Study Protocol

Project Title:	**Version Date:**
Prevention of skeletal muscle adaptations to traumatic knee injury and surgery	7-2-19

NCT number:	NCT02945553
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Summary

Injury to the knee joint and its associated soft tissues, such as the anterior cruciate ligament (ACL) and menisci, is common and highly debilitating. Surgical treatment improves knee biomechanics and function, but muscle weakness often persists for years despite rehabilitation, hindering resumption of normal activities, increasing risk of further injury and, in a majority of patients, accelerating the development of post-traumatic knee osteoarthritis (PTOA). The time interval from injury through the early, post-surgical period is critical for the development of functional deficits, as trauma from the injury and surgery combine with muscle disuse to reduce skeletal muscle size and function. Rather than attempt to remediate these adaptations after they occur, which is marginally successful, a more proactive approach that prevents these adaptations from developing may yield better long-term functionality and, in turn, improve clinical and patient-reported outcomes. The post-injury and early, post-surgical periods, however, are not amenable to classic rehabilitation strategies, requiring development of new rehabilitative approaches. To address these gaps in clinical treatment options early following ACL injury and surgical repair, our goals in this project are to: 1) to evaluate the utility of neuromuscular electrical stimulation (NMES), begun early following knee injury and maintained through the early, post-surgical period, to prevent muscle atrophy and intrinsic contractile dysfunction. Our rationale for these studies is that prevention of skeletal muscle fiber atrophy and intrinsic contractile dysfunction will maintain whole muscle functionality in the injured leg, as these cellular indices are fundamental determinants of whole muscle function. Accordingly, the effect of NMES to maintain whole muscle function may reduce the risk for re-injury and PTOA progression, as well as improve patient-reported outcomes. To accomplish our goals, patients with traumatic knee injury will be randomized to our current standard of care rehabilitation or rehabilitation plus early use of NMES or a sham NMES, with measurements of skeletal muscle structure and function at the whole body, tissue and cellular levels, as well as patient-reported outcomes. NMES will begin shortly following injury (within 3 wks) and run till 3 wks post-surgery, with volunteers being evaluated twice pre-surgery and then at 3 wks and 6 mos post-surgery for muscle size, function, clinical and patient-oriented outcomes and deterioration of knee joint cartilage. Primary outcomes of muscle fiber size and function will be measured from tissue acquired from skeletal muscle biopsies at 3 wks post-surgery from both the injured and non-injured legs. If successful, our results could shift conventional thinking/clinical practice in this field to emphasize the need for early rehabilitative interventions to prevent skeletal muscle atrophy and dysfunction. Moreover, our data will provide important preliminary data to set the stage for development of a randomized, controlled clinical trial to more adequately test the utility of NMES to prevent the progression of PTOA.

Purpose:

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Objectives:

Our *primary goal* is to evaluate the utility of NMES, begun early following knee injury and maintained through the early, post-surgical period, to prevent muscle atrophy and intrinsic contractile dysfunction. Prevention of skeletal muscle fiber atrophy and intrinsic contractile dysfunction will maintain whole muscle functionality in the injured leg (*secondary goal*), as these cellular indices are fundamental determinants of whole muscle function. Our *rationale* is that effects of NMES to maintain whole muscle function will reduce the risk for re-injury and PTOA progression, as well as improve patient-reported outcomes. Two aims are proposed:

Primary Aim: To define the effect of early use of NMES during the post-injury and early, post-surgery periods on adaptations in skeletal muscle fiber size and function in patients with traumatic knee injury.

Hypothesis: Early implementation of NMES will prevent or diminish skeletal muscle fiber atrophy and intrinsic contractile dysfunction.

Secondary Aim: To examine whether early NMES improves whole muscle function at short-term follow-up.

Hypothesis: Early NMES will improve whole skeletal muscle isokinetic contractile function.

Study Design:

Patients with recent, unilateral ACL rupture or combined ACL rupture/meniscus injury, who are undergoing surgical reconstruction, will be recruited and randomized to active NMES or control (placebo) interventions, with stratification for age, sex and graft type (knee extensor autograft, knee flexor autograft or allograft). All personnel performing assessments on patients/tissue will be blinded to group assignment. A within-subject design will be used, where the injured, surgically-treated leg will be compared to the contralateral, uninjured leg. NMES or control interventions will begin shortly following injury (within 3 wks) and run till 3 wks post-surgery. Patients will be evaluated twice pre-surgery and then at 3 wks and 6 mos post-surgery. There is the possibility for an additional visit prior to Pre-Surgery Testing #1 to assure that we consent volunteers and start the NMES/control intervention prior to 3 week post-injury. We will make every attempt to limit this

Pre-surgery testing #1 (within 3 wks of injury) will consist of clinical/patient-oriented assessments (IKDC, KOOS) and functional testing (uninjured leg only).

Consent/Device Training Visit will occur within 3 wks of injury to begin the NMES/control intervention if the Pre-surgery testing #1 visit cannot be scheduled within this time constraint. Volunteers will be consented and will undergo training in the use of the NMES or control intervention (detailed below).

NMES/Control intervention will begin within 3 wks of injury following pre-surgery testing, with patients randomized (1:1). Active NMES intervention will consist of active NMES 5 d per week, with each session lasting 60 min. For the control intervention, volunteers will receive a sham NMES device to maintain blinding and will be told that they will receive imperceptible, microcurrent stimulation for pain mitigation. In the sham device, electrical leads are disconnected so that no current can leave the NMES device.

Pre-surgery testing #2 (~1 wk pre-surgery) will be identical to Pre-surgery #1 testing, but will include strength testing of the injured leg.

Post-surgery testing #1 (3 wks) will consist of bilateral muscle biopsies for cellular structure and function measures and bilateral thigh muscle size assessments.

Standardized rehabilitation will begin 3 wks post-surgery, with both groups undergoing the same accelerated rehabilitation program that is standard of care within our practice.

Post-surgery testing #2 (6 mos post-surgery) will include bilateral thigh muscle size and strength, single leg hop test, clinical/patient-related outcomes and magnetic resonance imaging-based assessments of cartilage volume/composition. Physical activity will be measured by accelerometry (5 d each) throughout the study to be used as a possible covariate in our statistical model.

Procedures:

All of the procedures and interventions on volunteers recruited for these studies are carried out solely for research purposes, as none are part of standard therapy in ACL rupture patients that are candidates for surgical repair. We will describe procedures that will be performed for the Primary and Secondary Aims.

Primary Aim

Primary outcomes include: skeletal muscle fiber cross-sectional area (CSA) and contractile function.

Percutaneous skeletal muscle biopsy of the vastus lateralis (VL) will be performed on both the injured and non-injured leg 3 wks following surgery. Tissue will be proportioned for mechanical (single fiber function) and immunohistochemical (IHC) measurements. The VL was chosen because of its importance in attenuating shock to articular cartilage during normal ambulation. Thus, deterioration of function in the quadriceps muscle group may have implications for longer-term development of knee osteoarthritis in ACL injured/reconstructed patients. The following measures will be assessed from muscle tissue.

Single fiber function will be assessed on segments of chemically-skinned muscle fibers, as used routinely by our lab. *Cellular function* will be measured on chemically-skinned, fiber segments, including force, velocity and power, as described by us (1). These measures will be available on the most abundant fiber types: MHC I, IIA and IIAX (>90% of fibers in cancer patients (2)).

Single fiber cross-sectional area (CSA) will be measured by IHC, as described (1), with the addition of MHC IIA and IIX antibodies to delineate MHC II sub-types, as described (3), as these comprise the majority of fibers (MHC I, IIA, IIAX; >90%) in cancer patients (4).

Secondary outcome is accelerometry measures of weight-bearing activity. Procedures that will be performed on volunteers to obtain these primary and secondary outcome measures are described below.

Accelerometry will be performed (5 d each): at baseline and ~weekly throughout the 5 week intervention, as described (5).

Secondary Aim

Primary outcome is knee extensor torque.

Thigh muscle function will be assessed by isokinetic/isometric dynamometry (70° isometric and 60 and 180 °/sec isokinetic), as described (5), to determine whether use of NMES improves retention of knee extension torque by comparing between injured and non-injured legs.

Secondary outcomes include: clinical and patient-oriented outcomes, functional testing (single leg hop) and quadriceps muscle cross-sectional area. These outcomes are assessed with the goal of providing preliminary data to the expected randomized clinical trial if our hypotheses are proved correct.

Clinical/Patient-oriented outcomes including IKDC score, MOS-SF36 and KOOS scales.

Whole leg functional testing will be assessed using the single leg hop test, as described by us (6).

Quadriceps muscle cross-sectional area will be measured to examine whether protection of NMES against atrophy apparent at the single fiber level (primary outcome) is evident from whole muscle imaging measures. This would allow for easier tracking of the efficacy of NMES using whole muscle imaging in future trials.

Cartilage volume and composition will be measured in patients at 6 months post-surgery. This

measurement is included to evaluate whether NMES helps to mitigate the progression of PTOA, as measured by decline in cartilage volume, and is included to inform future trials. The MRI measurement will be conducted at UVMMC and post-processing of de-identified MRI scans will be accomplished by our collaborator, Dr. Brian Petrisimone, at the University of North Carolina.

Interventions

NMES will be conducted on the quadriceps of the injured/operative leg using a portable device (Empi Continuum; DJO Global), starting within 3 wks post-injury and continuing till 3 wks post-surgery, with NMES re-started 72 hrs post-surgery. The injured leg will be immobilized at 40º, with electrodes affixed to the anterior surface of the thigh, as we have shown that even maximal contraction at this angle produces minimal strain on the healing ACL graft (7). Symmetrical, biphasic pulses (400 μs duration at 50 Hz) will be used, with a duty cycle of 50% (10 s on, 30 s off) and maximal-tolerated, contractions below pain threshold using patient-selected intensity. NMES sessions will occur 5 d/week, once daily for 60 min per occasion (5 min warm-up, 50 min stimulation, 5 min cool down). Volunteers will self-report device use and stimulation intensity (see Appendix 1), both of which will be reviewed during weekly phone contacts, with self-reported adherence confirmed using the compliance monitoring feature built-in to the NMES device software.

An issue with the built-in compliance monitoring feature is that the research team only learns of volunteer non-compliance after s/he returns that device. That is, if the volunteer is not truthfully completing the self-reported compliance log and reporting non-compliance during weekly phone contacts, s/he could be skipping NMES sessions without the research team's knowledge. To overcome this problem and to improve compliance with the NMES intervention, we have designed a modified NMES device and smartphone/tablet app that allows for real-time monitoring of compliance with the NMES prescription. In collaboration with Dr. Chris Skalka, an assistant professor in the Dept. of Computer Science, as well as a senior engineering capstone design group, we have designed a cyber-physical system that provides real-time compliance tracking of NMES use. This is detailed in the attached proposal, which was funded by a LCOM/CEMS Biomedical Engineering Pilot Grant. Briefly, this system encompasses three components: an instrumented NMES device, a smartphone app and a back-end server program with automated compliance analysis capabilities. The instrumented NMES contains a low-cost, low-powered, embedded device that detects, quantifies and stores NMES device use data and can transmit these data via Bluetooth (detailed in attached Appendix to Amendment 11). The smartphone app is able to acquire data (data pull) from the instrumented NMES device and communicate the data to a back-end server via the Internet, where data will be stored, analyzed, and made available to care providers. Finally, there is software on a HIPAA compliant portion of the LCOM server that will store these data and analyze them to calculate compliance with the NMES regimen. We will ask volunteers to use this device to test the utility of this cyber-physical system to track compliance with the NMES prescription. The device itself does not work any differently than a standard NMES device, with the exception of the requirement to turn on an additional power switch. The smartphone/tablet app is simple to use and the volunteers will be instructed on its use. Finally, the server-based software is also designed to automatically send 'push' notifications to the volunteer's phone/tablet to provide positive reinforcement when s/he completes assigned NMES sessions and to inquire if there are any problems or if the volunteer would like to contact the research team if there is non-compliance. In addition to these contacts, the research coordinator will be in contact with the volunteer on the usual schedule of interactions (once per week) to inquire about compliance and any issues the volunteer might be having with the NMES device. Finally, the app is written for the iOS operating system. If the volunteer does not have a compatible device, we will loan them a device for the duration of the study.

Control intervention Volunteers randomized to control will receive a sham NMES device to maintain blinding and will be told that they will receive imperceptible, microcurrent stimulation for pain mitigation (8). In the sham device, leads are disconnected inside the device so that no electrical current is emitted. Patients in the NMES group will, in turn, be told that their intervention will both induce muscle contraction and provide pain mitigation, so that any placebo effect for pain mitigation will be evenly distributed between groups. Controls will undergo the same frequency of interaction with study personnel as the NMES group

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Questionnaires:

We will assess patient symptoms and functionality using the IKDC score, the MOS-SF36 and the KOOS knee score.

Risks/Benefits:

Potential risks: Below we have highlighted those procedures/measurements that have anything greater than negligible risk to the volunteers' health for each phase of the study.

Muscle biopsies: Risks associated with the muscle biopsy procedure include excessive bleeding, persistent numbness or infection. In general, all of these risks are well below 1% (1). Regarding bleeding risk, any volunteer with known coagulopathies will be excluded from participation. Any volunteer that is taking medications that may impact coagulation (eg, NSAIDS) will be instructed to discontinue this medication prior to the biopsy, as approved by their physician/surgeon. Our laboratory has never had an adverse event related to the muscle biopsy procedure. The muscle biopsy will be performed by trained, qualified clinicians in a closely-controlled, medical environment.

Muscle strength testing: There is risk for muscle soreness or injury resulting from whole muscle functional testing. Appropriate warm up exercises will be performed to prevent muscle soreness/injury.

Whole leg functional testing (single leg hop): The single leg hop tests carries a small risk that the healing ACL graft could be damaged. To minimize this possibility, we will not perform this assessment until the surgeon has cleared the volunteer for this test. Our laboratories (Beynnon) have extensive experience with performing this test on volunteers with ACL reconstruction at 6 months post-surgery without any adverse events.

Quadriceps muscle cross-sectional area: Each CT scan of the mid-thigh (2 per volunteer) exposes volunteers to the equivalent of 110 d of normal background radiation. The exposure from the CT is focused on a single slice at mid-thigh.

NMES intervention: NMES is a generally safe procedure, delivered in the proposed study by an FDA approved device. Although evidence is limited, some have suggested that NMES could increase the risk of DVT, which may have serious health consequences. However, the risk of DVT in this population is quite low and we will exclude any individual with a known coagulopathy. Moreover, because of the location of the stimulating electrodes (upper leg), the risk of NMES dislodging a DVT is likely minimal. Patients may experience some painful muscle contractions as they first adjust the stimulus to a tolerable level, this will be quickly mitigated by reducing the stimulation intensity. After treatment, muscle soreness may occur. The level of fatigue and/or soreness, however, will be similar to that which occurs following a standard exercise training session and should dissipate over time as the voluneer's muscles become accustomed to the electrically-stimulated contractions (ie, they become trained). The modified NMES device functions are identical to an unmodified device (certified by UVMMC TSP; see attached

email from Wallace Elliott). Thus, the risks of using the modified device are the same as above.

Control intervention: The modified NMES device will not emit any current. Thus, there is no risk associated with this intervention.

Magnetic resonance imaging (MRI): MRI is a generally safe procedure. The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. The subject may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. There is a small risk of decreased hearing immediately after an MRI scan. To help lessen this risk, subjects will be asked to wear earplugs or earphones while in the magnet. Some degree of fatigue or anxiety could occur while undergoing testing. Should this occur, efforts will be made to minimize discomfort.

Benefits: NMES may improve skeletal muscle structure or function and, in turn, preserve muscle strength, as it has been found in other orthopedic surgical conditions (2). If NMES is shown to have beneficial effects on skeletal muscle, further research and application of the technique to ACL injured patients may assist in the development of more effective post-injury/surgery care to mitigate long-term functional morbidity and the development of PTOA.

Literature cited

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Therapeutic Alternatives:

There are no therapeutic alternatives to NMES following injury and no standard of care rehabilitation interventions at this time. Following ACL reconstruction surgery, all patients will receive physical rehabilitation in accordance with current standard of care practices.

Data Safety and Monitoring:

Considering the size and scope of the study, which, because of the limited follow-up with the R21 mechanism, does not include assessment of final clinical outcomes (eg, progression of PTOA), as well as the low risk to participants, and pursuant to NIH guidelines, we will establish a formal Data Safety Monitoring Plan, which will provide oversight to protect against risk to safety and confidentiality.

The PIs (Toth and Beynnon) and Drs. Slauterbeck will monitor the safety of the research procedures for this study on a daily basis. If an event occurs that affects participant safety, the PIs and/or Dr. Slauterbeck will alert the Safety Officer (Clinical Orthopedist: Adam Shafritz), who will adjudicate the event with respect to its severity, expectedness and relatedness to participation in the study according to the aforementioned criteria. If any problems arise with the NMES intervention, the research coordinator, who will not be blinded to treatment status, will address this problem with the Safety Officer to determine the course of action that is in the best interest of the patient's safety and long-term health. Because numerous clinical trials in our laboratory have demonstrated the safety of the proposed regimen of testing in patients from a broad range of clinical backgrounds (eg, young knee trauma patients, heart failure patients, cancer patients, healthy elderly), we expect minimal problems related to testing. Thus, we do not feel that it is reasonable to incorporate "stoppage criteria" for the overall study. Instead, the Safety Officer will decide whether an individual participant should continue with the study following occurrence of any adverse events or unanticipated problems taking into consideration what is in the best interest of that individual.

On an annual basis, Drs. Toth, Beynnon and Slauterbeck will assess data being gathered and safety of volunteers to assess the pattern or frequency of events to identify occurrence of any event or problem that significantly alters the safety profile of the procedures being performed, unless occurrence of a serious adverse event or unanticipated problem necessitates re-evaluation of the expected risk of the study procedures at an earlier time point. Additionally, they will evaluate data collection and storage to ensure the confidentiality of data and quality. Each of these evaluations will be followed by reports of study progress and patient safety to the University of Vermont Committee on Human Research in the Medical Sciences via yearly progress reports and to the appropriate NIH program officer. The report will include information regarding study status, participant information and safety information. This report will

also be forwarded to the Safety Officer for his/her independent review. Following his/her review, an additional meeting between the Safety Officer and the PIs will be held to finalize that year's safety report.

Adverse Event and Unanticipated Problem Reporting:

Adverse events will be reported by one of 3 mechanisms. First, the joint University of Vermont/University of Vermont Medical Center (UVMC) Committee for Human Subject Research Adverse Event Reporting Document. These reports will be forwarded to the office of the Committee for Human Research in the Medical Science (CHRMS) within 5 days of the event. Reporting any adverse events will be the responsibility of the PI. The CHRMS will make a determination as to whether additional reporting requirements are indicated. Second, the UVMC Patient Safety Reporting system (SAFE), which may be initiated by health care center staff or study personnel. These forms will be forwarded within 3 days to the PI, UVMC Risk Management Office, CHRMS and other appropriate agencies, as indicated by the nature of the report. Finally, the UVMC Medication/IV Event Report Form, with distribution and timing as noted above. This latter mechanism might be used with events related to blood sampling. Reviews of protocol specific adverse events will be performed no less than annually. Additionally, any adverse event that occurs will be forwarded to the PI for reporting to the Human Subject Research Protection Office within 1 week of occurrence. Of note, these protections against risk include both physical risks to the volunteers, as well as risks associated with any breach in confidentiality.

On an annual basis, Drs. Toth, Beynnon, Slauterbeck and the Safety Officer will assess data being gathered and safety of volunteers to assess the pattern or frequency of events to identify occurrence of any event or problem that significantly alters the safety profile of the procedures being performed, unless occurrence of a serious adverse event or unanticipated problem necessitates re-evaluation of the expected risk of the study procedures at an earlier time point. Additionally, they will evaluate data collection and storage to ensure the confidentiality of data and quality. Each of these evaluations will be followed by reports of study progress and patient safety to the University of Vermont CHRMS via yearly progress reports and to the appropriate NIH program officer. The report will include information regarding study status and safety of volunteers (occurrence of AEs/SAEs. This report will also be forwarded to the NIH Program Officer for his review.

Withdrawal Procedures:

Volunteers will be withdrawn if the research team, clinician and/or safety officer feels that further participation in the study or performance of any procedure associated with this study would, in any way, put the volunteer at undue risk or not be in their best interest. Moreover, volunteers may be withdrawn if s/he fails to attend scheduled visits or do not comply with instructions from research staff.

Sources of Materials:

An individual research record will be kept on each volunteer in compliance with HIPAA standards. This record will contain identifying data, demographic information and results from all clinical research measurements and evaluations. The results of all testing will be kept confidential. In addition, skeletal muscle tissue samples will be taken and will be used for measurement of muscle size, structure and function. All materials gathered in conjunction with the proposed studies will be used for research purposes only and will be available only to research personnel working on these studies, who have obtained proper training in human subjects research and privacy protection.

DRUG AND DEVICE INFORMATION

Drug (s) [X] ***Not applicable***

Device (s) [ ] ***Not applicable***

The interventional device used in this study: EMPI Continuum complete electrotherapy system has received FDA approval (501K: K093324) for retarding disuse-related atrophy, which we believe is one of the primary mechanisms whereby muscle adaptations evolve in patients in the early, post-surgical period. That is, muscle disuse secondary to pain, limited range of motion and muscle weakness (the latter being due to neural inhibition caused by joint pain/swelling) causes skeletal muscle fiber atrophy and weakness.

For the control intervention, an EMPI 300PV that is modified to have its leads disconnected within the device will be used. For both leads on the device (1 and 2), the ferrites directly proximal to the leads are removed and a dummy load resistor (1 Megohm) is used to bridge the output to simulate the resistance of human skin (see Appendix 3). This bridging is necessary, as the device will not function if no load is detected. This yields a device that cannot deliver any electrical stimulus to the patient throughout the stimulus intensity range of the device.

FDA approval:

The EMPI Continuum is approved to mitigate muscle atrophy/dysfunction associated with muscle disuse (501K: K093324).

Risk assessment:

The device (and similar devices) has been used extensively in the orthopedic and neural rehabilitation settings by physical and occupational therapists and in numerous disease states (heart failure, chronic obstructive pulmonary disease, knee replacement) to improve muscle size and function in clinical trial settings. Thus, NMES is generally a safe modality, with a long safety record. Although evidence is limited, some have suggested that NMES could increase the risk of dislodging a deep vein thrombosis (DVT) because of the rhythmic muscle contractions induced by the electrical stimulation. However, several published reports show that NMES significantly reduces the risk of developing DVTs. In fact, the device we are using is FDA-approved for prevention of DVT of the calf muscles immediately following surgery, as it would function similar to intermittent pneumatic compression. Moreover, the population we are studying is generally at low risk for DVT and we will actively exclude any individual with a known coagulopathy or DVT. Because of the location of the stimulating electrodes (upper leg), the risk of NMES dislodging a DVT is likely minimal. Finally, during the first couple of NMES sessions, muscle soreness may occur, but this is comparable to what might occur with classical exercise training and dissipates over time.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection:

A single cohort of patients will provide data to address both aims. Patients with recent, unilateral ACL rupture or combined ACL rupture/meniscus injury, who are undergoing surgical reconstruction, will be recruited and randomized to NMES or control, with stratification for age, sex and graft type (knee extensor autograft, knee flexor autograft and allograft). A within-subject design will be used (Fig 3), where the injured, surgically-treated leg will be compared to the contralateral, uninjured leg.

We chose to study patients with ACL rupture, with or without meniscus injury, as this trauma is immediately disabling, dramatically reduces muscle strength and increases the risk of further injury and developing PTOA (1-4). Although neuromuscular adaptations differ slightly between ACL and combined ACL/meniscus injury post-surgery, injury types will be distributed equally by randomization. Inclusion of both injury types provides broader generalizability of our results. We will also stratify randomization by graft type (knee extensor autograft, hamstring autograft and allograft groups) using an adaptive randomization approach to assure that groups are frequency matched for the different graft types.

Use of the uninjured leg as a within-subject control is common in this field and justified by results from our labs (4) and others (5) showing that its size and function are maintained throughout the proposed study period (4, 5). While whole muscle strength in the uninjured leg is reduced slightly compared to uninjured control volunteers due to cross-over neural inhibition (6), there is no evidence that this would affect the intrinsic structure or function of its single muscle fibers differently in NMES and control groups. Nonetheless, we will assess strength in the uninjured leg repeatedly throughout the study to verify its constancy and, in turn, its suitability as a within-subject control, particularly for the secondary aim.

Within 3 wks of injury is the closest time point for initiation of NMES in our experience (7-12), with the rationale that starting closer to the index injury would best preserve muscle size and function. Practically speaking, individuals who tear their ACL and require surgical reconstruction typically do not get a final diagnosis of the ACL rupture and the requirement of surgical repair for 1-3 wks post-injury. Thus, the timeframe that we have chosen for starting the NMES or control intervention is in keeping with the typical timeframe that NMES could be used clinically. We will continue NMES till 3 wks post-surgery

because this is when patients typically begin more aggressive strengthening/anabolic exercises and increased weight-bearing activity that would substitute for the NMES stimulus. Building on this last point, we chose to assess our primary outcomes for the primary aim at 3 wks post-surgery, as this is likely their functional nadir based on post-surgical deficits in other orthopedic populations (13), which allows for resolution of the effects of NMES to mitigate atrophy and contractile dysfunction. Finally, we chose 6 mos for primary outcomes for the secondary aim (knee extensor strength) because this represents the time patients are typically tested for return to pre-injury activities, but when there are still marked functional deficits (12) that could adversely affect joint health.

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Number of Subjects:

We intend to enroll a total of 24 volunteers. This will allow for n=20 to complete the study, conservatively assuming 20% total attrition rate.

Inclusion/Exclusion Criteria:

Patients (50:50 men-women) will be included if they are/have: 1) 18-50 yrs; 2) BMI <35 kg/m^2; 3) acute, first-time, ACL rupture with or without meniscus injury and 4) scheduled to undergo reconstruction with any type of autograft or allograft. Patients will be excluded if they are/have: 1) history of prior knee/lower extremity surgery or non-surgical intervention (eg, intra-articular injection) on either leg; 2) abnormal laxity of any lower extremity ligament other than the injured ACL; 3) signs or symptoms of arthritis, autoimmune or inflammatory disease or diabetes; 4) grade IIIb or greater articular cartilage lesions (ICRS criteria) and/or 5) women who are/plan on becoming pregnant.

Inclusion of Minorities and Women:

Inclusion of Women

This study will include equal numbers of men and women.

Inclusion of Minorities

Every effort will be made to recruit minorities for the proposed studies. The contribution of minorities

to the total population of Vermont is 3.2%, with a similar minority profile in Chittenden County (3.6%), where the University of Vermont (UVM) is located.

Inclusion of Children:

The proposed studies will not include children. The rationale for this decision is based on the fact that children are a vulnerable population and it could be argued that performance of the invasive procedures proposed in these studies, such as muscle biopsies, would not be justified without proven efficacy of the NMES intervention. Based upon the Belmont Report (Part C, §3), there is an order of preference for performing research on volunteers, which stipulates that in research that does not have a known therapeutic value, or by extrapolation to the proposed studies, where the utility of the therapeutic intervention is in question, that those less burdened populations should be called upon first to accept the risks of research. In the context of this criterion, this would mean that adults be studied before children. Traumatic knee injury is indeed relevant to children, as a fraction of patients experience this injury in their late teenage years. However, we believe that it is prudent to first investigate the utility of NMES in the adult population before it is evaluated in children. If our studies are successful, we would anticipate that future randomized, controlled trials evaluating the efficacy of NMES to improve current rehabilitation strategies for recovery from traumatic knee injury and surgical repair would include children.

Recruitment:

Patients will be recruited from the Sports Medicine service of the UVMMC Department of Orthopedics and Rehabilitation. Additionally, because we have to identify volunteers within 3 week of injury, we will also receive referrals to our research group from other local clinical practices, local universities and University student health offices who have a suspected ACL rupture. These clinical practices will document patient's interest in the study and consent to have their contact information sent to our research team.

***Consent Procedures**:*

Someone with a treatment relationship will introduce the study to potential volunteers (UVMMC Department of Orthopedics and Rehabilitation, EMRAP, athletic trainers at local universities). If the patient expresses interest in the study and would like more information about the study, the research coordinator or PI will contact the volunteer, explain the study and will provide a copy of the informed consent. The PI and/or the research coordinator will answer any questions by phone or in person. Moreover, the PI or the research coordinator will discuss the protocol with the volunteer at length and answer any remaining questions.

Information Withheld From Subjects:

Volunteers randomized to the sham, microcurrent stimulation group will not be told that the device that they receive was modified to emit no electrical current. This deception is necessary so that we can achieve a proper sham intervention, which was requested by the NIH review group. The review group was concerned that the volunteer's knowledge of no intervention (if we had a standard of care control with no sham device being used) would affect their efforts on volitional tests, such as strength testing (secondary aim) and functional testing, or their report of quality of life and knee pain/function on questionnaires. The latter measurements were of particular concern, as the committee considers these metrics essential for future randomized controlled trials to test the efficacy of NMES in this patient population. Thus, they felt that a sham device was needed to eliminate bias. We will debrief volunteers at the completion of the study regarding this deception.

For debriefing of volunteers randomized to the sham control group, we will contact volunteers by phone to schedule a time to provide them with the Debriefing Form and explain the deception and sign the Debriefing Form. There is also a place on the form for volunteers to check "Yes" or "No" as to whether we may use their data. Many of the volunteers were students. Some of them have moved out of the area since their participation in the study. In these volunteers, we will try to contact them via phone, text or email to debrief them verbally. In this event, study personnel will use a script that mirrors the points noted in the debriefing memo. This Script will also be used to document the volunteers assent/decline to assent, as well as the date of the contact and, for those patients who we cannot contact, these dates of attempts to contact. We will provide the volunteers with a copy of the Debriefing Form and obtain their signature after the phone conversation. For those volunteers who we cannot contact, we will attempt to contact them two (2) times. Any volunteer who cannot be contacted for debriefing will be noted in the Continuing Review.