for this clinical trial.

Once the study protocol is approved for implementation, the DPHS will assign a Data Monitor to the study. The main responsibility of the Data Monitor will be to oversee progress of the clinical trial and ensure that the study is conducted and data are handled in compliance with the protocol, International Council for Harmonization/Good Clinical Practice requirements (ICH/GCP), and applicable state, local and federal regulatory requirements. Specifically, the Data Monitor will be responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. The Data Monitor will communicate directly with the PI and Research Team and will keep written records of all visits and communications (e.g., calls, emails, and letters) to the research team.

19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (**Error! Hyperlink reference not valid.**).

Indicate the process for identifying, recording and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member's role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The research team in the study team will evaluate healing of the tendon and report any AE to the study team. These AEs will be evaluated by a physician study team member (Dr. Bader) for their relatedness and severity, will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs. The PI will notify the IRB, the NIAMS and SO of all applicable AEs as appropriate.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, the NIAMS and the SO of all Unanticipated Problems/SAE's.

Our study will utilize a Data Monitor. The Monitor will confirm that the AEs are correctly entered into the case report forms. The monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Identifiable data include: Informed consent, master list with codes, contact information. De-identified data include: ultrasound images, questionnaires, pedometer data, heel-rise tests, and pain data. No specimens are collected in this study.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Study parameters will be stored in RedCap servers. De-identified raw data will be stored in a secured, password-protected PSU cloud system (OneDrive)

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

Identifiable data will be retained for 3 years after the completion of the study. De-identified research data may be retained indefinitely.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

IRB authorized team members will have access to RedCap and OneDrive.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

De-identified (statistical summaries) of the data will be released in the form of academic publication in conferences and scientific journals. De-identified data will also be release upon written request.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not Applicable

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

[1] A. A. Suchak, G. Bostick, D. Reid, S. Blitz, and N. Jomha, “The incidence of Achilles tendon ruptures in Edmonton,

Canada.," *Foot ankle Int.*, vol. 26, no. 11, pp. 932–6, Nov. 2005.

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[3] D. P. Gwynne-Jones, M. Sims, and D. Handcock, "Epidemiology and outcomes of acute Achilles tendon rupture with operative or nonoperative treatment using an identical functional bracing protocol.," *Foot ankle Int.*, vol. 32, no. 4, pp. 337–43, Apr. 2011.

[4] I. Lantto, J. Heikkinen, T. Flinkkilä, P. Ohtonen, and J. Leppilahti, "Epidemiology of Achilles tendon ruptures: increasing incidence over a 33-year period.," *Scand. J. Med. Sci. Sports*, vol. 25, no. 1, pp. e133-8, Feb. 2015.

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[6] N. Maffulli, S. W. Waterston, J. Squair, J. Reaper, and A. S. Douglas, "Changing incidence of Achilles tendon rupture in Scotland: a 15-year study.," *Clin. J. Sport Med.*, vol. 9, no. 3, pp. 157–60, Jul. 1999.

[7] J. A. Zellers, M. R. Carmont, and K. Grävare Silbernagel, "Return to play post-Achilles tendon rupture: a systematic review and meta-analysis of rate and measures of return to play," *Br. J. Sports Med.*, vol. 50, no. 21, pp. 1325–1332, Nov. 2016.

[8] A. Brorsson, R. W. Willy, R. Tranberg, and K. Grävare Silbernagel, "Heel-Rise Height Deficit 1 Year After Achilles Tendon Rupture Relates to Changes in Ankle Biomechanics 6 Years After Injury," *Am. J. Sports Med.*, vol. 45, no. 13, pp. 3060–3068, Nov. 2017.

[9] A. Brorsson, K. Grävare Silbernagel, N. Olsson, and K. Nilsson Helander, "Calf Muscle Performance Deficits Remain 7 Years After an Achilles Tendon Rupture," *Am. J. Sports Med.*, vol. 46, no. 2, pp. 470–477, Feb. 2018.

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[11] J. Heikkinen *et al.*, "Augmented Compared with Nonaugmented Surgical Repair After Total Achilles Rupture: Results of a Prospective Randomized Trial with Thirteen or More Years of Follow-up.," *J. Bone Joint Surg. Am.*, vol. 98, no. 2, pp. 85–92, Jan. 2016.

[12] S. G. Parekh, W. H. Wray, O. Brimmo, B. J. Sennett, and K. L. Wapner, "Epidemiology and Outcomes of Achilles Tendon Ruptures in the National Football League," *Foot Ankle Spec.*, vol. 2, no. 6, pp. 283–286, Dec. 2009.

[13] N. H. Amin, A. B. Old, L. P. Tabb, R. Garg, N. Toossi, and D. L. Cerynik, "Performance Outcomes After Repair of Complete Achilles Tendon Ruptures in National Basketball Association Players," *Am. J. Sports Med.*, vol. 41, no. 8, pp. 1864–1868, Aug. 2013.

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