The KNEEhabilitation Study: Improving Disability in Individuals with Knee Osteoarthritis

NCT number: NCT02634814

Document Date: September 22, 2015

The KNEEhabilitation Study: Improving Disability in Individuals with Knee Osteoarthritis

Manual of Operating Procedures (MOOP)

Version 1
Date 9/22/2015

ACRONYM GLOSSARY

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to capture all protocol-required information for a study.

Code of Federal Regulations (CFR)- is an annual codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government.

Clinical Research or Study Coordinator (CRC) – An individual that handles the administrative and day-to-day responsibilities of a clinical trial and acts as a liaison for the clinical site. This person may collect the data or review it before it is entered into a study database.

Conflict of Interest (COI) – A conflict of interest occurs when individuals involved with the conduct, reporting, oversight, or review of research also have financial or other interests, from which they can benefit, depending on the results of the research.

Data and Safety Monitoring Board (DSMB) –A group of individuals independent of the study investigators that is appointed by the NIAMS to monitor participant safety and data quality, and to assess clinical trial progress.

Food and Drug Administration (FDA) – An agency within the U.S. Department of Health and Human Services (DHHS) responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

Good Clinical Practice (GCP) – A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – The first comprehensive Federal protection for the privacy of personal health information. The Privacy Rule regulates the way certain health care groups, organizations, or businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI).

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – An independent body consisting of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other

things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and material to be used to obtaining and documenting informed consent of the trial participant.

Investigational New Drug Application (IND) – An IND is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application (21 CFR 312).

Manual of Operating Procedures (MOOP)/Manual of Procedures (MOP) – A "cook book" that translates the protocol into a set of operational procedures to guide study conduct. A MOOP/MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

Not Applicable (NA)- When recording data on a study form, if the information is not applicable, then the acronym NA should be used to fill out the field.

Not Available (NAV)- When recording data on a study form, if the information is not available, then the acronym NAV should be used to fill out the field.

Not Done (ND)- When recording data on a study form, if the evaluation required for a field is not done, then the acronym ND should be used to fill out the field..

Principal Investigator (PI)- The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial and administrative policies and regulations associated with the award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the sponsored research award rests with the Principal Investigator.

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.).

Safety Monitoring Plan (SMP) – A plan that outlines the oversight of a clinical trial.

Safety Officer (SO)- The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single-site clinical studies. The Safety Officer advises the NIAMS Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Serious Adverse Event (SAE) – Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization

- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Unknown (UNK)- When recording data on a study form, if the information is unknown, then the acronym UNK should be used to fill out the field.

1.0 INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH) must ensure compliance with Federal laws and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. In preparing to implement a study, the Principal Investigator must be aware of the terms of award outlined in their Notice of Grant Award with respect to required reporting, data and safety monitoring oversight, and Institutional Review Board (IRB) approval.

The purpose of this document is to assist investigators of current study in understanding the guidelines for the current clinical trial in the preparation of a study Manual of Operating Procedures (MOOP) by providing them with a guideline. A single-site study is defined as involving only one clinic (i.e., performance site) and a center (e.g., data coordinating center) to receive and process data. The role of the MOOP is to facilitate consistency in study implementation and data collection across study visits and participants. Use of the MOOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

2.0 Manual of Operating Procedures Overview

Once a grant application is funded, the investigator transforms it into a study protocol, which then must be approved by the Institutional Review Board (IRB).

A MOOP is useful for clinical interventional trials (e.g., drug, surgery, behavioral, device, etc.). The MOOP transforms the study protocol into a handbook and provides the operational detail to run the study consistently. The MOOP should serve as the study manual to help study staff in following study procedures. The study team (investigators, coordinators, statisticians, etc.) develops the MOOP and submits it to the NIAMS for approval before the study can commence.

The MOOP development requires that the final protocol, study forms (often called case report forms (CRFs), Investigator Brochure (IB) or Device Manual, and informed consent forms be completed. The timeline for development of study materials must be planned for and typically takes several months.

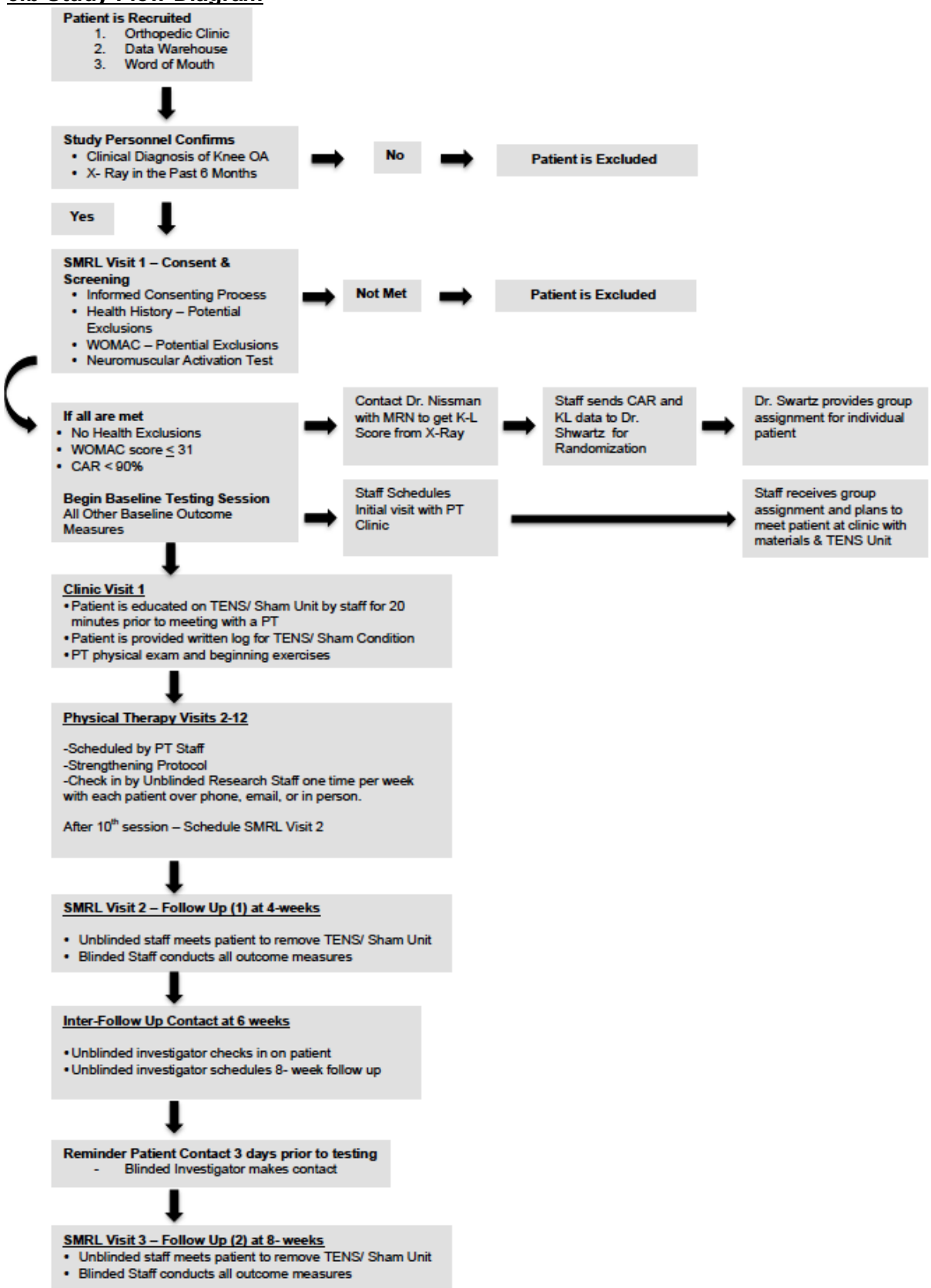
The MOOP is a dynamic document that will be updated throughout the study to reflect any protocol or informed consent amendments as well as the refinement of the CRFs and study procedures. The MOOP should be maintained in a format that allows it to be easily referenced and updated such as in a three-hole binder. For ease of organization, it is recommended that the MOOP be subdivided into sections separated by dividers. It is helpful to have each page of the MOOP contain the version number and date. Revised pages with an updated version number and associated date should replace the original page(s) in the MOOP. All previous versions should be archived. Any revisions to the MOOP should be submitted to the NIAMS with tracked changes for easy reference before finalization.

3.0 MOOP Contents and Organization

3.a Study Protocol

See Appendix A.

3.b Study Flow Diagram



3.c Staff Roster and Responsibilities

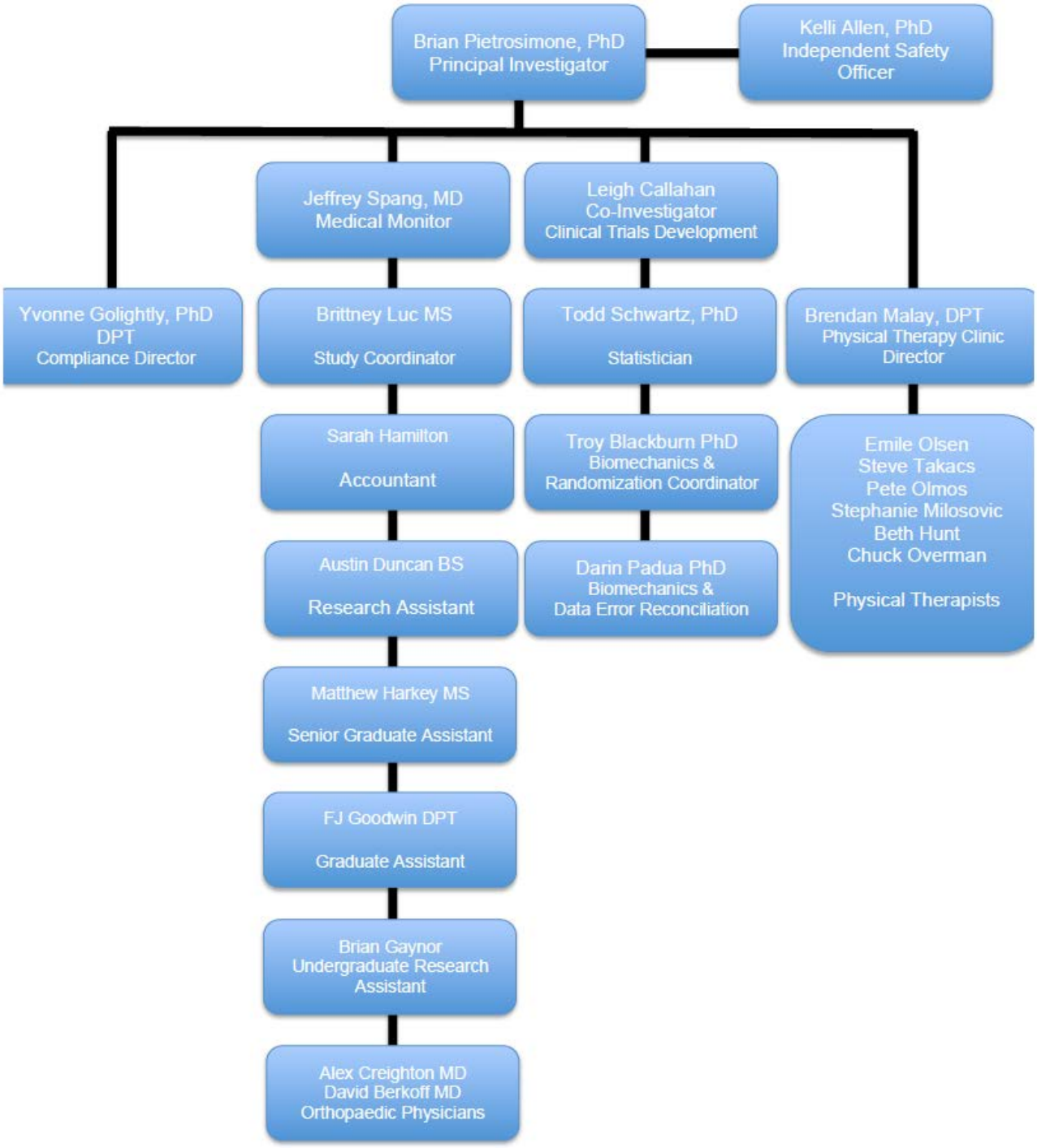
3.c Staff Roster and Responsibilities

Staff Roster, Roles and Contact Information			
Personnel	**Role**	**Email**	**Phone**
Key Personnel			
Brian Pietrosimone	Principal Investigator	brian@unc.edu	
Brittney Luc	Study Coordinator		
Jeffrey Spang	Medical Monitor		
Yvonne Golightly	Compliance Director		
Daniel Nissman	Radiologist		
Todd Schwartz	Statistician		
Sarah Hamilton	Accountant		
Co-Investigators			
Leigh Callahan	Clinical Trials Development		
Troy Blackburn	Biomechanics & Randomization Coordinator		
Darin Padua	Biomechanics		
Data Collection			
Matthew Harkey	Senior Graduate Assistant		
FJ Goodwin	Graduate Assistant		
Austin Duncan	Research Assistant		
Brian Gaynor	Undergraduate Research Assistant		
Orthopaedics			
Kaitlin Healy	Othopaedic Research Contact		
David Berkoff	Recruitment of Patients		
Alex Creighton	Recruitment of Patients		
Physical Therapy			
Brendan Malay	Physical Therapy Clinic Director		
Emile Olsen	Physical Therapist	emile.olsen@unchealth.unc.edu	
Steve Takacs	Physical Therapist	steven.takacs@unchealth.unc.edu	
Pete Olmos	Physical Therapist	peter.olmos@unchealth.unc.edu	
Stephanie Milosovic	Physical Therapist	Stephanie.milosovic@unchealth.unc.edu	
Beth Hunt	Physical Therapy Aid	Elisabeth.hunt@unchealth.unc.edu	
Chuck Overman	Physical Therapy Aid	Charles.overman@unchealth.unc.edu	
Data and Safety Monitoring			
Kelli Allen	Safety Officer		

Responsibilities		
Responsibility	Involved Personnel	Description
Development & Maintenance of all Study Materials	Brian Pietrosimone Brittney Luc Austin Duncan	Personnel in this section will create and maintain the documents that comprise the MOOP, as well as all regulatory and source documentation
Reporting & Monitoring of All Adverse Events	Brian Pietrosimone Jeffrey Spang Kelli Allen	All adverse events will be reported to the PI. The PI will discuss circumstances of the adverse events with the medical monitor and report all adverse events to the safety officer as outlined in section 3.k.
Recruitment	Brian Pietrosimone Brittney Luc Austin Duncan Jeffrey Spang David Berkoff Alex Creighton	These personnel will be in charge of recruiting directly from the orthopaedic physicians, as well as from the Carolina Health Warehouse.
Informed Consent & Scheduling	Brian Pietrosimone Brittney Luc Austin Duncan	These personnel will be in charge of consenting each patient, explaining the study to each participant and acquiring written informed consent from each participant. Brittney Luc and Austin Duncan will schedule patients for: 1) screening/baseline sessions, 2) the first physical therapy session (all other physical therapy sessions will be scheduled by the the clinic staff), 3) follow-up test one, and 4) follow-up test two.
Screening	Brittney Luc Austin Duncan Matthew Harkey FJ Goodwin	Screening will consist of central activation ratio and WOMAC score testing.
Collection of Data (Baseline and Follow-up Measures)	Matthew Harkey FJ Goodwin	These follow-up tests will be conducted by only the blinded investigators at baseline, follow-up one (4 weeks) and follow-up two (8-weeks).
Education on TENS unit and Sham TENS with Patients (Available to answer questions throughout study)	Brian Pietrosimone Brittney Luc Austin Duncan	These investigators will be unblinded and will be in charge of teaching patients how to utilize the active TENS and Sham TENS units immediately prior to the first physical therapy session. Additionally, phone numbers for Brittney Luc and Brian Pietrosimone will be provided if further assistance is needed.
Delivery of Physical Therapy Intervention	Brendan Malay Emile Olsen Pete Olmos Stephanie Milosovic Beth Hunt Chuck Overman	Patients will be scheduled to work independently with one of these clinicians. All clinicians will conduct therapeutic exercises according to the guidelines provided in g.1 .
Study Compliance & Accountability	Yvonne Golightly	Dr. Golightly will evaluate study compliance for 1) randomization, follow-up testing, IRB Compliance, and compliance of treatment protocols as described in section 3.m
Randomization of Patients	Brittney Luc Troy Blackburn Todd Schwartz	The randomization scheme will be developed by Todd Schwartz and Brittney Luc will determine each patient's group from a sealed envelopes. Dr. Blackburn will be unblinded and in charge of the randomization lists.
Data Entry, Error Identification and Correction	Matthew Harkey FJ Goodwin Todd Schwartz	Matthew Harkey and FJ Goodwin will perform double data entry. Todd Schwartz will calculate means and standard deviations separately for all outcomes measures. Dr. Schwartz will determine were potential errors are found and Darin Padua (Blinded

		Investigator) will be consulted to determine the correct outcome measure.
Creation of Reports- Enrollment, adverse events, participant status	Brian Pietrosimone Brittney Luc	These reports will be compiled as needed.
Ensuring Compliance with Human Subjects Regulation	Brian Pietrosimone Yvonne Golightly Kelli Allen	Dr. Pietrosimone will be in charge of ensuring compliance, which will be greatly improved by Dr. Golightly's reports detailing compliance. Dr. Allen is the independent safety officer which whom Dr. Pietrosimone will report adverse events.
Submission of Regulatory IRB Documents	Brian Pietrosimone Brittney Luc	All regulatory information, modifications, annual renewels and adverse event forms will be prepared by Brittney Luc and will be reviewed and submitted by Dr. Pietrosimone.

3.c.1 Study Personnel Organization



3.d Participant Recruitment, Screening and Eligibility Criteria

This study will be conducted within the Department of Exercise and Sport Science, Department of Orthopaedics and the Thurston Arthritis Research Center at the University of North Carolina at Chapel Hill.

We will first identify patients from the Orthopaedic Clinic who have a radiographically confirmed diagnoses of knee OA (Kellgren-Lawrence between 2-4), based on physician exam or electronic medical records. Our study team will be present during clinic hours for Dr. Creighton, Dr. Spang and Dr. Berkoff. If a diagnosis of knee OA is confirmed in a patient by one of these physicians, our study team will talk with the patients explaining the broad goals of the research study and provide them with materials describing the research study. If an individual is interested in participating in the study they will be scheduled for a screening visit or be encouraged to call Brittney Luc or Austin Duncan for further scheduling in the Sports Medicine Research Laboratory.

Our study team will further identify patients who have no exclusionary diagnoses, also based on electronic medical records using the Carolina Data Warehouse. We will mail introductory letters to patients who meet these criteria, on behalf of their primary care provider. These letters will include basic information about the study, as well as a telephone number that patients may call if they do not wish to receive a follow-up telephone call. We are giving patients this option to opt into the study.

3.d.1 Participant Retention Plan

3.d.1 Participant Retention

All members of the research team will be responsible for participant retention. The following section details the procedures for participant retention which will be carried out by the Research Assistant, the Study Coordinator and the Principal Investigator throughout the entire duration of the study.

Role of the Research Assistant, Study Coordinator and the Principal Investigator

The Research Assistant, Study Coordinator and the Principal Investigator will be responsible for ensuring participant recruitment and retention through 1) informing the research team of appropriate recruiting and retention procedures 2) determining the success of current strategies to recruit and retain study participants, and 3) evaluating and improving participant recruitment and retention strategies throughout the duration of the study. The following major principles will be implemented throughout the study in order to maximize participant retention.

Enhancing Participants Understanding of the Study

During the initial meeting with a potential study participant the Research Assistant will be responsible for describing all aspects of the study in detail in order to ensure the participant completely understands the scope of the study and what will be required of each participant. The Research Assistant will provide the participant with a copy of the informed consent form, and will talk through each component with the participant. The participant will be able to ask any questions necessary in order to ensure the participant is informed about the purpose of the study and what he/she will be asked to complete. Additionally, study participants will be made aware they have an active role in the research study and are a valuable part of the research team. Throughout the course of the study all participants will have the opportunity to meet directly with the Research Assistant, Study Coordinator or Principal Investigator each week in order to ask any questions the participant may have.

Determining Participant Satisfaction

Each study participant will receive a telephone call during each week of the intervention from the Research Assistant, Study Coordinator or the Principal Investigator. Research Assistant, Study Coordinator or the Principal Investigator will call each study participant in order to check in and to schedule a time to meet the study participant at one of their scheduled physical therapy sessions. The primary purpose of the meeting is to allow each participant to talk directly with the Research Assistant, Study Coordinator or the Principal Investigator each week in order to address any questions or concerns the participant may have. During the meeting the study participant will be given a likert scale in order to rate their current level of satisfaction with the intervention and the likelihood of retaining future appointments. If an individual marks less than 85% for either satisfaction or likelihood to maintain future appointments the participant will receive additional phone calls from the Research Assistant, Study Coordinator or the Principal Investigator in order to keep the participant interested in the study, determine the cause of decreased satisfaction and implement a proactive strategy in order to improve participant satisfaction.

Proactive Plan for Retention

The Study Coordinator will be responsible for building participant relations and participant satisfaction throughout the entire duration of the study. The Study Coordinator will create a quarterly study newsletter that will be mailed to all participants who are enrolled in the study or have completed the study. The study newsletter will include information on the current status of the study and will be mailed to study participants at the end of December 2015, March 2016, June 2016, September 2016, December 2016, March 2017, September 2017 and December 2017. All study participants will receive a weekly telephone call from the Research Assistant, Study Coordinator or Principal Investigator to discuss how they are doing and to set up a time for an in person meeting at one of their weekly physical therapy visits. Upon completion of the first two weeks of the intervention, each participant will receive a card in the mail thanking them for their participation in the study. Upon completion of the 4-week Follow-Up Assessment each participant will receive a t-shirt for completing the intervention to provide incentive for returning for the 8-week Follow-Up Assessment.

Identifying Potential Problems

The Principal Investigator will be responsible for monitoring participant recruitment and retention throughout the duration of the research study. The Principal Investigator will assess recruitment rates and retention rates each month and determine any potential problems. The Principal Investigator will also determine key retention factors that should be emphasized in order to maximize participant retention throughout the duration of the study. In the event retention issues arise throughout the study the Principal Investigator will develop new intervention strategies to maximize participant retention and revise the MOOP as necessary.

Role of All Study Personnel

All members of the study team will be responsible for ensuring participant retention throughout the duration of the study. The Principal Investigator, Study Coordinator and Research Assistant will hold an initial meeting with all members of the research team in order to discuss participant recruitment and retention procedures, and will hold bi-monthly meetings in order to continue to inform the research team of recruitment and retention rates and to modify the recruitment and retention procedures if necessary. All members of the research team will be made aware that retention efforts begin with participant recruitment, and informed consent is an ongoing process throughout the entire duration of the study.

Recruitment
All members of the research team will be instructed on the procedures for recruitment of all study participants. Referring orthopaedic physicians will be instructed to inform their knee osteoarthritis patients about the study during their clinic visit. The Research Assistant will be present at the othropedic physician's clinic, and if the patient would like additional information about the study the physician will notify the Research Assistant to discuss the study with the potential participant in person. Additionally, the orthopaedic physicians will be provided with recruitment information each month in order to remind the physicians of their crucial role in the recruitment of study participants.

Retention
All members of the research team will be responsible for ensuring participant retention throughout the entire duration of the study. Bi-monthly meetings will be held with all members of the study team in order to address any potential issues with participant retention. Bi-monthly meetings will address 1) participant recruitment and retention, 2) patient satisfaction, and 3) any study issues needing to be resolved.

During each meeting all members of the research team will be reminded to address all study participants with congeniality, respectfulness and friendliness during each interaction with a participant or potential participant. Additionally, all members of the research team will be asked to ensure all questions from the study participants and family members of the study participants are completely answered throughout each interaction with study participants.

The results of all participant satisfaction data will be presented at each bi-monthly meeting. If participant satisfaction is below 85% new strategies for improving participant satisfaction will be discussed and implemented as necessary. Additionally, all members of the research team will have the opportunity to discuss any issues that may have arisen since the last meeting in order to revise retention strategies as necessary throughout the duration of the study.

3.e Participant Screening and Eligibility Criteria

3.e.1 Participant Screening
A study team member will then administer a screening questionnaire via telephone to further assess eligibility. We will obtain participants' verbal consent to ask this limited number of questions. If patients meet telephone screening criteria and are interested in participating, they will be asked to meet a study team member at the Sports Medicine Research Laboratory to complete the consent process.

Following administration of the consent and HIPAA authorization, we will first assess Function with the WOMAC Score and measure height and weight to determine BMI. Next we will complete a burst superimposition test in the involved limb to determine the level of voluntary activation or Central Activation Ratio (CAR). If they do not meet the criteria for WOMAC, BMI or CAR.

If patients are not overweight according to BMI criteria, or if they do not meet clinical criteria for knee OA (and also do not have radiographic evidence of hip or knee OA in at least one joint), they will be excluded from the study.

If participants have knee or hip replacement surgery, their active involvement in the study will end, as these surgeries would likely confound study outcomes including pain and physical function. Also, if female participants become pregnant, their active involvement in the study will end because weight gain would also

likely confound study results. As part of the telephone screening process, women will be excluded if they self-report being pregnant or planning to become pregnant. Women of child-bearing potential will be further tested for pregnancy via urine test at the time of enrollment. This will occur following informed consent. Participants will only be allowed to continue with other study activities once a negative pregnancy test is confirmed. We will consider women to be of child-bearing potential unless they report EITHER having a hysterectomy or ceasing menstruation for at least 2 years. Given the average age of patients with hip and knee OA, we anticipate there will be few instances requiring pregnancy testing. Enrolled women who have had a negative pregnancy test will be informed that they must notify the study team immediately if they become pregnant during their active involvement in the study.

We will aim to ensure that subject selection is equitable and all relevant demographic groups have access to study participation by contacting (via initial letter and telephone call) all patients who meet inclusion / exclusion criteria, regardless of demographic characteristics. We have also aimed to produce recruitment and intervention materials that are appropriate for individuals with low literacy or education levels. We will continue to recruit patients until we reach our sample size goal of N=90.

Screening questionnaire data will be entered directly into the study database via the software package Epi Info. We will have paper copies of screening questionnaires that may be used in cases of computer network failure. We anticipate this will be rare. However, if paper forms are needed, data will then be entered into Illume as soon as possible. Any paper copies that are used will be stored in the subject's individual study folders, which are kept in a locked file cabinet in a locked office in the neuromuscular Research Laboratory.

The list of potential study participants, based on medical record review, will be transferred into a secure computerized tracking database. Likewise, subject data for all subjects enrolled in the study will be entered into a secure computerized enrollment log. This data will be accessible only to study personnel needing access to fulfill their study related duties.

3.e.2 Screening Log

See Appendix

3.e.2 Eligibility Criteria

All participants must meet the following criteria:

- between the ages of 40 and 75 years old
- All knee OA participants must exhibit symptomatic knee OA, which we will define as a normalized, person based, Western Ontario and McMaster Universities Arthritis Index (WOMAC) function subscale score > 31(out of 100 points, indicating most dysfunction)
- radiographic evidence of tibiofemoral OA (2-4 on the Kellgren – Lawrence scale) 39
- neuromuscular activation deficits, defined as quadriceps neuromuscular activation of less than 90% in the involved leg.3

Potential participants meeting any of the following criteria (based on the electronic medical record or in laboratory screening) will be excluded if:

- Diagnosed with a cardiovascular condition restricting exercise
- Have had a corticosteroid or hyaluronic acid injection in the involved knee in the previous 6-months
- Have pacemaker
- Have a neurodegenerative condition
- Have rheumatoid arthritis

- Have cancer
- Have a neural sensory
- Have dysfunction over the knee
- Have a Body Mass Index (BMI) over 35
- Have a history of lower extremity orthopaedic surgery in the past year
- Have a history of a traumatic knee injury in the past 6 months
- Have any history of a total knee arthroplasty in either extremity
- Have a diagnosed, non-reconstructed knee ligament tear.
- Need an assistive device to walk
- Currently pregnant

3.f Informed Consent and HIPPA

3.f.1 Informed Consent Process

Once a potential subject meets the telephone screening criteria for eligibility, and is interested in participating, he/she will be asked to meet a study team member at the Sports Medicine Research Laboratory to begin the consenting process.

We will use a University of North Carolina Health System IRB approved consent form with included language that satisfies the HIPAA requirements and outlines the protection of health information utilized in the study.

Informed consent will be obtained by a study team member in the Sports Medicine Research Laboratory in a private space. The study team member will read the IRB approved consent form to the potential subject, and provide an opportunity for him/her to ask any questions that they may have about the research study. We anticipate this process to take approximately 20 minutes, but this time will not be limited should a subject have additional questions or concerns regarding the study. During this phase of the consent process, it will be stressed that the subject is not obligated to participate in the study, that participation is completely voluntary, and that he/she may withdrawal from the study at any time without penalty. Also, potential risks from participating in the study are outlined in the consent form, as are the measures taken to protect against study specific risks.

During explanation of the TENS device, the investigator will describe TENS as a stimulus that is felt as tingly to some people will others report no feeling or have a “sub-sensory response”.

Once the information in the consent from is fully reviewed and understood by the subject, he/she will be asked to decide at that time if they would like to voluntarily participate in the research study. If the subject does choose to participate in the study, both the subject and the study team member will sign and date the consent form. In addition, each page of the consent form must be initialed by the subject. Each enrolled participant will then receive a signed copy of their consent form to keep for their records.

If after reviewing the consent form, subjects are not sure they would like to participate in the study at this time, they may choose to consider the study further at home, and then contact the study team if they decide later that they would like to participate.

Subjects will only be included if they have capacity to give legally effective consent.

The original signed consent forms will be kept in each subject’s individual study folder. These folders will be stored in a locked file cabinet in a locked cabinet of the neuromuscular research laboratory.

3.f.2 Informed Consent Form

See Appendix B for Approved Consent form

3.f.3 HIPPA Authorization

The privacy and confidentiality of research participants are to be respected and protected at all times. This research study will comply with the HIPAA Privacy Rule as well as all other state, federal, and institutional regulations intended to protect the rights, safety, and welfare of human participants involved in research studies. We will attempt to minimize the collection, storage, and transmission of information containing patients' personal identifiers, and, whenever identifiers are necessary, protect against unauthorized access or disclosure. In addition, we will employ several rigorous procedures for protecting against risks to participant privacy and confidentiality of data. We will only collect and store information about study participants that is relevant to the research as outlined in the protocol. We will minimize the use of paper documents by entering the majority of study data directly into secure computer databases. All study databases will be password protected and only study team members whose job functions require access to these data will have permissions. Whenever possible, data will not be stored on laptop computers. Individual patient data will not be shared with individuals outside the study team, except as required by law and/or for regulatory purposes.

All study staff must regularly fulfill certification requirements in Human Subjects Protection training. Study personnel are also regularly trained in stringent computer and information security procedures. All electronic study data will be securely backed up on a nightly, monthly, and biannual schedule.

Research study records will be maintained for no less than 7 years following the completion of the study, after which time personal identifying information will be removed. Research information in a subject's medical record will be kept indefinitely.

3.g Study Intervention

Intervention Overview

The current study is a **Phase 1 clinical trial** that will have three randomized groups. All groups will receive the same supervised, standardized TE program at the UNC Meadowmont Physical Therapy Clinic. *TENS+TE* and *sham TENS+TE* patients will be instructed to utilize their device during all 12 physical therapy sessions as well as 8 hours per day when they are the most active for 4-weeks (28 days).[1] Twelve TE sessions over 4 weeks is the current standard of care for patients with knee OA at the UNC Meadowmont Physical Therapy Clinic. Additionally, previous data indicate strong effect sizes for neuromuscular improvements following a 12 session/ 4-week intervention. Patients included in this study will be treated by 1 of 4 physical therapists (PT) associated with this study during each session (see participating physical therapists listed below). Patients in all groups will receive TE for their involved leg 3 times per week for 4 weeks (12 sessions). The PTs will review each patient's medical history and physician instructions before starting TE. A PT will conduct a lower extremity physical assessment prior to beginning rehabilitation and following the 4-week intervention for clinical use. *The overall goals of the TE program are to increase lower extremity strength and function.* Progressive exercise will be similar to that previously reported by the PI. Procedural reliability of the intervention will be maximized using: 1) training sessions for the PTs to ensure all exercises are taught and progressed in the same manner, 2) tracking compliance of *TENS/ sham TENS+TE*, 3) biweekly review patient charts regarding exercises, and 4) biweekly evaluation of therapeutic exercise delivery on a subset of patients at random time points using a rubric. Lower extremity strengthening will be progressed through open and closed chain strengthening (see exercises in tables X-X). Range of motion limitations and soreness will be addressed or managed with stretching, manual therapy, and/or cryotherapy. All strengthening exercises will be systematically progressed, on an individual basis, using the daily adjustable progressive resistive exercise system. Functional exercises will be progressed according to the patients' ability and any reactive inflammation from TE.

The Experimental TENS Group (*TENS+TE*): Patients assigned to the TENS+TE group will receive a *Select System TENS unit (EMPI, Inc., St. Paul, MN),* self-adhesive electrodes and batteries upon admission into the clinical trial and allocation into the TENS +TE group. TENS+TE patients will meet with a member of the study team in a private room at the Proaxis clinic prior to the initial visit with the PT. Patients will be taught how to apply the electrodes on the knee joint and educated on how to operate the TENS unit.[1] An instruction manual will be provided to the patients for reference purposes explaining device operation and a reminder for how to escalate dosing parameters; these dosing parameters were successfully used in our pilot study.[1] Patients will be provided with the phone number of an unblinded member of study team to call with questions. The primary method of collecting TENS compliance will be using a digital memory chip built into the TENS units that records the length of time each participant uses the device. Patients will log the hours of daily use as a backup.

The Sham Group (*sham TENS+TE*): Sham TENS+TE patients will receive a *Select System TENS unit (EMPI, Inc., St. Paul, MN) specifically configured to cease TENS current output 20 seconds after the participants initiation*. For blinding purposes, patients will be told that they should feel a brief stimulation (~20 seconds) that will become "sub-sensory" in nature. In reality, the Sham TENS unit will emit *no current* after 20 seconds. The sham TENS unit will have a functioning display identical to the active TENS units indicting the sham output voltage. The instruction manual that the sham group receives will not have any dose escalating procedures.

The Comparison Group (*TE only*): The role of the comparison group is to provide data on how traditional TE affects the outcome measures. The TE only group will allow us to assess how the addition of TENS and sham TENS to traditional TE will augment the effects of traditional TE. The TE only group will receive exactly the same TE as the TENS+TE and the sham TENS+TE in order to specifically determine what changes are attributed to TE only and not the neuromuscular changes brought about by *TENS+TE* or *sham TENS+TE*.

Transcutaneous Electrical Nerve Stimulation (TENS)

The Empi Select TENS unit has 510k approval (K090922) for use in the management of "symptomatic relief and management of chronic, intractable pain and relief of pain associated with arthritis". The Empi TENS unit is a battery powered single –function device to provide simple modulated pulse therapy. We will be using the TENS unit in the same capacity in patients with knee osteoarthritis.

TENS and Sham TENS Therapies

An unblinded investigator will meet the study participant in a private treatment room in the Meadowmont Physical Therapy clinic 20-minute before the first therapeutic exercise session. Patients will be provided information about applying electrodes, charging batteries, increasing and maintaining the TENS. Study participants will be provided time to ask questions and business cards with the telephone numbers and email addresses for the unblinded study investigators. The TENS units will all come with a manual as well as a short "How to Work Your Empi TENS Unit" manual. The instructions will be slightly different for the Active TENS and Sham TENS units.

Knee-habilitation Study Guide – ACTIVE TENS

How to work your Empi TENS Unit

The Empi TENS unit is configured by the study team to output the proper TENS treatment to your knee. You will be responsible for this 4-step process:

1) Applying the TENS electrodes on your knee correctly
2) Ensuring that charged batteries are in the TENS units
3) Increasing the stimulus to the correct intensity
4) Maintaining a proper dose of TENS throughout the day

Applying the TENS Electrodes
Before putting TENS electrodes on you skin make sure that your skin is clean (free from oils, dirt or lotions). Remove the sticky portion from the clear plastic backing and apply around the outer potions of your kneecap. Keep the electrodes off of your thigh and leg muscles, thereby focusing the TENS treatment on the front of the knee. The red electrodes and the black electrodes should be crossed in the fashion shown below. After a day of use the electrode can be stored on the same clear plastic backing.

Ensuring that Charged Batteries are in the TENS Units
It is important that the batteries are charged at the beginning of the day. Store the batteries in the charger at night. A red light on the charger indicates that the batteries are not fully charged. A green light on the charger indicates that the batteries are charged. Charged batteries should be removed from the charger and placed in the TENS unit in the morning. You will receive multiple sets of batteries that can be recharged and used in the TENS unit. The TENS unit will indicate if it is low on battery life; please change the batteries and recharge at this time. If for some reason you need new AAA batteries, please notify the study personnel who can supply these to you.

Increasing the TENS Stimulus to the Correct Intensity
First turn on the TENS unit with the middle button that is marked: “on/off”.
Next increase channels 1 and 2 slowly until you achieve a strong sensory tingly feeling in you knee. You should LOWER the stimulation if you feel your muscles contracting or you feel discomfort in your knee. You should increase (HIGHER) the stimulation if you do not feel a tingly feeling around the knee. We would like you to increase the stimulation to a point were you feel a strong but comfortable stimulation.

Maintaining a Proper TENS Dosage
Some people may accommodate to the stimulation minutes to hours after applying the stimulus. If you accommodate to the stimulation we would like you to increase the intensity of the simulation with the button marked “ HIGHER” until a strong but comfortable stimulation is felt.

Knee-habilitation Study Guide – Sham TENS

How to work your Empi TENS Unit

The Empi TENS unit is configured by the study team to output the proper TENS treatment to your knee. You will be responsible for this 4-step process:
1) Applying the TENS electrodes on your knee correctly
2) Ensuring that charged batteries are in the TENS units
3) Increasing the stimulus to the correct intensity
4) Maintaining a proper dose of TENS throughout the day

Applying the TENS Electrodes
Before putting TENS electrodes on you skin make sure that your skin is clean (free from oils, dirt or lotions). Remove the sticky portion from the clear plastic backing and apply around the outer potions of your kneecap. Keep the electrodes off of your thigh and leg muscles, thereby focusing the TENS treatment on the front of the knee. The red electrodes and the black electrodes should be crossed in the fashion shown below. After a day of use the electrode can be stored on the same clear plastic backing.

Ensuring that Charged Batteries are in the TENS Units
It is important that the batteries are charged at the beginning of the day. Store the batteries in the charger at night. A red light on the charger indicates that the batteries are not fully charged. A green light on the charger indicates that the batteries are charged. Charged batteries should be removed from the charger and placed in

the TENS unit in the morning. You will receive multiple sets of batteries that can be recharged and used in the TENS unit. The TENS unit will indicate if it is low on battery life; please change the batteries and recharge at this time. If for some reason you need new AAA batteries, please notify the study personnel who can supply these to you.

Increasing the TENS Stimulus to the Correct Intensity
First turn on the TENS unit with the middle button that is marked: "on/off".
Next increase channels 1 and 2 slowly until you feel a tingly feeling around your knee. Some people may accommodate to the stimulation, meaning you may not feel any tingly feeling, within one minute of applying the stimulus. Please keep the stimulation intensity between 3 and 5 at all times. Remember to check and make sure throughout the day that the stimulator is indicating that TENS is being delivered to your knee, if the TENS unit is not one try pushing "on" or "changing the batteries".

Therapeutic Exercises

All therapeutic exercises will be instructed, supervised and progressed by physical therapists at the Meadowmont Physical Therapy Clinic. Over twelve 45-minute sessions that will take place in a 4-week period. The goal will be to complete at least 1 session per week with a 4 session per week maximum. The study team will assist with scheduling the first physical therapy session, while Meadowmont Physical Therapy personnel will schedule all additional sessions. The study team will check in with Meadowmont Physical Therapy personnel and the patient to ensure that the patients are being scheduled at the correct frequency.

Muscle Stretches
Quadriceps Stretch- Patient lays prone on the table and the physical therapist moves the ankle towards the gluteal muscles. Three stretches are held for 20 seconds in both limbs.

Hamstring Stretch- Patient sits at the edge of chair with knee straight, heal contacting the ground, and ankle dorsi flexed. The participant will bend at the hips until a stretch is felt in the hamstring. Three stretches are held for 20 seconds in both limbs.

Calf Stretch- Patient will stand in a staggered stance with palms against wall. Heal will be push to ground with knee flexed to 30 degrees and knee straight at 0 degrees. Three stretches are held for 20 seconds in both limbs.

Strengthening Exercises

Quadriceps Sets- Patients will be positioned on the table supine or seated with knees extended. Patients will be instructed to contract their quadriceps in order to fully extend the knee with the goal of lifting their heal off of the table. Tactile feedback can be provided to the posterior knee (instructing patient to put pressure on the therapist's hand) or to the quadriceps in a manner to cue the patient on which muscle to contract. Each repetition of should be held for 5 seconds.

Short Arc Quadriceps- Patients will be positioned on the table supine or seated with a bolster under the knee (half to full foam roller based on patient size). The knee should be in approximately 20-30° of knee flexion. Patients will be instructed to contract their quadriceps in order to fully extend the knee with the goal of lifting their heal off of the table and finishing with a fully extended knee. Tactile feedback can be provided to the posterior knee (instructing patient to put pressure on the therapist's hand) or to the quadriceps in a manner to cue the patient on which muscle to contract.

Straight Leg Raises (Flexion)- Patients will be positioned on the table supine with knees extended. The contralateral limb will be in knee flexion in order to create a ~45° angle at the hip. Patients will be instructed to

perform an initial quadriceps set (1 second hold) and keep knee extended while lifting the involved limb and heal off the table to ~45° angle. The patients will lower the limb back to the table slowly over a 2 second period. Tactile feedback can be provided to the quadriceps in a manner to cue the patient on which muscle to contract. If needed- the physical therapist may actively assist the first several repetitions by lifting the heal in the correct plane of motion. Cuff weights can be added to the ankle and the DAPRE system will be used to progress weight.

Straight Leg Raises (Abduction)- Patients will be positioned on the table side-lying on the uninvolved limb with knees extended. The uninvolved limb should be positioned with the hip and the knee flexed to 90°. The involved hip should be abducted to ~45° while keeping the knee extended. The patients will lower the limb back to the table slowly over a 2 second period. Tactile feedback can be provided to the gluteus medius in a manner to cue the patient on which muscle to contract. If needed- the physical therapist may actively assist the first several repetitions by lifting the heal in the correct plane of motion. Cuff weights can be added to the ankle and the DAPRE system will be used to progress weight.

Step-ups- Patients will be instructed to stand facing the step at a distance of about 6-inches. Patients will then be asked to put the involved limb on the step and contract quadriceps and hip musculature to bring both limbs onto the step. After pausing for one second the patient will be instructed to step off the back of the step with the uninjured limb in an lower the body slowly to the ground with the control of the muscles in the injured limb that is still on the step. Both feet should return to the floor before another repetition is started. Patients should progress to the next phase if they complete two sets in a row without increased knee pain and body mechanics are deemed within normal by the therapist. Patients will progress from the 4” to the 6” and 8” step and will further progress by holding a weight in the ipsilateral hand. Weights should increase in 5lb increments.

Long Arc Knee Extension- Knee extension will be performed seated on a table with knees flexed. The lever arm will be adjusted to have the foam pad make contact with the tibia approximately one-third of the way up the distal tibia. Patients will be instructed to extend the knee until full extension is achieved and patients “squeeze the quadriceps” for a 1-2 second hold. If patients experience knee pain the therapist should adjust the arc of knee extension motion to a point that minimizes pain. The weight should then be lowered to the resting position in approximately 2-3 seconds. Weights can be added to the table and the DAPRE system will be used to progress weight.

Long Arc Knee Flexion- Knee flexion will be performed seated on a table with knees extended. The lever arm will be adjusted to have the foam pad make contact with the leg approximately one-third of the way up the distal calf on the posterior side. Patients will be instructed to flex the knee until ~90° is achieved and patients “squeeze the hamstrings” for a 1-2 second hold. If patients experience knee pain the therapist should adjust the arc of knee flexion motion to a point that minimizes pain. The weight should then be lowered to the resting position in approximately 2-3 seconds. Weights can be added to the table and the DAPRE system will be used to progress weight.

Heal Raises – Patients will stand next to a plinth and be allowed to use the plinth for balance. They will be instructed to raise their heals off the ground over a 2 second period until they are on their toes. The patients will be instructed to hold this position for 2 seconds and lower slowly over a two second period. Patients should progress to the next phase if they complete two sets in a row without increased knee pain and body mechanics are deemed within normal by the therapist. The patients can be progress to one limb and then by using weight in the contralateral hand (increasing in 5lb increments).

Ball Squats- The physical therapist will determine the appropriate sized physio-ball to be used in this exercise based on the size of the patient. The physio-ball will be placed at the lumbar spine of each patient between their back and the wall. The patient will keep arms at their side or crossed over the chest and their feet shoulder width apart and in front of them enough that during the squat the knees do not move anterior to the toes. The patients will squat as far as they feel comfortable aiming for between ~45 to 90° of knee flexion. The

concentric and eccentric phases of the exercise should be controlled and last 3-4 seconds in each direction with a 1-2 second hold at maximum knee flexion.

Balance Exercises

Balance exercises will be performed with the following progressions. Patients will be supervised by a physical therapist and will perform balance exercises next to a wall, table or within a doorway to decrease risk of falling during the exercise.

Balance Progressions

Single Limb Stance Progression

Stance (3x 30s)*: *Progress when there are no touch downs in all 3 sets

Level -2: Double Limb firm surface, eyes Open
Level -1: Double Limb firm surface, eyes Closed
Level 1: Single limb firm surface, eyes open
Level 2: Single limb firm surface, eyes open, **perturbation**
Level 3: Single limb firm surface, eyes **closed**
Level 4: Single limb firm surface, eyes closed, **perturbation**
Level 5: Single limb **foam** surface, eyes open
Level 6: Single limb foam surface, eyes open, **perturbation**
Level 7: Single limb foam surface, eyes **closed**
Level 8: Single limb foam surface, eyes closed, **perturbation**

3.g.1 Randomization

Individuals who screen into the study and complete baseline testing will be randomized to one of 3 groups. Participants will be randomized into an intervention group before meeting the patient at the clinic but following a confirmation phone call. The confirmation phone call will occur 72- 24 hours prior to the first physical therapy appointment. The purpose of the confirmation phone call is to minimize the risk that patients drop out of the study prior to being randomized to a group. After screening, patients will be stratified to one of four strata based on CAR (low < 80%, High≥ 80%; Low Kellgren-Lawrence 2, High Kellgren-Lawrence 3 and 4). A separate blocked randomized list (block of 6) will be created by Dr. Todd Schwartz for each strata. A set of opaque sealed envelopes will contain the randomized group assignment for each participant. Dr. Troy Blackburn will have the randomized lists in case cross-referencing is ever needed in the future. The principal investigator will check with Dr. Blackburn for each of the first 10 participants that are randomized from each list match the assignment from the envelopes, and at every 5th randomized participant for the rest of the study. During assembly of the envelops a 5th strata list will be developed and crossed referenced immediately after assembly as a quality control measure.

Strata

Strata A = Low CAR, Low Kellgren- Lawrence
Strata B =High CAR, Low Kellgren- Lawrence
Strata C= Low CAR, High Kellgren- Lawrence
Strata D= High CAR, High Kellgren- Lawrence

The unblinded investigator, Brittney Luc, will pull the next envelope from the appropriate strata after the patient visit is confirmed and as close to the visit as possible to allow for adequate setup time. Before randomizing a participant the investigator will confirm that a cancelation email or message has been received. Again the goal is to avoid randomizing a participant that eventually drops out of the study to a treatment group. Following randomization the envelop will be shredded by the unblinded investigator.

3.h Blinding and Unblinding

The current study is a double-blinded randomized controlled trial, where the investigators evaluating study outcomes as well as patients in the TENS+TE and Sham TENS + TE groups will be blinded. There will be no effort to blind patients in the control or TE only group.

The unblinded personnel in the study will be Troy Blackburn (in charge of back-up randomizations lists), Brittney Luc (in charge of screening, randomization and scheduling), Brian Pietrosimone (in charge of screening, randomization and scheduling), and Todd Schwartz (in charge of initial randomization and study analysis). All efforts will be made to maintain the blinding of all other study personnel collecting data as well as the patients in the study. We will assess blinding of patients and study personnel at the end of the study to determine efficacy of the blinding procedures. We will not unblind any of the blinded personnel until after the study has been completed and all outcome measures for all patients have been analyzed and imputed into databases.

We will unblind the patients if: 1) they sustain a medical condition that requires that they know their group assignment or 2) they request the information in writing following the completion of the project in that all outcome measures for all patients have been analyzed and imputed into databases.

3.i Participant Evaluations and Follow-up

3.i.1 Timeline and Visit Schedule

Once the Patient is enrolled in the study there are three testing sessions that will be conducted in the Sports Medicine Research Laboratory (Baseline, Follow-up 1 [4-weeks] and Follow-up 2 [8-weeks]). In addition there are data that will be collected in the physical therapy clinic before the therapeutic exercise session begins on the last session of each week. The schedule of when evaluations take place must is specified in the second row of the Timeline (Appendix A).

3.i.2 Scope

Outcome Measures are sectioned into Consent and Demographics, Self-reported outcomes, strength, function & gait and intervention outcomes. On baseline and follow-up testing performed in the Sports Medicine Research Laboratory the order of testing will always occur with Consent and Demographics, Self-reported outcomes, strength, and function & gait.

Collecting of Recruitment, Inclusion and Retention Rates: We will determine: 1) the number of patients recruited from various clinics and the frequency of recruitment using different recruitment modes (physician recommendation, mailings or other), 2) the percentage of patients that screen into the study compared to the number recruited, and 3) the percentage of patients retained at the 4- and 8-week post-tests (frequency of reasons for drop-out will be collected).

Collecting Compliance, Adherence, and Tolerability of the Interventions Data: We will determine the frequency and percentage of TE sessions that patients complete and record the usage of the TENS and sham TENS units. We will report adherence of all patients to the completion of 12 TE sessions over a 4-week period. A 10cm visual analog scale (VAS) will be used to quantify tolerability.

Informed Consent

The informed consenting process will be conducted as outlined in Appendix B, and we will not continue study procedures until written informed consent from the participant is collected.

Inclusion and Exclusion Criteria & Knee Injury Questionnaire

Study Inclusion and Exclusion Criteria will have previously been checked as part of a pre-screening measure prior to scheduling the participant. The study participant will physically read and check “yes or no” for each of the exclusion criteria on the first page of the Knee Injury Questionnaire during the screening session. If the

participant has a question he/she can ask study personnel, who will answer the question in a polite and understanding manner. If an exclusion criteria is checked yes the study personnel will talk with the participant and ensure that the answer was not a mistake after asking for an elaboration on the answer. If the exclusion criteria is indeed present the study personnel will explain why the participant can not be enrolled in the study and he/ she will be excluded. If no exclusionary criteria are present the participant will complete the knee Injury Questionnaire and then be provided a Western Ontario and McMaster University Osteoarthritis (WOMAC) Index.

Western Ontario and McMaster University Osteoarthritis (WOMAC) Index
The Participant will be provided a quiet room with a desk and access to an investigator. The participant will fill out all subsections of the WOMAC (Pain, Stiffness and Function). The investigator will score the function section by adding the numbers associated with the various answers. A WOMAC Function score of 23 or higher indicates that the participant is experiencing enough dysfunction to be included in the study. The participant will then undergo quadriceps central activation ratio testing.

Neuromuscular Activation: We will assess quadriceps central activation ratio as a representative variable of lower extremity neuromuscular activation. Quadriceps central activation ratio has been demonstrated to be significantly decreased in knee OA compared to healthy, matched controls[3], and we have reported acceptable measurement reliability ($ICC_{2,k}$ = 0.85) over 4 weeks.[41] Quadriceps central activation ratios will be collected as previously reported by the PI [1,5,42] using an automated triggered method to improve reliability of this technique.[43]

Gait Biomechanics: Peak sagittal plane knee kinematics and kinetics will be collected during the first 50% of stance phase and processed in our 3-dimensional, 10-Camera (Vicon) motion capture laboratory.[44-47] Gait will be collected at a self-selected speed; speed at pre- and post-tests will be used as a time-dependent covariate

Physical Function: Physical function will be measured with the three core performance-based tests (30-s chair-stand test, 40 m fast-paced walk test, a stair-climb tests) endorsed by the Osteoarthritis Research Society International guidelines.[48]

Physical Activity: Self-reported physical activity will be quantified using the Physical Activity Scale for the Elderly (PASE), which is a valid tool to assess self-reported participation in physical activities of varying intensities.[49]

The Self-Efficacy for Physical Activity (SEPA): The SEPA scale will be used to assess the respondents' confidence in their ability to be physically active despite common barriers (adverse weather, lack of time, when tired, in a bad mood, or on vacation).[50] The SEPA has demonstrated good internal consistency[50] and construct validity as well as acceptable retest reliability (0.9) over 2 weeks.[50]

Quality of Life, Disease Related Self-Reported Disability, and Visual Analog Scales (VAS): A paper version of the Short-Form (SF) 12 will be used to quantify the patients' quality of life.[51] A paper version of the WOMAC score will be administered to each patient in a quiet room as previously performed by the PI.[1] The total WOMAC score is useful as a measure of disability, yet important WOMAC subscale information regarding pain, stiffness and disability will also be analyzed separately. Although the focus of this study is TENS use to treat neuromuscular activation, we recognize that it may affect pain and will use the WOMAC pain subscale as a secondary outcome to assess pain. Three separate 10 cm VAS questionnaire will be used to assess the 1) current tolerability of walking, 2) the likelihood to continue the same level of physical activity, and 3) current pain level.

3.j Concomitant Medications

All medications that the each patient is currently prescribed or using as well as been prescribed and has taken in during the previous 4 weeks will be collected at the baseline visit. We will also collect data about the medications on a daily basis using a medication log. We will restrict certain medications for the entirety of the study, at certain time points during the study and for a period of time before the screening visit.

Medication Restrictions

Corticosteroid injections into the knee or any lower extremity joint will be restricted for 14 days prior to the screening visit (based on the drug half-life) and throughout the entirety of the study period including the 8-week follow-up test. We will collect information about when the latest corticosteroid injection occurred for each participant at the prior to screening in order to determine when each participant can attend the screening visit.

Hyaluronic acid injections into the knee or any lower extremity joint will be restricted for 14 days prior to the screening visit (based on the drug half-life) and throughout the entirety of the study period including the 8-week follow-up test. We will collect information about when the latest hyaluronic acid injection occurred for each participant at the prior to screening in order to determine when each participant can attend the screening visit.

Prescription Depressants (Examples: opiates and opioids, barbiturates, tranquilizers and benzodiazepines) will be restricted 4-weeks prior to screening and throughout the study period as these medications may affect the neuromuscular function.

Prescription Stimulants (Example: amphetamines) will be restricted 4-weeks prior to screening and throughout the study period as these medications may affect the neuromuscular function.

Non-steroidal anti-inflammatory drugs (NSAIDs) will be restricted 24 hours prior to screening or follow-up testing sessions. We will track NSAIDs and instruct patients not to change their NSAIDs usage during the 8-weeks of the study.

Acetaminophen will be restricted 24 hours prior to screening or follow-up testing sessions. We will track Acetaminophen and instruct patients not to change their Acetaminophen usage during the 8-weeks of the study.

3.k Safety Reporting

The Principal Investigator (PI) and study staff members are responsible for the safety of study participants. It is not anticipated that there will be any significant physical or psychological risks associated with this study. However, federal regulations require prompt reporting to the University of North Carolina at Chapel Hill Institutional Review Board (IRB), all injuries, adverse events, or other unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in this research study.

Study team members who become aware of any adverse event related to the study will notify the principal investigator, Dr. Pietrosimone, immediately. Study team members will have contact information for Dr. Pietrosimone for daytime, evening and weekend hours. If Dr. Pietrosimone is not available for contact when a study team member becomes aware of a study-related adverse event, Dr. Spang, Medical Monitor on the study, will be contacted. Once Dr. Pietrosimone or Dr. Spang are contacted about the adverse event, he will make a determination about the reporting requirements in accordance with the University of North Carolina at Chapel Hill IRB guidelines. This will include notification of the University of North Carolina at Chapel Hill IRB within one week for a serious adverse event, and within 2 weeks business days if a protocol deviation/violation, or other unanticipated problem.

The Principal Investigator will report all adverse events and protocol deviations to the safety officer, Kelli Allen, on a biannual basis, or as requested. The PI or co-investigator will report all serious adverse events to the

study's safety officer within 48 hours of being made known to the investigator. This immediate report will be followed by a detailed written report as soon as possible.

All adverse events will be collected, analyzed, and monitored in the study's adverse event log, which is kept in the Investigator's regulatory files within a locked file cabinet.

Definitions

- ***Adverse Event (AE)*** - An adverse event is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period, which increased in severity.
- ***Serious Adverse Event (SAE)*** – A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

3.k.1 Adverse Event Reporting

All AEs are collected, analyzed, and monitored by using an Adverse Event Form, a sample of which is shown in **Appendix B**. AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety will be reported to the NIAMS, the independent safety officer (Kelli Allen) and the . All AEs experienced by the participant during the time frame specified in the protocol (e.g., from the screening visit until the 8 week follow-up) will be reported, as outlined in the protocol.

3.k.2 Unanticipated Problems

Unanticipated Problems are not included in the 45 CFR part 46, but are defined by the OHRP as any incident, experience or outcome that meets all of the following requirements:

(1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

(2) Related or possibly related to participation in the research. *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects; suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks;
- provision of additional information about newly recognized risks to previously enrolled subjects.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. For further information see http://www.hhs.gov/ohrp/policy/advevntguid.html.

3.k.3 Serious Adverse Event Reporting

All serious adverse events (SAEs), unless otherwise specified in the protocol and approved by the IRB and the NIAMS, require expedited reporting by the Principal Investigator (Brian Pietrosimone) to the study's safety monitoring officer (Kelli Allen). SAEs must be reported to the independent safety monitoring officer and the NIAMS, through the NIAMS contractor within 48 hours of being reported to the Investigator. The immediate reports should be followed by detailed, written reports as soon as possible. Follow up information may be required. All interventional studies, independent of phase or type, must report SAEs.

If a potential SAE is reported to any study personnel that study personnel should make Dr. Pietrosimone aware of the potential SAE at once. Dr. Pietrosimone will make Dr. Allen, the independent safety officer and the Medical Monitor, Dr. Jeffery Spang, aware of the nature of the SAE by phone in the first 24 hours of the SAE being reported to the study personnel. Dr. Pietrosimone will personally collect information from healthcare professionals involved in the study, the study participant and close relatives (if possible), and other study personnel. Dr. Pietrosimone will provide written documentation to the 1) independent safety officer (Dr. Kelli Allen), 2) NIAMS and 3) the Institutional Review Board at the University of North Carolina at Chapel Hill within 48 hours of learning about the SAE. A single form **(Appendix B)** will be completed and sent to all three people/ institutions by electronic mail with signatures of the Principal Investigator, Brian Pietrosimone, and the Medical Monitor, Dr. Jeffery Spang. The action regarding the treatment of that specific patient taken by Dr. Pietrosimone and Dr. Spang will be indicated on the form (Dose decreased, Dose increased, Dose delayed, Discontinued permanently, Discontinued temporarily, Other), as well as actions that are taken for the study in general (No action, Modification of consent documents to include a description of newly recognized risks, Revise protocol to eliminate apparent immediate hazards to subjects, Notify currently enrolled subjects, Suspension of enrollment of new subjects, other). The safety officer, IRB and NIAMS will be asked to notify Dr. Pietrosimone if they disagree with the specific actions taken within 72 hours.

If the safety officer, IRB and NIAMS disagree with actions taken by Dr. Pietrosimone and Dr. Spang regarding a specific SAE a conference all between aforementioned personnel and institutes will be scheduled with 72 hours of Dr. Pietrosimone being notified of the disagreement. Study recruitment will be halted until the conference call has occurred and an agreement is conferred among all personnel and institutional representatives about stipulations regarding reopening study recruitment.

3.l Data and Safety Officer

The principal investigator will oversee data collection monitoring and all issues related to participant safety, data collection protocols, and participant confidentiality. All adverse events will be collected by physical therapists supervising the therapeutic resistance exercise and any study-related issues pertaining to safety or adverse events will be reported to the TARC Methodology Core, which works directly with the Regulatory Core of the NC TraCS Institute for monitoring adverse events of studies conducted through TARC. Dr. Kelli Allen, Co-Director of the TARC Methodology Core, will be responsible for the decisions and communication with NC TraCS Regulatory Core since she is not a co-investigator or collaborator on this project. Dr. Kelli Allen has previous experience as a principal investigator in physical therapy based interventions for patients with knee osteoarthritis and therefore has the experience and knowledge regarding the scientific area of study and study design which will be important in understanding the analysis and interpretation of the data to ensure participant safety as well as ethical, scientifically rigorous study conduct. The conf*lict of Interest (COI) Statement* forms have been collected from Dr. Kelli Allen (See **Appendix G**).

3.n Data Collection and Study Forms

3.n.1 Source Documentation

All data will be recorded on paper using black ink. All study forms will be printed prior to the beginning of the study and will be organized into participant binders which will contain all study documents necessary to collect each piece of data throughout the entirety of the study. All forms will be distributed to the study participant by either the Principal Investigator, Study Coordinator, or Research Assistant. The member of the study team will describe each of the questionnaires to the study participant, and will read allowed the instructions. The study participant will be allowed to ask any questions about the study questionnaires.

Each study participant will have one complete binder of study forms which consists of consent forms, case report forms, and all questionnaires to be completed by study participants. Each binder will contain packets of study forms, which correspond to the data needing to be collected during the following times throughout the course of the study: 1) initial screening, 2) baseline assessment 3) duration of the intervention, 4) 4-week follow up assessment and 5) 8-week follow up assessment. The study forms contained in each packet are individually described below.

All binders of study forms will be maintained in a locked file cabinet located within the Neuromuscular Research Laboratory. The Neuromuscular Research Laboratory is secured through UNC ID Card swipe access. The Principal Investigator, Study Coordinator, and Research Assistant are the only individuals who will have access to the file cabinet in which the participant binders are stored.

Initial Screening
Three study forms will be completed during the initial screening session, which includes 1) the informed consent form, 2) the Knee Injury History Form and 3) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Informed Consent Form
Written and verbal consent will be obtained before any additional questionnaires are completed or any study data is collected. The Principal Investigator, Study Coordinator or Research Assistant will provide the potential study participant with the consent form and explain each part of the consent form with the potential study participant. The potential study participant will be allowed to ask any additional questions about the study. Upon providing verbal and written consent, a copy will be made of the signed consent form. One copy will remain in the participant's binder and the other copy will be given to the study participant to keep for their records.

Knee Injury History Form
The Knee Injury History Form first asks a series of yes or no questions in order to determine if the study participant meets the specific inclusion and exclusion criteria for the study. The next set of questions asks about previous knee osteoarthritis treatments such as intraarticular injections and physical therapy, and asks for detailed information regarding each type of treatment. The last section of Knee Injury History Form asks a series of questions about types of medication use that is taken specifically for pain as well as any other medications taken. Participants are asked to complete a medication log which details the type of medication, as well as the dose, frequency and time of day the medication is taken. Data from the medicate use and medication logs will be used as potential statistical covariates.

WOMAC
The WOMAC will be used to assess self-reported disability. The WOMAC consists of 24 items divided into three subscales which individually assess pain, stiffness and physical function in individuals with knee osteoarthritis. The pain subscale consists of 5 items and assesses the magnitude of knee pain during walking, using stairs, in bed, sitting or lying, and standing. The stiffness subscale consists of 2 items and assesses the magnitude of stiffness after first waking in the morning and later in the day. The physical function consists of 17 items and asks about the magnitude of difficulty when ascending and descending stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on and taking off socks, rising from bed, lying in bed, getting in and out of the bath, sitting, getting on and off the toilet, completing heavy household duties, and completing light household duties. Each item is presented in a 5 point Likert-type format and uses the following descriptors for possible answer choices none, mild moderate, severe, and extreme. Each descriptor corresponds to an ordinal scale of 0-4. The scores are summed for the items in each subscale, with possible ranges as follows: pain=0-20, stiffness=0-8, physical function=0-68. Higher scores on the WOMAC indicate greater amounts of pain, stiffness, and functional limitations.

Baseline Assessment
Five questionnaires will be completed during the baseline assessment, which occurs within 7 days prior to the initiation of the intervention and includes 1) the Physical Activity Scale for the Elderly (PASE), 2) Self-Efficacy for Physical Activity (SEPA), 3) the Short Form 12 (SF-12), 4) the Charlson Morbidity Index, and 5) Visual Analog Scales (VAS) to determine the likelihood to continue current level of physical activity, current level of knee pain, and tolerability of walking.

PASE
The PASE measures the level of physical activity in individuals age 65 and older. The PASE is comprised of measures of self-reported occupational, household, and leisure activities during a one-week period. The PASE consists of 12 items which determine the frequency and duration of leisure activities (e.g., sports, jogging, swimming, strengthening and endurance exercise), household activities, and work-related activities. Items are scored differently depending upon the type of activity that is being quantified. Participation in leisure-time and strengthening activities are scored as never, seldom (1-2 days per week), sometimes (3-4 days per week), and often (5-7 days per week). Duration of these activities is scored as less than 1 hour, 1-2 hours, 2-4 hours and more than 4 hours. Household and work related activities are scored as yes or no. In work related activities, paid or unpaid work is scored in total hours per week. The total PASE score is computed by multiplying either the time spent in each activity (hours per week) or participation (i.e., yes/no) in an activity, by empirically derived item weights and then summing overall activities. The overall PASE score ranges from 0 to 400 or more, where higher scores indicate greater levels of physical activity.

SEPA
The SEPA questionnaire assesses how confident individuals are in their ability to be physically active in a variety of situations, including when they are: tired, in a bad mood, do not feel they have enough time, on vacation, when it is snowing or raining. The SEPA consists of 5 items and each item is presented in a 5 point Likert-type format. Each item uses the following descriptors for each item: not at all confident, slightly

confident, moderately confident, very confident, and extremely confident. These correspond to an ordinal scale of 1-5. The point value from each question is summed for a total score. Higher scores indicated higher levels of confidence in the ability to by physically active.

SF-12
The SF-12 is used to assess functional health and well-being from the patient's point of view. The SF-12 consists of 12 items which assess all 8 domains of health, including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning role-emotional and mental health. Each item is presented in either a 3 or 5 point Likert-type format. Pre-coded values are assigned to each possible answer for each item. Raw scores from each item are totaled, and raw scores can be transformed into 0-100 scale scores. Higher scores on the SF-12 indicate better general health perceptions.

Charlson Comorbidity Index
The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data. Each comorbidity category has an associated weight, based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.

VAS to determine tolerability of walking, current level of knee pain, and likelihood to continue current level of physical activity
The VAS for tolerability of walking will be completed immediately upon completion of the first trial of the 20-meter walk test Participants are asked to make a vertical line on a 100mm solid line to indicate how tolerable they feel walking was during the task just completed. The VAS ranges from "Not at all Tolerable" on the left to "Extremely Tolerable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater tolerability of walking. The VAS for the current level of knee pain asks participants to make a vertical line on a 100mm solid line to indicate how much pain they currently have in their knee. The VAS ranges from "No Pain" on the left to "Worst Pain Imaginable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater amount of knee pain. The VAS for the likelihood to continue their current level of physical activity asks participants to make a vertical line on a 100mm solid line to indicate how likely they are to continue their current level of physical activity. The VAS ranges from "Not at all Likely" on the left to "Extremely Likely" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater likelihood of continuing the current level of physical activity

Duration of the Intervention
During each week of the intervention, participants will be asked to complete a daily medication log and will be given a VAS in order to assess 1) tolerability of the intervention, 2) satisfaction with the intervention, 3) likelihood to retain following week's appointments.

Medication Log
For each day of the week participants will be asked to write down each medication taken. Participants are asked to include the name of the medication, the dose of the medication, the frequency of use, and the time of day the medication is taken. Medication use throughout the study will be used as a statistical covariate if necessary.

VAS to assess tolerability of the intervention, satisfaction with the intervention, and likelihood to retain future appointments
The VAS for tolerability of the intervention asks participants to make a vertical line on a 100mm solid line to indicate how tolerable they feel the intervention was during the past week. The VAS ranges from "Not at all Tolerable" on the left to "Extremely Tolerable" on the right. VAS scores closer to 100, or marks closer to the

rightward end, indicate a greater tolerability of the intervention. The VAS for satisfaction with the intervention asks participants are to make a vertical line on a 100mm solid line to indicate how satisfied they are with the intervention during the past week. The VAS ranges from “Not at all Satisfied” on the left to “Extremely Satisfied” on the right. VAS scores closer to 100, or marks closer to the rightward end indicate a greater satisfaction of the intervention during the past week. The VAS for likelihood to retain future appointments asks participants to make a vertical line on a 100mm solid line to indicate how likely they are to retain their future appointment. The VAS ranges from “Not at all Likely” on the left to “Extremely Likely” on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater likelihood of retaining following appointments

4-Week Follow Up Assessment
Five questionnaires will be completed during the baseline assessment, which occurs within 7 days prior to the initiation of the intervention and includes 1) the Physical Activity Scale for the Elderly (PASE), 2) Self-Efficacy for Physical Activity (SEPA), 3) the Short Form 12 (SF-12), 4) the Charlson Morbidity Index, and 5) Visual Analog Scales (VAS) to determine the likelihood to continue current level of physical activity, current level of knee pain, and tolerability of walking.

PASE
The PASE measures the level of physical activity in individuals age 65 and older. The PASE is comprised of measures of self-reported occupational, household, and leisure activities during a one-week period. The PASE consists of 12 items which determine the frequency and duration of leisure activities (e.g., sports, jogging, swimming, strengthening and endurance exercise), household activities, and work-related activities. Items are scored differently depending upon the type of activity that is being quantified. Participation in leisure-time and strengthening activities are scored as never, seldom (1-2 days per week), sometimes (3-4 days per week), and often (5-7 days per week). Duration of these activities is scored as less than 1 hour, 1-2 hours, 2-4 hours and more than 4 hours. Household and work related activities are scored as yes or no. In work related activities, paid or unpaid work is scored in total hours per week. The total PASE score is computed by multiplying either the time spent in each activity (hours per week) or participation (i.e., yes/no) in an activity, by empirically derived item weights and then summing overall activities. The overall PASE score ranges from 0 to 400 or more, where higher scores indicate greater levels of physical activity.

SEPA
The SEPA questionnaire assesses how confident individuals are in their ability to be physically active in a variety of situations, including when they are: tired, in a bad mood, do not feel they have enough time, on vacation, when it is snowing or raining. The SEPA consists of 5 items and each item is presented in a 5 point Likert-type format. Each item uses the following descriptors for each item: not at all confident, slightly confident, moderately confident, very confident, and extremely confident. These correspond to an ordinal scale of 1-5. The point value from each question is summed for a total score. Higher scores indicated higher levels of confidence in the ability to by physically active.

SF-12
The SF-12 is used to assess functional health and well-being from the patient’s point of view. The SF-12 consists of 12 items which assess all 8 domains of health, including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning role-emotional and mental health. Each item is presented in either a 3 or 5 point Likert-type format. Pre-coded values are assigned to each possible answer for each item. Raw scores from each item are totaled, and raw scores can be transformed into 0-100 scale scores. Higher scores on the SF-12 indicate better general health perceptions.

Charlson Comorbidity Index
The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data. Each comorbidity category has an associated weight, based on the adjusted risk of mortality or resource use, and the sum of all

the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.

VAS to determine tolerability of walking, current level of knee pain, and likelihood to continue current level of physical activity

The VAS for tolerability of walking will be completed immediately upon completion of the first trial of the 20-meter walk test Participants are asked to make a vertical line on a 100mm solid line to indicate how tolerable they feel walking was during the task just completed. The VAS ranges from "Not at all Tolerable" on the left to "Extremely Tolerable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater tolerability of walking. The VAS for the current level of knee pain asks participants to make a vertical line on a 100mm solid line to indicate how much pain they currently have in their knee. The VAS ranges from "No Pain" on the left to "Worst Pain Imaginable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater amount of knee pain. The VAS for the likelihood to continue their current level of physical activity asks participants to make a vertical line on a 100mm solid line to indicate how likely they are to continue their current level of physical activity. The VAS ranges from "Not at all Likely" on the left to "Extremely Likely" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater likelihood of continuing the current level of physical activity.

8-Week Follow Up Assessment

Six questionnaires will be completed during the baseline assessment, which occurs within 7 days prior to the initiation of the intervention and includes 1) the Physical Activity Scale for the Elderly (PASE), 2) Self-Efficacy for Physical Activity (SEPA), 3) the Short Form 12 (SF-12), 4) the Charlson Morbidity Index, 5) Visual Analog Scales (VAS) to determine the likelihood to continue current level of physical activity, current level of knee pain, and tolerability of walking, and 6) Knowledge of Group Assignment for Study Participants. One questionnaire will be completed by the member of the research team who will be conducting the 8-week follow-up which is the Knowledge of Group Assignment for Study Investigators.

PASE

The PASE measures the level of physical activity in individuals age 65 and older. The PASE is comprised of measures of self-reported occupational, household, and leisure activities during a one-week period. The PASE consists of 12 items which determine the frequency and duration of leisure activities (e.g., sports, jogging, swimming, strengthening and endurance exercise), household activities, and work-related activities. Items are scored differently depending upon the type of activity that is being quantified. Participation in leisure-time and strengthening activities are scored as never, seldom (1-2 days per week), sometimes (3-4 days per week), and often (5-7 days per week). Duration of these activities is scored as less than 1 hour, 1-2 hours, 2-4 hours and more than 4 hours. Household and work related activities are scored as yes or no. In work related activities, paid or unpaid work is scored in total hours per week. The total PASE score is computed by multiplying either the time spent in each activity (hours per week) or participation (i.e., yes/no) in an activity, by empirically derived item weights and then summing overall activities. The overall PASE score ranges from 0 to 400 or more, where higher scores indicate greater levels of physical activity.

SEPA

The SEPA questionnaire assesses how confident individuals are in their ability to be physically active in a variety of situations, including when they are: tired, in a bad mood, do not feel they have enough time, on vacation, when it is snowing or raining. The SEPA consists of 5 items and each item is presented in a 5 point Likert-type format. Each item uses the following descriptors for each item: not at all confident, slightly confident, moderately confident, very confident, and extremely confident. These correspond to an ordinal scale of 1-5. The point value from each question is summed for a total score. Higher scores indicated higher levels of confidence in the ability to by physically active.

SF-12

The SF-12 is used to assess functional health and well-being from the patient's point of view. The SF-12 consists of 12 items which assess all 8 domains of health, including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning role-emotional and mental health. Each item is presented in either a 3 or 5 point Likert-type format. Pre-coded values are assigned to each possible answer for each item. Raw scores from each item are totaled, and raw scores can be transformed into 0-100 scale scores. Higher scores on the SF-12 indicate better general health perceptions.

Charlson Comorbidity Index
The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data. Each comorbidity category has an associated weight, based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.

VAS to determine tolerability of walking, current level of knee pain, and likelihood to continue current level of physical activity
The VAS for tolerability of walking will be completed immediately upon completion of the first trial of the 20-meter walk test Participants are asked to make a vertical line on a 100mm solid line to indicate how tolerable they feel walking was during the task just completed. The VAS ranges from "Not at all Tolerable" on the left to "Extremely Tolerable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater tolerability of walking. The VAS for the current level of knee pain asks participants to make a vertical line on a 100mm solid line to indicate how much pain they currently have in their knee. The VAS ranges from "No Pain" on the left to "Worst Pain Imaginable" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater amount of knee pain. The VAS for the likelihood to continue their current level of physical activity asks participants to make a vertical line on a 100mm solid line to indicate how likely they are to continue their current level of physical activity. The VAS ranges from "Not at all Likely" on the left to "Extremely Likely" on the right. VAS scores closer to 100, or marks closer to the rightward end, indicate a greater likelihood of continuing the current level of physical activity.

Knowledge of Group Assignment – Study Participant
Participants are asked to indicate which of the interventions groups they feel they were assigned to during the intervention. Data from this questionnaire will determine if participant blinding was achieved.

Knowledge of Group Assignment – Study Investigator
Study investigators are asked to indicate which of the interventions groups they feel the participant they collected the 8-week follow up assessment on was assigned to during the intervention. Data from this questionnaire will determine if investigator blinding was achieved.

3.n.2 General Instructions for Completing Forms

Instructions for Study Participants

All questionnaires are to be completed by study participants in black ink. Individual instructions for completing each questionnaire are clearly written on the top of the first page of the questionnaire. Participants will be read the instructions by either the Principal Investigator, Study Coordinator, or Research Assistant. Study participants are instructed to only write in the spaces provided, to not skip any questions, and to not use abbreviations. If an error has been made on any study form, a single line will be placed through the erroneous entry. The date of the error will be recorded and the participant initial next to the error. The participant will be asked to indicate the correct response in the event an error is made.

Instructions for Study Investigators

Study investigators will complete the header of each questionnaire prior to completion. The study participants ID will be written on each page of every questionnaire. The date of completion will be written in a Month/Day/Year format, and time of completion will be written using a 24 hour clock. If an error has been made on any study form, a single line will be placed through the erroneous entry. The date of the error will be recorded and the investigator initials next to the error. The investigator must indicate the correct response in the event an error is made.

Minimizing Incomplete Forms

In order to minimize incomplete study forms, the Principal Investigator, Study Coordinator or Research Assistant will review each study form the participant completes. In the event a participant has failed to complete a question, the participant will be asked to complete the question that was not completed. If data is not available for an item, the item is to be circled and the reason the data is not completed is to be written next to the item. If an evaluation was not done, ND will be written next to the incomplete item with the reason the evaluation was not done or the item was not completed. If the information is not available, but the evaluation or form was completed, then NAV is to be written on the study form. In the event NAV is written on a study form, the Principal Investigator, Study Coordinator or Research Assistant will contact the participant in order to attempt to obtain all information and ensure all study forms are complete.

Following completion of the self-reported study forms the Principal Investigator, Study Coordinator or Research Assistant will review each study form the participant completes in order to ensure all items are completed properly and each answer is legible. If the answer to an item is not legible, the member of the study team will ask the study participant to clarify their answer and ensure it is legible.

Guidelines for Incomplete and Illegible Forms

If an item on a study form is incomplete or illegible the item will be circled on the study for by the Principal Investigator, Study Coordinator or the Research Assistant. The reason for incomplete or illegible will be written on the top of the first page of the study form if the entire document is incomplete or illegible. If only certain items are incomplete or illegible the reason will be written next to the circled item. If an entire page of a study form cannot be completed a diagonal line will be drawn through the form. The Principal Investigator, Study Coordinator or Research Assistant will then write NOT DONE, NOT AVAILABLE, or NOT APPLICABLE on the page as appropriate. Regardless of whether or not a form is incomplete or illegible the header information will be completed on each and every page of the study forms.

3.n.3 Retention of Study Documents

All study related files will be maintained for **at least 7 years**, as mandated by the Institutional Review Board at the University of North Carolina at Chapel Hill. All study files will remain in a locked file cabinet located within the Neuromuscular Research Laboratory, which is secured via swipe card access. Once 7 years' time has passed, all study documents will be shredded.

3.n.4 Administrative Forms

Five administrative forms have been included in order to assist with the management of participant enrollment. Each administrative form is described below and is included.

Telephone Contact Log
The telephone contact log will be used to document all conversations regarding the study and study participants. The contact log will be used any time the Principal Investigator, Study Coordinator or Research Assistant makes a telephone call to either a member of the research team or a study participant in regards to

this study. The Principal Investigator, Study Coordinator or Research Assistant will record the date of the phone call, their name, the individual the call is made to, the reason for the call and the length of the conversation.

Screening Log
The screening log will be used to record all participants which are screened for participation into the study. The screening log will be kept up to date at all times throughout the study.

Participant Identification Code List
The participant identification code list will be used to document the participant's name, medical record number, randomization number, and study entry and study exit dates. The participant identification code list will be kept within a located filing cabinet located in the Principal Investigators office, which is a secure location and separate from all other study files.

Signature Log
The signature log will contain the signature of all member of the study team. The Principal Investigator and Study Coordinator will be responsible for designating members of the research team who are approved to make form entries and changes. In the event a member of the research team is removed from the team for any reason, the Principal Investigator will record the date the member of the research team is removed.

Site Visit Log
The Principal Investigator, Study Coordinator and Research Assistant will each visit the Meadowmont Physical Therapy Clinic in order to complete initiation and training, as well as to meet with study participants each week of the intervention in order to collect all study forms. The name of the research team member and the date, time and reason for the visit to the physical therapy clinic will be recorded each time a visit is made.

3.m Study Compliance

Definitions

Protocol deviation - any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

Protocol violation - a deviation from the IRB-approved protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data.

Procedures

In order to minimize the risk of a protocol deviation or protocol violation Dr. Yvonne Golightly, a licensed physical therapist, will track compliance of the study procedures related to informed consent, randomization, follow up testing, IRB compliance, and compliance to treatment protocols.

Randomization – Dr. Golightly will confirm that the first 10 patients that are found to be eligible for the study meet all inclusion and exclusion criteria prior to randomization. For patients 10-90, Dr. Golightly will monitor patient recruitment by checking the patient files for all patients that where randomized to a group on a monthly basis (approximately 5 at a time). Potential violations will include: informed consent not obtained or a patient is randomized that does not fit inclusion/ exclusion criteria). Dr. Golightly will confirm that the first 5 participants are randomized to the correct group by cross referencing randomization lists, which will ensure that assignments in randomization envelops correspond with the master randomization lists. Randomization will be crossed referenced by a randomly selected patient each month.

Follow-Up Testing – Each month Dr. Golightly will ensure that follow-up testing of each patient was performed in

IRB Compliance - Dr. Golightly will confirm each month that protocol information and consent forms used are approved by the IRB and any changes in the protocol are confirmed with the IRB and have been included in the revised protocol and regulatory documentation.

Compliance of Treatment Protocols – Dr. Golightly will use visit the Meadowmont Physical Therapy Clinic on a monthly basis and observe the administration of the therapeutic exercises that are detailed in section 3.g. Dr. Golightly will determine and document if the Physical Therapists are complaining with the descriptions of the exercises and dictating treatment progressions correctly.

All reports will be provided to Dr. Pietrosimone, the principal investigator 72 hours after the evaluation and any protocol deviations or violations will be dealt with accordingly. Biweekly meetings are scheduled with the study team to assist in a rapid implementation for any issues brought up in Dr. Golightly's reports, yet the PI may take immediate action with the study team to ensure adherence of study protocols if an urgent issue is brought to attention. The PI will report protocol violations and deviations to the IRB at the University of North Carolina at Chapel Hill with in 48 hours of the violation/deviation via the online IRBIS reporting system. Protocol deviations will addressed by modification to the IRB protocol, informed consent form and manual of operating procedures if necessary. All events will be reported at the time of the biannual at submission of the safety report. The study coordinator, Brittney Luc, will maintain a log of all protocol deviations/violations and should report them to Dr. Kelli Allen each month.

In the case of serious violations a review of the personnel involved will be performed by Dr. Kelli Allen and Brian Pietrosimone. Depending on the nature of the violation or deviation, study recruitment and treatment may be stopped until the violation/ deviations is addressed. Actions may be taken to remove a patient from the data set if the deviation affects the data collected. It is possible that if a violation is deemed egregious study personnel may be dismissed from further involvement in the study in order to ensure future validity of the data collected and safety for study participants.

3.m.1 Biannual Reporting

The study team will complete biannual reports that have been approved by the SO as well as NIAMS personnel prior to starting study recruitment. Open session Data and Safety Monitoring reports will detail enrolment for the previous 6-month period as well as the overall study. We will report screening rates/ failures, actual vs expected enrollment, participant demographics, participant enrollment status, key baseline participant characteristics, study duration for participants, missed visits, CRF, adverse events, deaths, unanticipated problems and protocol deviations. The reports can be found in Appendix and will be electronically mailed to the SO, Kelli Allen, and NIAMS on a biannual basis. Final closeout reporting will entail the same detailed information for the final study period as well as the entire study. Final closeout reporting documents can be found in Appendix and will be electronically mailed to the SO, Kelli Allen, and NIAMS.

3.O Data Management

Epi Info, which is a product of the Centers of Disease Control, will be used to enter outcomes data and export data to SPSS which will be used for data analysis.

Data tracking – The status of enrollment will be tracked with Epi Info. A separate telephone call log will be kept with the number of people that contact the study team who are interested in the study. We will also keep a log of encounters the study team may have with patients at the clinic. We will keep data indicating how may patients screen out of the study over the telephone or in the clinic due to exclusion criteria or disinteresting

participating. We will collect the number of patients that complete the initial consenting process and screen into the study following the screening visit to the laboratory. Finally we will determine how many people that screen into the study are randomized into a treatment condition.

Data Entry – Data will be entered from electronic files or paper surveys. Outcome measures will be cut and pasted from excel or collection software into Epi Info to minimize data entry error. Two separate investigators will calculate paper questionnaire scores with a Microsoft Excel spreadsheet to minimize mathematical error prior to entry. All outcome measure data will be entered into separate spreadsheets by two individual investigators.

Data Editing – Data means and standard deviations will be calculated each month and crossed- referenced between databases for each investigator. If means are different investigators will look to determine which outcomes differ. In the case that investigators cannot come to a consensus on the correct outcome measure, Dr. Darin Padua will act as an arbiter.

Updating – Data may need to be updated due to an error in data entry. After the incorrect data point has been determined the investigator in charge of that data set should be notified and the Signature Log should be signed indicating who changed data in the spread sheet, what data was changed, for what reason was it changed as well as the time and date it was changed. A new database with the current date should be created. The previous database with the error should not be deleted.

Reporting – Investigators will report the number of patients that were recruited each week at the study meetings. Investigators will anticipate 4 and 8 week follow–up testing in scheduling laboratory visits and report data that was not collected for follow-up time points due to patient drop outs. Report

Statistical Analyses – All data will be reported directly from Epi Info to SPSS.

3.0.1 External Data

The only external data that will be collected in this study will be Kellgren-Lawrence Score which will determined by Dr. Nissman from Radiographs that are stored in each patients medical record. These data will be requested from Dr. Nissman by supplying each patient's name and date of birth. Dr. Nissman will provide the study team with a value for both knees which will be used for stratification prior to randomization into a treatment group.

3.p Quality Control

3.p.1 Standard Operating Procedures

The Sports Medicine Research Laboratory (SMRL), directed by Dr. Darin Padua, will be the site for data collection and analysis. All questionnaire data collected in the clinic will be immediately brought returned to the clinic. Participant research folders with signed consent forms will be located in locked cabinets. File drawers of these cabinets will be locked at all times and only study personnel will have access to keys that will open these drawers. All electronic data will be saved on password protected computers which will only be accessible to the study team. All Investigators will comply with all ethical standards that are mandated by the University of North Carolina IRB. The PI in study procedures, methods for data collection, data entry, and consenting procedures will train all study personnel.

3.p.2 Data and Forms Check

Data will be checked using several methods including the data entry, data editing and data updating that have been outlined in section 3.O. We will use a double data entry technique and clean data as it becomes available in the Info Track databases. Means and standard deviations will be checked weekly to determine that the double data entry databases provide the same values for central tendency and variability for all outcome measures. Two separate investigators, using a Microsoft Excel calculation spreadsheet, will calculate outcomes from forms. Versions of forms and spreadsheets will be evaluated every time data is entered into the spreadsheets or when forms are provided to the patients.

3.p.3 Data Double Entry

We will use a double data entry technique and clean data as it becomes available in the Info Track databases. Means and standard deviations will be checked weekly to determine that the double data entry databases provide the same values for central tendency and variability for all outcome measures. Two separate investigators, using a Microsoft Excel calculation spreadsheet, will calculate outcomes from forms.

3.p.3 Clinical Monitoring

Dr. Golightly will use visit the Meadowmont Physical Therapy Clinic on a monthly basis and observe the administration of the therapeutic exercises that are detailed in section 3.g. Dr. Golightly will determine and document if the Physical Therapists are complaining with the descriptions of the exercises and dictating treatment progressions correctly. These monitoring procedures have been described in 3.m.

3.r Study Completion and Closeout Procedures

Types of Study Close-out

The two types of closeouts include a scheduled closeout, which occurs upon completion of the trial and an unscheduled closeout which may occur as a result of failure to obtain continuation funding, negative or positive findings, findings in other studies that impact on the clinical trial, or other unforeseen events. Dr. Pietrosimone is responsible for ensuring the following activities are completed prior to study close-out along with the Participant Close-out Procedures described below.

Study Forms

- All outstanding Case Report Forms (CRFs) should be collected, organized, and any corrections made, where necessary.
- All data queries should be corrected and resolved.

Safety Reporting

- All adverse events (both serious and non-serious) should be recorded and followed up to resolution in accordance with procedures detailed in the protocol.
- All serious adverse events (SAEs) should have been reported to the Data and Safety Monitoring Board (DSMB) or Safety Officer, Institute, Institutional Review Board (IRB), and other organizations, as specified in the protocol and Safety Monitoring Plan.

- All adverse events should have been reported as specified in the protocol.

Study Files

The investigator's study files should be complete and up-to-date with originals of the following maintained in the Study Binder, as relevant:

- Investigators Curriculum Vitae(s) (CVs), Investigator's Brochure(s) as relevant
- IRB approval letters for the protocol, all amendments, Informed Consents, annual reviews and advertisements (including updated approvals)
- IRB membership list
- All IRB correspondence
- Signature log
- TENS logs
- Copy of randomization code for randomization
- All informed consents should be signed and on file.
- Record retention procedures should be documented with respect the seven-year length of retention outlined in the manual of operating procedures.

Clinical Supplies

- Donjoy Global, who supplied the EMPI Select TENS units will be notified of the end of the study and TENS units will be shipped back to the company.

3.r.1 Participants Notification

After all data for main outcome measures are calculated and published in peer-reviewed publications we will notify participants about the main finding of the study with a summary publication electronically mailed or mailed through the United States Postal Service (determined via participant preference). The study site should prepare a letter that thanks each study participant and could include the following information:

- Study findings
- Treatment assignment, as relevant to patients in the TENS + TE or the Sham TENS + TE group
- Treatment options, as relevant, whether continued treatment (TENS + TE or TE only) is indicated, and how and where treatment may be obtained
- Rights to confidentiality, privacy, and to no further contact from study staff, if that is participant's preference
- Subsequent updates or new and important information regarding knee osteoarthritis treatment
- Contact information of study staff

A copy of the letter should be included in the participant's file.

3.s Policies

3.s.1 Privacy and Confidentiality Procedures

The privacy and confidentiality of research participants are to be respected and protected at all times. This research study will comply with the HIPAA Privacy Rule as well as all other state, federal, and institutional regulations intended to protect the rights, safety, and welfare of human participants involved in research studies. We will attempt to minimize the collection, storage, and transmission of information containing patients' personal identifiers, and, whenever identifiers are necessary, protect against unauthorized access or disclosure. In addition, we will employ several rigorous procedures for protecting against risks to participant privacy and confidentiality of data. We will only collect and store information about study participants that is relevant to the research as outlined in the protocol. All electronic data will be collected and stored on password protected computers. Some paper documents, such as the consent form, will be required, and these will be stored in a locked file cabinet in a locked office of a study team member. We will establish a shared folder on a secure University of North Carolina at Chapel Hill server to house all study data. This folder, as well as all study databases, will be password protected, and only study team members whose job functions require access to these data will have permissions. Individual patient data will not be shared with individuals outside the study team, except as required by law and/or for regulatory purposes.

All study staff must regularly fulfill certification requirements in Human Subjects Protection training. Study personnel are also regularly trained in stringent computer and information security procedures. All electronic study data will be securely backed up on a nightly, monthly, and biannual schedule. Monthly and biannual backups will be kept on static media throughout the duration of the study and for at least 5 years after study completion.

Research study records will be maintained for no less than 7 years following the completion of the study, after which time personal identifying information will be removed. Research information in a subject's medical record will be kept indefinitely.

3.s.2 Publication Policy

The study team will seek to publish and present study findings as soon as they are available. We will aim to write papers describing the study design, baseline sample characteristics, and other analyses of interest regarding baseline measures, prior to publishing the results of the specific aims. We process data throughout the study so that analyses of main study outcomes may begin very shortly after the final assessments are completed. The study team will follow guidelines for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). We expect that manuscripts describing main study outcomes will involve authorship of all study co-investigators (as long as ICMJE criteria are met). Other manuscripts must be reviewed and approved by the Principal Investigator, at minimum, before submission. All main outcome measures for study objectives reported on clinicaltrial.gov will be published regardless of if results confirm *a priori* hypotheses.

3.t MOOP Maintenance

Dr. Pietrosimone and Brittney Luc will maintain and update the Manual of Operations and Procedures (MOOP) throughout the study. To ensure accuracy and facilitate revisions and/or additions, pages of the MOOP will contain the version date. If any piece of a MOOP is changed the date on the front cover of the MOOP will be adjusted for easy identification. If a new version of the MOOP is created it will be electronically mailed to all participants on the study team. Additionally, the MOOP will be maintained in a three-hole binder and available to all study staff members for review. MOOP maintenance will be on the meeting agenda each month

Appendices

Appendix A. IRB Protocol
Appendix B. Consent Form
Appendix C. Screening Log
Appendix D. Intervention
Appendix E. Study Visits and Evaluations
Appendix F. Adverse Events Forms
Appendix G Confidentiality and Conflict of Interest Statement for Safety Officer
Appendix H. Sample Protocol Deviation / Violation Log
Appendix I: NIAMS Clinical Trial Closeout Procedures and Check List