Neuromuscular Mechanisms of Manual Therapies in Chronic Ankle Instability Patients

NCCIH: 1 R21 AT009704-01

ClinicalTrials.gov: NCT03418051

Version 1: October 11, 2017

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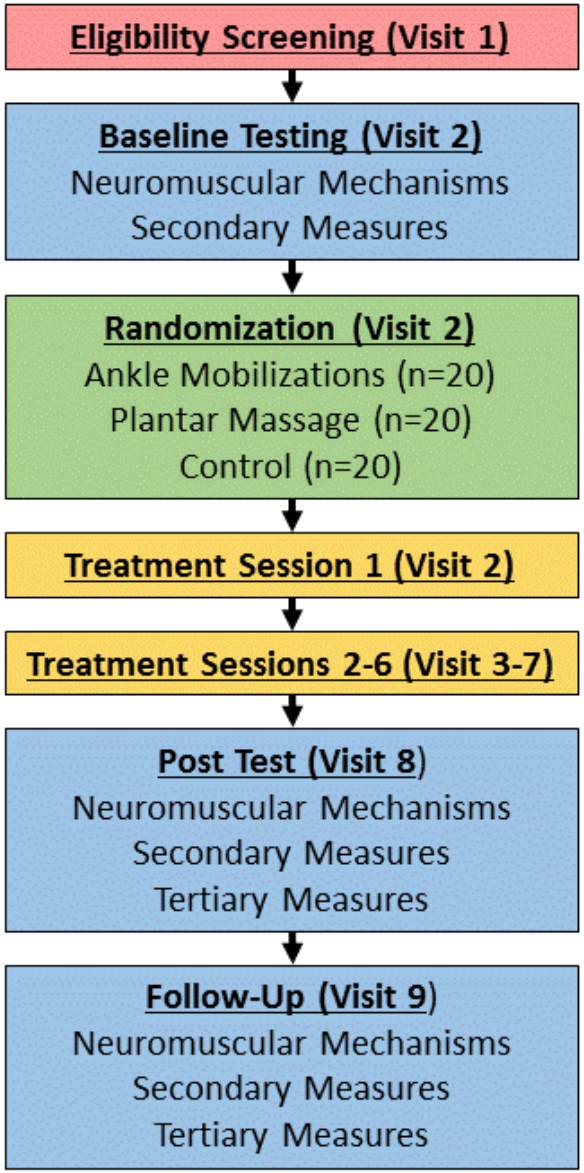
MOOP: Neuromuscular Mechanisms of Manual Therapies in Chronic Ankle Instability Patients

SECTION A: Schedule of Visits & Evaluations

*****Further detail regarding each test session and individual test can be seen in the Study Protocol (Appendix 1).*****

Study Visits / Study Days	Balance Questionnaire (Appendix 2)	PRO Testing AII (Appendix 3) FAAM (Appendix 4) FAAM-S (Appendix 4) Treatment Expectations (Appendix 5)	Informed Consent (Appendix 6)	Neuromuscular Mechanism Testing Joint Position Sense Light-touch Thresholds H-Reflex Corticomotor mapping Corticomotor excitability Cortical Activation % Modulation	Biomechanical Testing Gait Analysis Jump Landing Balance Testing Range of Motion Testing	Treatment Delivery	Adverse Event Monitoring
Visit 1 Eligibility Screening	X	X					
Visit 2 Baseline Testing			X	X	X	X	X
Visits 3-7-						X	X
Visit 8 Post-Test 1				X	X		X
Visit 9 4-week follow up				X	X		X

SECTION B: Study Flow


Eligibility Screening (Visit 1)
Baseline Testing (Visit 2)
Neuromuscular Mechanisms
Secondary Measures
Randomization (Visit 2)
Ankle Mobilizations (n=20)
Plantar Massage (n=20)
Control (n=20)
Treatment Session 1 (Visit 2)
Treatment Sessions 2-6 (Visit 3-7)
Post Test (Visit 8)
Neuromuscular Mechanisms
Secondary Measures
Tertiary Measures
Follow-Up (Visit 9)
Neuromuscular Mechanisms
Secondary Measures
Tertiary Measures

SECTION C: Study Organization

C.1 Roster

Primary Investigator
Erik A. Wikstrom, PhD, ATC
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Co-Investigators
Brian Pietrosimone, PhD, ATC

Troy Blackburn, PhD, ATC

Jason Franz, PhD

Feng-Chen Lin, PhD

Graduate Research Assistants

To Be Determined

For the following situations, please contact the listed individual(s):

Protocol Questions: Erik Wikstrom

To report an Adverse Event at UNC: Erik Wikstrom

To report a Protocol Deviation at the UNC: Erik Wikstrom

All protocol deviations and adverse events will be reported to the PI and Internal Quality Assurance Coordinator, then to the respective IRBs and finally to the sponsor. See Appendices 8 and 9 for the protocol deviation log and adverse event reporting procedures. Appendix 10-12 represent the adverse event reporting forms.

C.2 Coordination of Study

As this investigation has a research team, the official coordinator is Dr. Wikstrom. If unable to contact Dr. Wikstrom, the Internal Quality Assurance Coordinator should be contacted. The following activities will be discussed and agreed upon from monthly in person meetings.

- Development and maintenance of the MOOP
- Randomization scheme and procedures
- Development and implementation of schedules and data tracking
- Development of procedures for data entry, error identification, and error correction
- Adverse event monitoring and reporting
- Communication, scheduling of meetings, responding to and documenting ad hoc communications
- Quality control procedures
- Creating reports – enrollment, adverse events, participant status (e.g., withdrawals)
- Maintaining the study binder (regulatory and clinical documents)
- Preparing study materials
- Assuring the study is conducted according to the protocol and MOOP
- Participating in a Steering Committee and other committees
- Identifying, recruiting, screening and enrolling participants
- Protecting participants' rights
- Obtaining informed consent from each participant
- Collecting study data and following participants through study completion

- Compliance and accountability of administration of study intervention
- Retaining specific records, (e.g., questionnaires)
- Preparing and sending required reports, assuring IRB review and approval

C.3 Pharmacy Activities

N/A

C.4 Steering Committees

As this is a single site investigation, the steering committee will consist of the PI and Co-Investigators (Pietrosimone, Blackburn, Franz, Lin) as well as other key members of the research team (e.g. Graduate Research Assistants. The steering committee will be responsible for:

- General design and conduct of the study
- Preparation of the essential study documents, including the protocol, protocol amendments, MOOP, and data collection forms
- Review of data collection practices and procedures
- Changes in study procedures as appropriate
- Review of study progress in achieving goals
- Review and implementation of recommendations from the Safety Officer.
- Review and response to other general advice and/or recommendations (e.g., from the NIAMS Program Officer)

C.5 Executive Committee

The executive committee of this investigation will be the same as the steering committee.

SECTION D: Training Plan

D.1. Training Process

All staff will be trained through the Collaborative Institutional Training Initiative for Biomedical Research involving human subjects. In addition, all staff will be trained by the PI or a senior member of the research team based on expertise in the following prior to engaging in any research activities associated with this project:

1. Determining subject eligibility
    a. Proper instructions for each questionnaire (Appendices 2-4)
    b. Using the eligibility checklist (Appendix 13)
    c. Enrolling a participant who is eligible (Appendix 7)
2. Securing informed consent (Appendix 6 and &)
3. All data collection procedures (Appendix 1)
4. Randomization process and sequence for each participant (Appendix 1)
5. Data storage and analysis. (Appendix 1)
6. Reporting adverse events and protocol violations (Appendices 8 & 10-12)
7. Using the MOOP

The training of each staff member will be documented using the training checklist included as Appendix 16 and signed by both the staff member and the PI/QA coordinator.

D.2. Informed Consent Process

All staff will be trained in the consent process to ensure that each member understands that participants are initially screened with the questionnaires mentioned in Appendices 2-4. If a potential participant is considered to be eligible, the staff member will read through the consent form with the participant and answer any questions. If the participant would like to enroll in the study, he/she will be asked to sign and date the consent form on the signature page. A copy of the signed consent form will be given to each participant enrolled in the study. The original consent form will be stored in the participant's folder which will be stored in the Sports Medicine Research Lab. Records of obtaining consent will be maintain as observed in Appendix 6.

D.3. Communication

While the primary study personnel are familiar with the data collection and intervention procedures monthly meetings will be used to discuss issues that arise with both data collection and treatment delivery. Additionally, PI will meet annually with study personnel involved at their respective sites to ensure proper and timely dissemination of the following information:

1. Adverse Events,
2. Protocol violations
3. Compliance issues
4. Protocol amendments

D.4. Communication Records

In order to ensure consistency in communication across the sites, minutes of each meeting will be recorded and distributed to all study personnel within 72 hours of the phone conversation. Similarly, all study personnel involved with this project will be required to maintain current training through the Collaborative Institutional Training Initiative and remain up to date on the study protocol and amendments (Appendix 1), AEs and SAEs (Appendix 9-12, or Section M of the MOOP), and the documentation plan.

SECTION E: Communication Plan

Monthly conversations and/or meetings among the key personnel have been a regular occurrence. This communication pattern will be maintained throughout the duration of the study in the form of a monthly in person meeting. A log will be kept of meeting minutes. These will be shared between the research team within 72 hours of the meeting.

SECTION F: Recruitment Screening & Eligibility Criteria

F.1 Recruitment Plan

The primary recruitment method at each institution will be word of mouth. This recruiting technique will occur primarily in classroom settings where the PI or research assistants will describe the study and ask those individuals who are interested to complete the screening questions listed above (Appendix 1, section 9.a and section F.2 of the MOOP). The secondary recruitment methods at each institution will be posters and research advertisements (email) that have been approved by their respective IRBs.

F.2 Screening

Interested individuals will be asked to complete 4 questionnaires (per section A of the MOOP and 9.1 in Appendix 1), the balance questionniare, Ankle Instability Instrument (AII); a Foot and Ankle Ability Measure (FAAM); and a FAAM Sport (Appendix 2-4). Based on their responses, eligibility will be determined.

F.3 Screening Log

Because of the use of a partial waiver of consent, as approved each institution's IRB, a minimal screening log (Appendix 14) will be maintained. This is because the partial waivers allow the research team to quickly assess eligibility before consent is obtained and therefore it would be unethical to collect certain information about the individual in question such as age, ethnicity and race. This information will be collected on those enrolled in the study (Appendix 13). See format below:

Example Screening Log Table					
Number	Date	Eligible for Study	Date Enrollment Confirmed	Ineligible for Study	Reason
1	9-1-17	X	9-8-17		
2	9-3-17			X	FAAM score was above 90%
3	9-15-17	X	9-18-17		

F.4 Eligibility Criteria

Inclusion Criteria (per Appendix 13): Males and females between the ages of 18 and 45 with self-reported CAI; defined as self-reported episodes of recurrent ankle sprains and/or the feeling of instability or "giving way" after an initial ankle sprain. Inclusion criteria will consist of a history of at least two episodes of "giving way" within the past 6 months; answering 5 or more questions of "Yes" on the Ankle Instability Instrument (AII) (Appendix 2); a score of <90% on the self-reported Foot and Ankle Ability Measure (FAAM); a score of <80% on the FAAM Sport (Appendix 3 & 4).

Exclusion Criteria (per Appendix 13): Exclusion criteria will consist of failing to meet the inclusion criteria as well as reporting an acute ankle sprain within the past 6 weeks; a previous history of ankle surgeries; lower extremity surgeries associated with internal

derangements, reconstructions, or repairs; lower extremity injuries within the past 6 months (other than ankle sprains); and balance deficits, neuropathies or other disorders or conditions known to affect balance.

Each investigator who evaluates the eligibility of a potential participant will complete an eligibility checklist (Appendix 13) to determine whether the participant fits the inclusion criteria for the study. The investigator is required to check the appropriate boxes, identify and mark the relevant gender and racial/ethnic information (once eligibility is determined), and sign and date the checklist. The PI will then sign the form as well.

SECTION G: Informed Consent & HIPAA

G.1 Informed Consent Process

After eligibility is determined, based on the approved IRB protocol (see Appendix 18 and informed consent document (Appendix 6) [see Appendix 19 for approval letters] participants will be scheduled to come in and meet with the PI or research assistant to review the informed consent document (see Appendix 6) and begin the first test session. All questions will be answered before any data collection begins and the participants will be given as much time as they desire to read the informed consent document and ask questions of the PI or research assistant. When satisfied, both the participant and PI or research assistant will sign the form and a copy of the signed document will be given to the participant upon request. Included in the informed consent material is language indicating that the participants are volunteers and that there is no penalty for not participating. Records of obtaining consent will be maintained per Appendix 7.

If a participant is determined to be ineligible for the investigation (per Appendix 1, section 9.a and section F.2 of the MOOP) then the data collected (to determine eligibility) will be immediately destroyed. Specifically, the Balance questionnaire, AII, FAAM, and FAAM-S data sheets will be shredded to protect participant rights. No other data will be collected prior to the potential participant reading and signing the informed consent document.

G.2 Informed Consent Document

See Appendix 6 for the approved Informed Consent documents.

G.3 HIPAA Authorization

HIPAA authorization is not applicable for this investigation since protected health information will not be collected at any time.

SECTION H: Randomization

Participants will be randomized to one of the three groups (Massage, Joint Mobilizations, or Control) in a 1:1:1 ratio using sealed envelopes generated by the biostatistician. More specifically, we will be using a block randomization technique at each institution so that preliminary data analysis, data monitoring, and safety evaluations will be based on similar, if not identical, numbers in each group. Each block of envelopes will be made and sealed before study enrollment begins and randomization will occur after the baseline evaluation (see section 9.b of Appendix 1). The biostatistician will generate the master randomization list and distribute the envelopes. Each participant will select a sealed envelope containing their group assignment. This assignment will be noted by the research team and recorded.

SECTION I: Blinding / Unblinding

As per section 11 of Appendix 1 blinding will be used in the current investigation. Due to the nature of the intervention, participants will not be blinded but the assessors of the outcome measures will be blinded to group assignment.

SECTION J: Study Intervention

The treatments as outlined in section 9.c of Appendix 1 will include:

Sensory-Targeted Rehabilitation Strategies. This intervention will consist of 6, 5-minute treatments the following over a 2-week period:

Ankle Joint Mobilization: The joint mobilization treatment will consist of 2 sets of Grade III anterior-to-posterior ankle joint mobilizations and one minute between sets. This mobilization will be operationally defined as large-amplitude, 1-s rhythmic oscillation from the joint's mid-range to end range with translation taken to tissue resistance. The objective of this therapy technique is to glide the ankle into the area which restricts range of motion and gently stretch the restricted area. To begin this treatment, a mild traction to the ankle joint to lightly distract the bones of the ankle joint. Then two sets of joint mobilizations, each for two minutes, will be applied. Each repetition will consist of gently gliding the ankle joint in the backward direction until an area of restriction is reached. We will mobilize the joint into the restriction and then glide the ankle back to the starting position. This grade of joint mobilization was selected because it attempts to increase the capsular endpoint and the oscillation spans the length of the joint providing the greatest stimulation of joint receptors. This manual therapy technique is commonly used in athletic training practice and presents minimal risk to participants.

Plantar Foot Massage: The plantar foot massage treatment will consist of 2 sets of 2 minutes of plantar foot massage. This massage will be operationally defined as two minutes of light petrissage (similar to kneading bread) and effleurage (gentle stroking motions) to the plantar surface of the foot from the ball of the foot to the heel. The objective of this therapy technique is to provide stimulation to the plantar cutaneous receptors of the foot. To begin this treatment, we will place our hands on the participant's foot with his thumbs on the plantar surface and his fingers of both hands on the dorsal surface of the foot. We will then apply two sets of massage, each for two minutes. Each set will consist of gently massaging the plantar surface of the foot to the comfort of the participant. This manual therapy technique is commonly used and presents minimal risk to participants.

SECTION K: Participant Evaluations & Follow-Up

K.1 Timeline and visit schedule

See section A (schedule of visits and evaluations) and section B (study flow) of the MOOP.

K.2 Scope

Step by step procedures of each visit are outlined below and illustrated in Figure 1, a replication of section A.

K.2.a Pre-Study (Participant Eligibility)

Interested participants will be asked to fill out on-line questionnaires regarding their age, history of ankle injury (AII), ankle function (FAAM, FAAM-S), and any balance issues to determine eligibility for participation in the study (Appendix 2-4). To be eligible, individuals must meet the following criteria as outlined in section 7 of Appendix 1 and section F.4 of the MOOP. In addition, participants will complete three 1-item questionnaires related to their expectations of treatment efficacy (Appendix 5). These responses will be used to match participants based on their expectations of the treatments to be provided.

Males and females between the ages of 18 and 45 with self-reported CAI; defined as self-reported episodes of recurrent ankle sprains and/or the feeling of instability or "giving way" after an initial ankle sprain. Inclusion criteria will consist of a history of at least two episodes of "giving way" within the past 6 months; answering 5 or more questions of "Yes" on the Ankle Instability Instrument (AII); a score of < 90% on the self-reported Foot and Ankle Ability Measure (FAAM); a score of < 80% on the FAAM Sport. Exclusion criteria will consist of reporting an acute ankle sprain within the past 6 weeks; a previous history of ankle surgeries; lower extremity surgeries associated with internal derangements, reconstructions, or repairs; lower extremity injuries within the past 6 months (other than ankle sprains); and balance deficits, neuropathies or other disorders or conditions known to affect balance.

**If a participant is determined to be ineligible for the investigation, then the data collected (to determine eligibility) will be immediately destroyed. Specifically, the AII, balance questionnaire, FAAM, and FAAM-S, data sheets must be shredded immediately. No other data can be collected prior to the participant reading and signing the informed consent document.

K.2.b Visit 1:

<u>Informed Consent Process</u>

Once eligible, participants will be schedule to report to the research laboratory of the PI at their respective institution. Once there, eligible participants will first read and sign the informed consent document as outlined in section H. Information will then be collected regarding height, leg length, foot measurements, and weight (see Appendix 17) as well as physical activity and overall function (see Appendix 3 & 4). Height, leg length, and

foot size will be measured with a tape measure. Weight will be measured with a scale. Participants will be asked to wear shorts for all testing procedures.

1st Evaluation (Baseline)

The following neuromuscular mechanisms and secondary measures will be completed at baseline:

Peripheral Neuromuscular Mechanisms:

Ankle joint position sense will be used to assess changes in a participant's ability to detect the position of the foot/ankle complex relative to the body. The theoretical premise of this mechanism is that CAI participants have an impaired ability to detect ankle joint position due to altered input from damaged mechanoreceptors.[7] Postural control improvements following manual therapies may be the result of improved input from mechanoreceptors. Ankle joint position sense will be assessed at the mid-range of plantar flexion and inversion as these positions have the greatest sensitivity to CAI associated impairments. Participants will be seated with their foot in neutral (0 degrees of plantar flexion) before an active repositioning technique is used to quantify the absolute and constant error for each movement.

Plantar light-touch thresholds will assess changes in somatosensation on the plantar foot. These thresholds are increased in CAI patients and thought to be the result of repetitive trauma to the mechanoreceptors. The effects of manual therapies may be the result of improved plantar mechanoreceptor sensitivity in CAI patients. To assess this neuromuscular mechanism, we will use a protocol that requires participants to lie prone while thresholds are assessed at the head of the 1st and base of the 5th metatarsal. Thresholds will be determined using Semmes-Weinstein monofilaments and a highly reliable 4-2-1 stepping algorithm.[100]

Spinal Level Neuromuscular Mechanisms:

The Hoffman reflex (H-Reflex) is the electrical analog of the monosynaptic stretch reflex and thought to provide insights into the neuromuscular mechanism mediating postural control. H-Reflex modulation is reduced in CAI patients and correlated to self-reported functional limitations. Thus, improvements in spinal reflexive excitability (increased H-Reflex values) may represent an underlying neuromuscular mechanism responsible for improved postural control following ankle joint mobilization and plantar massage. We will assess spinal reflexive excitability in the soleus and fibularis longus using our established methodology. While lying supine, a stimulating electrode will be positioned over the sciatic nerve in the popliteal space. Peak-to-peak Hoffmann reflexes (H-reflex) will be measured and the stimulus intensity increased until a maximal H-reflex is observed. Three H-reflexes for each muscle will be recorded and normalized to the

maximal M-response, representing the ratio of the motor neuron pool reflexively activated to the amount of the motor neuron pool available (H:M ratio). Higher H-reflex values and H:M ratios indicate greater excitability.

Supraspinal Level Mechanisms:

The corticospinal motor system plays a critical role in controlling movement by optimizing muscle activation. Abnormal facilitation or inhibition from the corticospinal pathway is associated with impairments of the ankle joint musculature and hypothesized to contribute to the postural instability associated with CAI. As such, cortical excitability may represent a plausible neuromuscular mechanism underlying improvements following ankle joint mobilization and plantar massage. Corticomotor measures of the soleus and fibularis longus will be assessed using Transcranial Magnetic Stimulation (TMS) methodology previously used by the research team. A Magstim 200 (Magstim Company, Wales, UK) will be used to produce a magnetic stimulus (max 2.0 Tesla) over the motor cortex contralateral to the test limb. Testing will be performed over the area generating the greatest motor evoked potential (MEP) while participants perform mild isometric contractions (20%) on an isokinetic dynamometer. Active motor threshold (AMT) will be determined as the lowest stimulator intensity required to elicit an MEP peak-to-peak amplitude ≥100μV in at least 4 of 8 trials. A higher AMT indicates decreased excitability, as a greater stimulus intensity is required to elicit an MEP. Eight stimuli will be delivered at 120%, 130%, and 140% of AMT, and peak-to-peak MEP amplitudes will be recorded for each trial. The cortical silent period (CSP) will be measured as the distance from the end of the MEP to a return of the mean EMG signal plus two times the standard deviation of the baseline (pre-stimulus) EMG signal. A longer CSP indicates a greater corticospinal inhibition.

Corticomotor output mapping provides further insight into the function of the motor cortex by identifying the size of an area within the motor cortex associated with a select muscle. Improved postural control following manual therapies may be the result of a reorganization of the corticomotor output in CAI patients (i.e. an increased map area and/or volume of a given muscle). Corticomotor mapping of the soleus and fibularis longus muscle will be assessed using TMS methods consistent the literature and our own protocols. After AMT is quantified, a 6x6 cm grid (3cm lateral-medial and 3cm anterior-posterior) will outline the hotspot for each muscle and a stimulator intensity of 100% AMT will be used. Three consecutive stimuli will be delivered at each grid location in a random order in order to produce reliable and reproducible maps. Average peak-to-peak MEP amplitudes for each grid site will be normalized to M-max. Cortical representation of the soleus and fibularis longus will be calculated using map area and map volume. Map area is the number of stimulus positions whose stimulation evoked an average MEP ≥MEP threshold and an increase would suggest an expansion of the cortical representation of a selected muscle. Map volume will be calculated as the sum of the mean normalized MEPs recorded with an increase suggesting greater cortical excitability.

Alterations in cortical activation could represent an underlying cause of postural control improvements following manual therapies as postural control improves following the application of manual therapies and balance is controlled, at least in part, cortically. To assess changes in cortical activity, participants will complete single limb balance assessments with eyes open and closed while cortical activation is simultaneously assessed using electroencephalography (EEG). A V-Amp 16 active channel EEG system (BrainVision LLC, Morrisville, NC) will be used to acquire the EEG data from three channels (Fz, Cz and POz) based on a 10-20 system. The impedance of each electrode will be kept below 40 kW. Bandpass filters of 0.1 Hz and 65 Hz at 3 dB attenuation will be used to remove environmental artifacts. Post-processing will include identifying and decontaminating artifacts as previously described. The primary mechanisms of interest are the power spectral densities (PSD) of the alpha (8-12 Hz), beta (13-19Hz), and sigma (30-40Hz) bandwidths which will be computed for each condition to create a relative PSD. Changes in the relative PSD will be compared among the interventions and control group.

Sensory Organization Strategies [Primary Mechanism of Interest] represents a plausible neuromuscular mechanism as evidence indicates that in lieu of reliable somatosensory information, CAI patients increase reliance on visual information. Further, an increased reliance on visual information is hypothesized to explain the repeated ankle sprains and episodes of giving way associated with CAI. Changes in sensory organization strategies may represent the underlying neuromuscular mechanism of ankle joint mobilizations and plantar massage and these manual therapies improve postural control and reduce giving way episodes in CAI patients. Changes in our primary mechanism of interest will be calculated using the % Modulation measure used previously by our group. This measure estimates the weight given to visual information during eyes open stance based on the magnitude of postural instability that occurs when vision is removed. Raw ground reaction force data will be collected at 200Hz using an Accusway Plus Balance force platform (AMTI, Watertown, MA). Raw data will be filtered appropriately before the % Modulation for center of pressure velocity is calculated from eyes open and eyes closed stance data. Additional postural control measures such as time-to-Boundary (TTB) will also be calculated.[0]

Secondary Measures

Both walking gait and jump landing biomechanics will be assessed. Three-dimensional kinematics (sampled at 100Hz) and kinetics (sampled at 1000Hz) will be obtained during both tasks using a 10-camera Vicon motion capture system. During gait trials, participants will walk at a self-selected speed over multiple embedded force plates. Speed will be enforced with timing gates centered over the force plates during the five test trials. Jump landing biomechanics will be assessed with a drop vertical jump protocol that requires participants to jump from a 30cm platform placed at a distance of 50% of the participants' height away from the edge of the force platform, with an immediate rebound jump for maximum height. Five test trials will be completed. Both discrete variables and profile plots of the kinematic and kinetic data will be calculated for the ankle, knee, and hip in the sagittal, frontal, and transverse

planes. All secondary measure methodology is consistent with those previously used by our research team.

Tertiary Measures

All participants will also be asked to stand barefoot on one leg with eyes closed and hands on hips on the floor for 20 seconds to quantify their balance. Each participant will perform up to 5 trials on each leg. During each trial, the investigator will count the amount of balance errors the participant commits. Errors include any of the following: (1) lifting the hands off the iliac crests; (2) opening the eyes; (3) stepping, stumbling, or falling; (4) moving the hip into more than 30 degrees of flexion or abduction; (5) lifting the forefoot or heel; or (6) remaining out of the test position for longer than 5 seconds. The *Weight Bearing Lunge Measure (WBLT) is a* method of measuring dorsiflexion range of motion and is completed barefoot by placing the participant's great toe in line with their heel on top of a tape measure on the floor. While keeping the heel firmly on the ground, participants are asked to bend their supporting knee to touch the wall in front of them. This is completed through a slow and controlled lunging action. Using the tape measure on the floor, the maximum distance each participant can place their foot away from the wall while keeping both the heel flat on the floor and knee touching the wall will be recorded. This test will be repeated 6 times during each laboratory session. All tertiary measure methodology is consistent with those previously used by our research team.

Randomization

As per section 8 of Appendix 1 and H of the MOOP, participants will be randomized to one of the three conditions in a 1:1:1 ratio using sealed envelopes after being stratified based on treatment expectations (Appendix 5). More specifically, we will be using a block randomization technique so that preliminary data analysis, data monitoring, and safety evaluations will be based on similar, if not identical, numbers in each group. Each block of envelopes will be made and sealed before study enrollment begins by the biostatistician and randomization will occur after the baseline evaluation (see section 9.b of Appendix 1 or K.1.a of the MOOP). Each participant will select a sealed envelope containing their group assignment. This assignment will be noted by the respective PI and recorded.

First Treatment Session

Participants in the manual therapy groups (massage and joint mobilization) will undergo their first treatment session immediately after randomization. Participants in the control group will be given instructions on when to return in 2-weeks. All participants should maintain normal activities over the 2-week period.

K.2.c Visit 2-14: Treatments

Participants in the manual therapies group will then receive treatments over the next 2 weeks (see section K.2.b.2 of the MOOP). Each treatment day should be separated by at least 24 hours over the course of 2 weeks. Preferably, 3 treatments will be spread across each week of the 2 week intervention. Visit 7 will be the final treatment.

K.2.d Visit 15

Post Test 1

Following the last treatment (within approximately 72 hours) each participant will be reassessed on the measures described above.

4-week Follow up

Each participant will be reassessed on the measures described above.

K.3 Retention Initiatives

Participants will be actively followed through all visits in the study. In order to follow participants across the study duration, all participants will be contacted at the end of each week of participation. The investigators will set a treatment schedule that accommodates that schedule of each participant and send email reminders to each participant within 48 hours of the next treatment or assessment session.

If a study participant is discontinued from the study (for any reason), he/she will still be followed to the end of their respective study period in order to monitor or adverse events.

Figure 1 Copy of Section B: Schedule of Visits & Evaluations

Study Visits / Study Days	Balance Questionnaire (Appendix 2)	PRO Testing AII (Appendix 3) FAAM (Appendix 4) FAAM-S (Appendix 4) Treatment Expectations (Appendix 5)	Informed Consent (Appendix 6)	Neuromuscular Mechanism Testing Joint Position Sense Light-touch Thresholds H-Reflex Corticomotor mapping Corticomotor excitability Cortical Activation % Modulation	Biomechanical Testing Gait Analysis Jump Landing Balance Testing Range of Motion Testing	Treatment Delivery	Adverse Event Monitoring
Visit 1 Eligibility Screening	X	X					
Visit 2 Baseline Testing			X	X	X	X	X
Visits 3-7-						X	X
Visit 8				X	X		X

Post-Test 1				
Visit 9 4-week follow up		X	X	X

SECTION L: Participant Retention

In order to maximize retention for this protocol, the investigator will ensure the ongoing process of participant retention from the beginning of the protocol with participant recruitment all the way to the 3-month follow-up by :

- Compensating the participants monetarily ($250) for their participation. Compensation will be tracked with a payment log (see Appendix 20).
  - $100 at Post Test 1
  - $150 at the 1-month follow-up
- Emphasizing the importance of congeniality, respectfulness and friendliness in interactions with participants
- Giving patients and their families the opportunity to address questions and concerns pertaining to chronic ankle instability.
- Enhancing participant's understanding of the study's mission and the protocol
- Stressing the idea that participants have an active role in the research and are part of the research team
- Verbally surveying participants on a regular basis, understanding their expectations, and gaining insight into their experiences and satisfaction
- Identifying potential problems and key retention factors and developing intervention strategies regarding retention
- Assessing each patient's drop out potential and intervening as needed to keep patients interested in continuing to participate.
- Emailing participants reminders prior to each assessment and treatment session to ensure that they know what time and what place to meet.

SECTION M: Data & Safety

M.1 Concomitant medications

There is no concomitant medication restrictions associated with this protocol.

M.2 Data & Safety Monitoring Plan

M.2.a Purpose of Study

The purpose of this study is to elucidate the neuromuscular mechanisms underlying the significant positive effects observed following 2-weeks of independent ankle joint mobilization and plantar massage interventions in chronic ankle instability patients.

M.2.b Adherence Statement

The Data Safety Monitoring Plan (DSMP) outlined below for 1 R21 AT009704-01 will adhere to the protocol approved by the University of North Carolina at Chapel Hill IRB.

M.2.c Protocol Amendments

All protocol amendments, other than minor administrative changes as defined by the NCCIH Guidance on Changes in Clinical Studies in Active Awards will be submitted in a prospective manner to NCCIH except when necessary to protect the safety, rights, or welfare of subjects. Prior to submission to NCCIH the proposed changes will be reviewed and approved by the Independent Monitor(s). IRB-approval will not be sought until after NCCIH approval of the protocol amendment has been obtained.

M.2.d Confidentiality

Protection of Subject Privacy

Subject confidentiality will be strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality will extend to cover testing of biological samples and genetic tests, should such data be collected in future protocol amendments, in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study Independent Monitoring Committee (IMC) or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The study site will permit access to such records.

Confidentiality During Adverse Event (AE) Reporting

AE reports and annual summaries will not include subject or group-identifiable material. Each report will only include the identification code.

M.2.e Expected Risks

Expected risks to the subject are as follows:

- Rare (<1%) of mild skin irritation due to taping the kinematic markers sensors to the skin. This risk will be minimized by a member of the research team removing the tape with care.
- Rare (<1%) of seizure. Overall estimate is that seizure risk is < 1:1000 (0.1%) and this risk is associated with Repetitive TMS, which will not be conducted in this investigation.
- Infrequent (5%) of head and neck aches, hearing shifts, and fainting during and/or immediately after TMS. The research team will disclose this information to the participant prior to enrollment and remind them prior to testing. This is attributed to local stimulation of muscles and nerves near the stimulating coil, a tapping of the scalp by the coil during discharge, and wearing a tight-fitting swim cap. Other stimulation-related effects include teeth aches, facial twitches, odd taste in mouth, and discomfort from blinking and twitches of scalp muscles. All symptoms resolve after cessation of the TMS protocol. TMS may induce fainting or feelings of lightheadedness or dizziness. If symptoms of dizziness, lightheadedness, or feeling faint occur, the TMS protocol will be stopped. The subject will be allowed to lay down or put their head down to prevent fainting. If subjects faint, they must not be allowed to leave the laboratory until fully recovered. TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud click can result in temporary ringing in the ear and subclinical auditory threshold shifts. To prevent transient hearing threshold shifts due to TMS, subjects and investigators will be wear earplugs during TMS.
- Infrequent (10%) of itching/scratching of the scalp during EEG testing. Care will be taken during the application of the EEG cap, electrodes to measure brain wave activity, and the insertion of the gel.

These risks are considered to be minimal and are addressed in the protocol and consent form."

Because the manual therapies can cause mild discomfort (<1%), all participants will be monitored at each treatment session during the study. The manual therapies are designed to be pain free and are commonly applied in clinical scenarios but because of the rare risk of discomfort, participants will be monitored for expected and unexpected AEs related to the manual therapies.

M.2.f Adverse Event/ Unanticipated Problems

M.2.g Definitions

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

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

Serious Adverse Event (SAE)

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

M.2.h Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

M.2.i Characteristics of an Adverse Event

Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

Expectedness of SAEs

The Study PI and Independent Monitoring Committee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

M.2.j Reporting Procedures

Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Research protocol title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Reporting of Pregnancy

Women that are known (via self-report) to be pregnant will be excluded. If a woman becomes pregnant while enrolled, she will not be removed from the study and treatment will be discontinued. Safety follow-ups will be continued for the projected treatment time period. Reporting of participants who become pregnant and are withdrawn from the study will be included in the regular IMC reports as participant drop outs.

M.2.k Halting Rules

Safety findings including, but not limited to, higher than anticipated SAEs, a higher number of a particular SAE than anticipated, and/or increased frequency of AEs.

M.3 Quality Control and Quality Assurance

M.3.a Data Management

Data will be collected both in hard copy & electronically. All computers in the associated research laboratories are password protected. In order to protect the integrity of the original electronic data files, copies will be made of electronic data files to be used for data manipulation at a later date. Any data file that is amended, cleaned, or updated will be given a new name with the corresponding name of the original file followed by _modified and dated with the month_, day_, and 2-digit year it was modified (i.e. 01_trial_1_modified_4_1_17).
Additionally, data collected in hard copy will be de-identified and transferred to our electronic database as soon as possible. Additionally, hard copy files that have yet to be transferred and originals will be stored in a locked cabinet within the laboratory (i.e. double lock protection). The transfer of data between the PIs for the purpose of monitoring and analysis will only use de-identified data. Further details can be seen in the Confidentiality section below.

M.3.b Data Entry Procedures, Flow, and Checks

1. The programs and data entry sequence that will be used to record the data entered into an electronic database system are as follows:
    i. Members of the research team will be using Microsoft Excel to electronically record the data from the hard copy forms collected from the participants.
    ii. Upon completion of data entry in Excel, the data will then be transferred to an electronic database on Microsoft Sharepoint that is identical to the Excel spreadsheet. The Sharepoint account will be maintained at the University of North Carolina at Chapel Hill and only the research team will have access to the site using a unique user name and password.
2. All hard copy data will be entered in to the Excel and Sharepoint electronic databases by members of the research team. The data will be entered in/transferred to the electronic databases within 5 business days of data capture.
3. Process for data checks.
    i. Based on data entry plan, this will be a single data entry check. In order to ensure consistency of data entry, the research team will discuss and inspect data entry in the Sharepoint database in the teams regular meetings.
    ii. Any issues associated with data entry will be discussed during these meetings and may be resolved with a double data entry audit.

iii. In order to ensure consistency of changes, the PIs will also modify the database files and denote the change in the title of the file (e.g. NMC STARS_database_revised_11_1_18).

4. Audit and tracking system for evaluating data flow and data entry.
    i. The team will discuss the flow of the database and any data entry issues that they may have in their meetings.
    ii. In the event that the investigators run into an item that does not produce the desired results (e.g. a question that could be worded more clearly for participants on a form), the PIs will discuss it, come up with a strategy to address it, implement the strategy, and ensure that only the most revised version of the item in question is used.
5. Description of data transmission from the databases to the statistical analysis package IBM SPSS Statistics (SPSS).
    i. All data from the Sharepoint databases will be formatted to transfer directly into SPSS via copy and paste.
    ii. All electronic trials will be analyzed using MatLab. The analyzed output in MatLab has been designed to be directly pasted into an Excel database.
        1. During MatLab analysis, all results will be immediately pasted into the Excel database.
    iii. The team will discuss and review the SPSS database in their meetings to ensure consistency of data.

M.3.c Quality Control Procedures

The team will hold regular meetings to discuss any issues with the study. If problems arise, they will be addressed in a timely manner as outlined above. The team will conduct a self-assessment every six months of their performance of collecting, maintaining, reporting, and storing relevant study materials and information. Every month, the PI will audit study materials to ensure consistency in documenting and signing consent forms as well as use the quality control checklist to perform a data entry audit.

The MOOP will be reviewed every six months to ensure that the procedures outlined reflect the most current state of study collection and data entry. If there is a change to the protocol that requires an amendment to the MOOP, this change will be made by Dr. Wikstrom and distributed to all study personnel, the IMC, and NCCIH.

M.3.d Training Plan

All staff will be trained through the Collaborative Institutional Training Initiative for Biomedical Research involving human subjects. In addition, all staff will be trained by the PI in the following prior to engaging in any research activities associated with this project:

8. Determining subject eligibility
    a. Proper instructions for each questionnaire
    b. Using the eligibility checklist
    c. Enrolling a participant who is eligible
9. Securing informed consent
10. All data collection procedures
11. Randomization process and sequence for each participant
12. Data storage and analysis

13. Reporting adverse events and protocol violations
14. Using the MOOP

The training of each staff member will be documented using the training checklist included in the MOOP and signed by both the staff member and the PI.

All staff will be trained in the consent process to ensure that each member understands that participants are initially screened with the approved questionnaires. If a potential participant is considered to be eligible, the staff member will read through the consent form with the participant and answer any questions. If the participant would like to enroll in the study, he/she will be asked to sign and date the consent form on the signature page. A copy of the signed consent form will be given to each participant enrolled in the study. The original consent form will be stored in the participant's folder which will be stored in a locked filing cabinet in the PI's office.

Regular monthly meetings of the research team will be used to discuss issues that arise with both data collection and treatment delivery. Additionally, the PI will meet with study personnel involved with this project to ensure proper and timely dissemination of the following information:

5. Adverse Events
6. Protocol violations
7. Compliance issues
8. Protocol amendments

In order to ensure consistency in communication, minutes of meeting will be recorded and distributed to all study personnel within 72 hours of the meeting. Similarly, all study personnel involved with this project will be required to maintain current training through the Collaborative Institutional Training Initiative and remain up to date on the study protocol and amendments, AEs and SAEs, and the documentation plan.

Quality control and quality assurance checks will be conducted monthly by the PI/Internal QA Reviewer.

M.4 Subject Accrual and Compliance

M.4.a Measurement and Reporting of Subject Accrual

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the recruitment phase to ensure that a sufficient number of participants are being enrolled, in keeping with proposed recruitment projections, and that they meet eligibility criteria and fulfill the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table).

M.4.b Measurement and Reporting of Participant Adherence to Treatment Protocol

Data on adherence to the treatment protocol will be collected for each participant by research staff and reviewed monthly by the PI/Internal QA Reviewer. Adherence of participants will be evaluated by review of the scheduled vs attended treatment sessions. Available data on the use of manual therapies suggests an overall compliance rate of 100%. If adherence falls below the suggested rate, which might inhibit the ability of the study to test its primary hypotheses, the Internal QA Reviewer will suggest a conference call for study investigators to discuss methods for improving adherence.

M.5 Justification of Sample Size

Changes in sensory organization strategies has been chosen as the primary mechanism of interest and will be assessed by calculating the % Modulation of the resultant center of pressure velocity between eyes open and eyes closed stance.

To achieve Aim 1, 18 participants per group are needed to ensure significant changes in the primary mechanism of interest following both interventions relative to the control group. Between group (i.e. massage vs. control [d=0.53] & mobilization vs. control [d=0.69]) pre to post effect sizes from our preliminary data (See Preliminary Studies) were used to calculated the needed sample size. Using GPower (3.1), a repeated measures, between factors ANOVA model for three groups and two time points was used. Parameters included a purposefully conservative intra-measure correlation=0.90, α=0.05, and 1-β=0.90. To achieve Aim 2, 16 participants per group are needed to identify significant correlations. This value was calculated based on previously established correlations between neuromuscular mechanisms and biomechanical measures of postural control. Parameters for this analysis included a correlation of r=0.5 (range from literature: 0.50 to 0.58), an α=0.05, and 1-β=0.90. Thus, we will recruit 20 participants per group and plan for a 10% dropout rate, which would leave 18 subjects per group. Our previous work[42] had a 98.75% (79/80) retention rate using the same intervention protocol and all participants completed 100% of the treatment sessions.

M.6 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial."

M.7 Designation of a Monitoring Committee

The Independent Monitoring Committee for this study is comprised of Drs. Ty Hopkins, Cathleen Crowell, and Dr. Cynthia Coffman. Drs. Hopkins, Crowell, and Coffman are not associated with this research project and work independently of the PI, Dr. Erik Wikstrom. They are not part of the key personnel involved in this grant and are not affiliated with the University of North Carolina at Chapel Hill. No member of the Committee has collaborated or co-published with the PI within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise. Dr. Coffman is a PhD biostatistician. The CVs of all members of the IMC are attached.

M.8 Safety Review Plan

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the IMC semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the IMC and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis

M.8.a Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team will generate Study Reports for the IMC and will provide information on the following study parameters: including patient recruitment, retention/attrition, and AEs. Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

M.8.b Submission of On-Site Monitoring/Audit and Inspection Reports

The IRB, IMC, and NCCIH Program Officials will receive copies of all study monitoring/audit or inspection reports within 14 day of PI receipt. For example, the NCCIH (Westat) monitoring report will be submitted to the IRB and IMC (NCCIH does not require copies of Westat monitoring reports). Any FDA inspection report will be submitted to the IRB, IMC, and NCCIH Program Officials.

M.8.c Table A

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Data entry quality control checks on 5% of charts	Monthly	QA Reviewer
Adherence data regarding study visits and intervention	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
AEs and rates (including out-of-range lab values)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
	Annually	NCCIH, FDA (If Applicable)
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor (s) NIH/NCCIH, FDA (if applicable)
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitor (s), NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB, FDA (if applicable)

M.9 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

M.9.a General Instructions for Completing Forms

When completing study forms, PRINT IN CAPITAL LETTERS using black ink. Note, participants must not be identified by name on any study document submitted with the forms (e.g., ECG tracing, lab reports). Replace the participant name with the participant initials and identification (ID). number.

- ***Header:*** Complete the header information on EVERY page, including pages for which no study data are recorded.

- ***Participant ID:*** The participant ID must be recorded on **EVERY** page, including pages for which no study data are recorded.

- ***Time***: Use a 24 hour clock (e.g., 14:00 to indicate 2:00 p.m.) unless otherwise specified***.***

- ***Dates***: All dates must be verifiable by source documents. **Historical dates** are sometimes not known (e.g., date of first symptom); therefore, conventions for missing days and/or months should be described (e.g., UNK or 99).

- ***Abbreviations:*** Use of abbreviations not specifically noted in the instructions for completing the forms can be problematic and should be held to a minimum.

- ***Extraneous Writing***: Comments written extraneously on forms cannot be captured in the database; thus, write only in the spaces indicated.

- ***Correcting errors***: If an error has been made on the study forms, place a *single* line through the erroneous entry and record the date and your initials. Indicate the correct response.
  - ***Example of correcting an error***: Make sure to strike through the error with a single line and make the correction immediately following the error. Then initial and date.

    - *Participant complained of pain on ~~Wednesday~~ Tuesday, September 8th.*

- ***Skipping items***: Do not skip any items. Some items may carry "Unknown" or "Not Applicable" response choices which should be checked when necessary.

- ***Incomplete data***: Data may not be available to complete the form for various reasons. Circle the item for which data is not available and indicate the reason near the appropriate field:
  - If an evaluation was not done, write ND and provide a reason.
  - If the information is not available, but the evaluation was done, write NAV.

Note: Only in rare circumstances, as in the case of lost documentation*, should NAV be recorded on the form. Every effort should be made to obtain the information requested.*

  - If an evaluation is not applicable, write NA.

Incomplete or Illegible forms: Incomplete forms that do not have adequate explanation (as described above) compromise the integrity of the entire study. Errors, such as incomplete or illegible forms, are problems that require time and energy to resolve.

- If an entire page of the forms cannot be completed (e.g., no parts have any responses), and it is unlikely that it will be completed, draw a diagonal line through the form and write NOT DONE, NOT AVAILABLE or NOT APPLICABLE, as appropriate

- The header information must be completed even though no data are recorded on the form. If a form can only be partially completed at the time of monitoring, but will be completed when the information becomes available, follow the direction of the clinical monitor

- Do not leave forms incomplete or unused without explanation

M.9.b Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

M.9.c Database Protection

This study will use a Sharepoint database. The database will be secured with password protection. The research team will only enter coded information. Electronic communication with the research team will involve only unidentifiable information. The Sharepoint folder allows for an electronic audit trail and modified database files will be labeled as indicated above.

M.9.d Source Document Protection

All participants will be coded upon entry into the investigation. The master sheet (listing names with code numbers) will be stored on a password protected computer in the primary investigator's personal office. Data will be collected both in hard copy & electronically. Hard copy coded data sheets will be kept in a locked filing cabinet until they are transferred to electronic format. Upon transfer, they will remain in a locked filing cabinent inside the research laboratory associated with the project (double lock protection). As data sheets are transfer to electronic files for data analysis (within 5 days), the electronic records associated with the investigation will also be coded and de-identified, and kept on the password protected computer in a separate folder/location from the master sheet. Electronic data will be collected on computers in the research laboratories which are accessed via unique passwords for each member of the research team. As soon as feasible, the PIs will transfer the, already de-identified, electronic data to the study databse (Sharepoint folder/file). The Sharepoint folder is also password protected and passwords are unique to each member of the research team. Hard and electronic copies of the MOOP and associated source forms will be maintained in the research laboratory and the PI's office.

M.10 Schedule and Content of Reports

Reports will be generated per the schedule outlined in Table A. In addition, preliminary data analysis will occur on a semi-annual basis.

M.11 Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent

document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care and/or academic status will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record.

M.12 Reporting Changes in Study Status

During the funding of this study, any action by the IRB, the IMC, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Official within 3 business days of notification.

SECTION P: Documentation

P.1 Source Documentation

The following have been identified as source documentation:

- Electronic Source documents (recorded data)
  - Gait Trials
  - Jump Landing Trials
  - EEG Trials
  - TMS Trials
  - H-Reflex Trials
  - Balance Trials
- Case Report Forms (data collection sheet)
  - Single Limb Balance
  - Dorsiflexion range of motion
  - Joint Position Sense
  - Light-Touch Thresholds
- Signed consent forms
- Questionnaires completed by the participant
  - Balance History Questionnaire
  - FAAM
  - FAAM-S
  - AII
  - Treatment Expectations

P.2 Study Forms

Data must be collected consistently across participants and sites so that any variability is limited to participants' characteristics and responses to the intervention. Study forms, also called CRFs, provide the vehicle for consistent data collection. Below is the list of study forms:

- Study forms and their collection schedule
  - Treatment Expectations
    - Collected at the eligibility session.
    - See appendix #5 for complete description.
  - Foot and Ankle Ability Measure
    - Collected at the eligibility session.
    - See appendix #4 for complete description.
  - Ankle Instability Instrument
    - Collected at the eligibility session.

        - See appendix #3 for complete description.
    - Balance questionnaire
        - Collected at the eligibility session
        - See appendix #2 for complete description.
    - Adverse Event Reporting Form
    - Master list of participant names and ID numbers
- Maintenance of forms
    - All forms will be maintained by Dr. Wikstrom who will serve as the contact person for answering any questions about the forms to other study personnel. If there are any amendments to the forms, these will be approved by the IMC and IRB prior to implementing them into the study. All amendments will be noted in the minutes of the research team meetings.

P.3 General Instructions for Completing Forms

When completing study forms, PRINT IN CAPITAL LETTERS using black ink. Note, participants must not be identified by name on any study document submitted with the forms (e.g., ECG tracing, lab reports). Replace the participant name with the participant initials and identification (ID). number.

- ***Header:*** Complete the header information on EVERY page, including pages for which no study data are recorded.

- ***Participant ID:*** The participant ID must be recorded on **EVERY** page, including pages for which no study data are recorded.

- ***Time***: Use a 24 hour clock (e.g., 14:00 to indicate 2:00 p.m.) unless otherwise specified***.***

- ***Dates***: All dates must be verifiable by source documents. **Historical dates** are sometimes not known (e.g., date of first symptom); therefore, conventions for missing days and/or months should be described (e.g., UNK or 99).

- ***Abbreviations:*** Use of abbreviations not specifically noted in the instructions for completing the forms can be problematic and should be held to a minimum.

- ***Extraneous Writing***: Comments written extraneously on forms cannot be captured in the database; thus, write only in the spaces indicated.

- ***Correcting errors***: If an error has been made on the study forms, place a *single* line through the erroneous entry and record the date and your initials. Indicate the correct response.
    - ***Example of correcting an error***: Make sure to strike through the error with a single line and make the correction immediately following the error. Then initial and date.

- ***Participant complained of pain on ~~Wednesday~~ Tuesday, September 8th.***

- ***Skipping items***: Do not skip any items. Some items may carry "Unknown" or "Not Applicable" response choices which should be checked when necessary.

- ***Incomplete data***: Data may not be available to complete the form for various reasons. Circle the item for which data is not available and indicate the reason near the appropriate field:
  - If an evaluation was not done, write ND and provide a reason.
  - If the information is not available, but the evaluation was done, write NAV.

Note: Only in rare circumstances, as in the case of lost documentation*, should NAV be recorded on the form. Every effort should be made to obtain the information requested.*

  - If an evaluation is not applicable, write NA.

Incomplete or Illegible forms: Incomplete forms that do not have adequate explanation (as described above) compromise the integrity of the entire study. Errors, such as incomplete or illegible forms, are problems that require time and energy to resolve.

- If an entire page of the forms cannot be completed (e.g., no parts have any responses), and it is unlikely that it will be completed, draw a diagonal line through the form and write NOT DONE, NOT AVAILABLE or NOT APPLICABLE, as appropriate

- The header information must be completed even though no data are recorded on the form. If a form can only be partially completed at the time of monitoring, but will be completed when the information becomes available, follow the direction of the clinical monitor

- Do not leave forms incomplete or unused without explanation

SECTION Q: Data Flow

All participants will be coded upon entry into the investigation. The master sheet (listing names with code numbers) will be stored locally at each site in the site primary investigator's personal office within a locked filing cabinet. Data will be collected both in hard copy & electronically. Hard copy coded data sheets will be kept in a locked filing cabinet until they are transferred to electronic format. As data sheets are transfer to electronic files for data analysis (done as soon as possible), the electronic records associated with the investigation will also be coded and de-identified, and kept within a Sharepoint folder and files. Electronic data will be collected on computers in the research laboratories associated with this study which are password protected (unique passwords for each study team member) until the data is uploaded to Sharepoint.

SECTION R: Retention of Study Documentation

All documents and data collected from participants in this study must be retained for three years in accordance to IRB protocol.

SECTION S: Administrative Forms

The MOOP should contain a complete set of administrative forms. Administrative forms assist study documentation and may include the following, as relevant:

- ***Informed Consent Documentation Form*** – *Appendix 7*
- ***Protocol Deviation Log*** – *Appendix 8*
- ***AE Reporting Form*** – *Appendix 10*
- ***Unanticipated Problem Reporting Form*** – *Appendix 11*
- ***Serious AE Reporting Form*** – *Appendix 12*
- ***Eligibility Log*** – *Appendix 13*
- ***Screening Log*** - Appendix 14
- ***Master List –***Appendix 15
- **Training Log** – Appendix 16
- **Data Collection Form** – Appendix 17
- **Payment Log** – Appendix 20
- **Study Completion Form** – Appendix 22
- **IMC Reporting Template** – Appendix 23

SECTION T: IRB Policies

See https://research.unc.edu/files/2017/05/SOP-June-2-2017-bookmarked-and-TOC-links.pdf for IRB SOPs.

APPENDICES

Appendix 1: Study Protocol

1 Background

Musculoskeletal injury associated with physical activity is a leading reason for physical activity cessation. Physical inactivity is clearly linked to a decreased quality of life and significant long-term negative sequelae. CAI is associated with reduced physical activity levels and lower quality of life. Thus, proper treatment of CAI is crucial to preventing sedentary behavior and disease.

STUDY SYNOPSIS

Objective

To determine the neuromuscular mechanisms of ankle joint mobilization and plantar massage in CAI patients

Significance

Elucidating neuromuscular mechanisms of manual therapies is vital developing effective multi-model interventions for CAI patients.

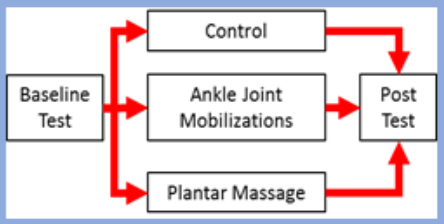
Innovation

•Comprehensive assessment strategy to elucidate the multifaceted mechanisms of prevalent but understudied manual therapies in CAI patients.

Approach

Patients: 60 CAI patients randomized to 3 groups.

Interventions: 6, 5-minute treatments will be given over a 2-week period. The control group will receive no treatment.



Neuromuscular Mechanisms: Ankle joint proprioception, Light-touch Discrimination Thresholds, Soleus & Fibularis Longus H-reflex, Cortical activity, cortical excitability & mapping, and Sensory Reweighting **(PRIMARY).**

Secondary Measures: Jump Landing & Gait Biomechanics.

Lateral Ankle Sprains & their Sequelae Represent a Significant Healthcare Burden. An estimated 932,000 lateral ankle sprains were seen in United States (US) emergency departments in 2010. Just the acute care of these lateral ankle sprains resulted in over $1 billion in healthcare charges. The total financial impact of initial treatment and time-loss is estimated at $12,000/lateral ankle sprain. Coupled with our data, this equates to potentially spending >$11 billion annually on lateral ankle sprains. However, lateral ankle sprains are not a one-time injury as 40-75% of those who sustain a lateral ankle sprain will develop CAI and up to 78% of those with CAI develop post-traumatic ankle osteoarthritis. The financial burden of treating CAI has remains unknown but CAI surgical procedures rose by >17% from 2007-2011.

Neuromuscular Impairments Perpetuate a Continuum of Disability. Peripherally, diminished proprioception and increased cutaneous receptor thresholds in CAI patients are thought to alter gait biomechanics and the increased reliance on visual information while balancing (i.e. altered sensory organization strategy). These alterations may subsequently increase recurrent injury risk. Spinal level dysfunction, as measured by diminished H-reflex/M-Response ratios and slower reflex reactions have been noted, as have reduced cortical excitability and reduced corticomotor map sizes of the fibularis longus. These supraspinal alterations suggest a functional reorganization of motor networks and a systemic effect on the neuromuscular control system. These

neuromuscular impairments manifest clinically as an inability to generate appropriate motor responses that perpetuates the continuum of disability (left). Until, the neuromuscular mechanisms responsible for the significant positive effects of manual therapies are elucidated, clinicians will not be able to strategically leverage manual therapies as a treatment to break the CAI associated continuum of disability.

Ankle Joint Mobilization & Plantar Massage are Prevalent but understudied CAM Treatments. The use of complementary and alternative medicine (CAM) linearly increased between 2002 and 2012, particularly in younger (18-44) Americans.[65] Ankle joint mobilization and plantar massage are manipulative and body based therapies that are among the most commonly used by American adults. In 2007 alone, American adults made over 354 million visits to CAM practitioners for an out-of-pocket expense of $11.9 billion and roughly 75% of the reported visits and out-of-pocket expenses were associated with manipulative and body based therapies. CAM visits for musculoskeletal joint pain are common, especially among females who are at an increased risk of sustaining a lateral ankle sprain.

2 Aims & Hypotheses

The objective of this study is to elucidate the neuromuscular mechanisms underlying the significant positive effects observed following 2-weeks of independent ankle joint mobilization and plantar massage interventions in CAI patients. The following specific aims will be used to achieve our objective:

Aim 1: Determine changes in peripheral, spinal, and supraspinal neuromuscular mechanisms after 2-week manual therapy interventions (ankle joint mobilization, plantar massage) relative to a non-treatment control group in CAI patients.
Neuromuscular mechanisms will be quantified before and immediately after a 2-week intervention. Mechanisms will include a comprehensive group of peripheral (ankle joint position sense, plantar light-touch discrimination thresholds), spinal (H-reflex of the soleus and fibularis longus), and supraspinal measures (cortical activity during stance using electroencephalography [EEG], corticomotor excitability and mapping of the soleus and fibularis longus via transcranial magnetic stimulation [TMS], and sensory organization strategies during stance). Our primary mechanism of interest is sensory organization strategies. Sixty CAI patients will be randomized into three equal groups (ankle joint mobilization, plantar massage, control) to complete 6 treatment sessions over 2-weeks.

Hypothesis 1. Both interventions, relative to the control group, will result in significant sensory organization strategy changes, representing a reduction in the CAI patient's reliance on visual information during stance.

Hypothesis 2. Each intervention will result in unique combinations of peripheral, spinal, and supraspinal mechanistic pathways relative to the control group.

Aim 2: Determine the associations among peripheral, spinal, and supraspinal neuromuscular mechanisms, secondary biomechanical measures, and sensory organization strategies in CAI patients. These associations will be quantified to elucidate the unique combination of peripheral, spinal, and supraspinal mechanistic pathways thought to contribute to a reducing in the reliance of visual information during stance. Secondary measures which will include jump landing and gait biomechanics will be assessed before and immediately after the 2-week interventions. We will use an analytical approach (see statistical analysis) to determine simple associations at baseline, post-test, and among change scores in neuromuscular mechanisms and secondary measures.

Hypothesis 1. Each intervention will result in unique combinations of changes in peripheral, spinal, and supraspinal mechanistic pathways will be strongly associated with changes sensory organization strategies.

Hypothesis 2. Each intervention will result in secondary measure changes associating with changes in sensory organization strategies as well as peripheral, spinal, and supraspinal mechanistic pathways.

3 Study Design

We plan to use a single-blind randomized study design to quantify changes in the hypothesized neuromuscular mechanisms following ankle joint mobilization and plantar massage. Assessors will be blinded to group assignment.

4 Primary & Secondary Endpoints

This study will have 1 primary endpoint at the conclusion of the 2-week intervention. This study will have 1 secondary endpoint 1-month after the conclusion of the 2-week intervention. All outcomes will be assessed at both endpoints.

5 Type & Number of Sites

A total of 1 site will be used during this study: the University of North Carolina at Chapel Hill.

6 Patient Population & Numbers

Only those with CAI, as defined by the International Ankle Consortium (IAC) will be enrolled. Specific inclusion criteria will be identical to our previous work and consist of a history of at least two episodes of "giving way" within the past 6 months; scoring ≥ 5 on the Ankle Instability Instrument (AII), scoring ≤90% on the Foot and Ankle Ability Measure (FAAM), and scoring ≤80% on the FAAM Sport (FAAM-S). Exclusion criteria

will consist of acute ankle sprains <6 weeks, previous ankle surgeries, lower extremity surgeries associated with internal derangements, and conditions affecting neuromuscular control.

Changes in sensory organization strategies has been chosen as the primary mechanism of interest and will be assessed by calculating the % Modulation of the resultant center of pressure velocity between eyes open and eyes closed stance.[33]

To achieve Aim 1, 18 participants per group are needed to ensure significant changes in the primary mechanism of interest following both interventions relative to the control group. Between group (i.e. massage vs. control [d=0.53] & mobilization vs. control [d=0.69]) pre to post effect sizes from our preliminary data (See Preliminary Studies) were used to calculated the needed sample size. Using GPower (3.1), a repeated measures, between factors ANOVA model for three groups and two time points was used. Parameters included a purposefully conservative intra-measure correlation=0.90, α=0.05, and 1-β=0.90. To achieve Aim 2, 16 participants per group are needed to identify significant correlations. This value was calculated based on previously established correlations between neuromuscular mechanisms and biomechanical measures of postural control.[16, 95] Parameters for this analysis included a correlation of r=0.5 (range from literature: 0.50 to 0.58), an α=0.05, and 1-β=0.90. Thus, we will recruit 20 participants per group and plan for a 10% dropout rate, which would leave 18 subjects per group. Our previous work[42] had a 98.75% (79/80) retention rate using the same intervention protocol and all participants completed 100% of the treatment sessions.

7 Inclusion & Exclusion Criteria

Inclusion criteria will consist of the following:

- Male or female 18-45 years of age
- History of ankle sprain with at least two episodes of “giving way” within the past six months
- Score of ≥ 5 on the Ankle Instability Instrument (AII)
- Score of ≤ 90% on the FAAM-ADL
- Score of ≤ 80% on the FAAM-S.

Exclusion criteria will consist of the following:

- Younger than 18 or older than 45 years
- No history of ankle sprain or episodes of “giving way” in the past six months
- Score of ≤ 5 on the Ankle Instability Instrument (AII)

- Score of ≥ 90% on the FAAM-ADL
- Score of ≥ 80% on the FAAM-S.
- An acute ankle sprain within the past 6 weeks.
- Previous history of lower extremity surgery with internal derangements, reconstructions, or repair
- Lower extremity injury within the past 6 months (other than ankle sprains)
- Presence of balance deficits or conditions known to affect balance as noted on the Balance Questionnaire including diabetes and/or vertigo.

8 Randomization Plan

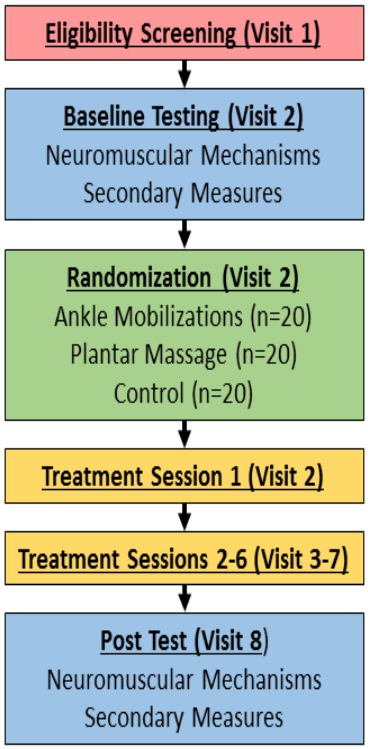
Participants will be randomized to one of groups in a 1:1:1 ratio after stratification based on treatment expectation responses. This process will happen using sealed envelopes prepared by the study biostatistician. More specifically, we will be using a block randomization technique at each institution so that preliminary data analysis, data monitoring, and safety evaluations will be based on similar, if not identical, numbers in each group. Each block of envelopes will be made and sealed before study enrollment begins and randomization will occur after the baseline evaluation (see section 9.b below). The biostatistician will be responsible for generating the master randomization list and each participant will select a sealed envelope containing their group assignment. This assignment will be noted by the PI and recorded. Assessors will be blinded to group assignment.

9 Screening Process, Baseline Evaluation, Study Treatment, & Final Evaluation

9.a Screening Process

The screening process will be performed at a specific eligibility screening session. At this session, potential participants will complete the Balance Questionnaire (Appendix 2), AII (Appendix 3), FAAM (Appendix 4), FAAM-Sport (Appendix 4), and Treatment Expectation (Appendix 5) questionnaires. If eligible, participants will be scheduled for baseline testing which will be the first of 3 testing sessions. The first will take place on the day of baseline evaluation. The second will take place at the end of the 2-week intervention. The third will take place 1-month after the final treatment session.

9.b Baseline & Post-Test Evaluations



The baseline evaluation will include gathering general information regarding age, height, leg length, foot measurements, weight. Participants will then receive instruction on the testing procedures and will perform several warm-up trials on all assessments to become familiarized with the testing procedures. Next, participants will have their ankle range of motion, postural control, and lower extremity biomechanics tested. Finally, participants will complete the possible neuromuscular mechanism measures. All outcomes will be performed at all test sessions. More detailed descriptions are provided below:

Peripheral Neuromuscular Mechanisms:

Ankle joint position sense will be used to assess changes in a participant's ability to detect the position of the foot/ankle complex relative to the body. The theoretical premise of this mechanism is that CAI participants have an impaired ability to detect ankle joint position due to altered input from damaged mechanoreceptors.[7] Postural control improvements following manual therapies may be the result of improved input from mechanoreceptors. Ankle joint position sense will be assessed at the mid-range of plantar flexion and inversion as these positions have the greatest sensitivity to CAI associated impairments. Participants will be seated with their foot in neutral (0 degrees of plantar flexion) before an active repositioning technique is used to quantify the absolute and constant error for each movement.

Plantar light-touch thresholds will assess changes in somatosensation on the plantar foot. These thresholds are increased in CAI patients and thought to be the result of repetitive trauma to the mechanoreceptors. The effects of manual therapies may be the result of improved plantar mechanoreceptor sensitivity in CAI patients. To assess this neuromuscular mechanism, we will use a protocol that requires participants to lie prone while thresholds are assessed at the head of the 1st and base of the 5th metatarsal. Thresholds will be determined using Semmes-Weinstein monofilaments and a highly reliable 4-2-1 stepping algorithm.[100]

Spinal Level Neuromuscular Mechanisms:

The Hoffman reflex (H-Reflex) is the electrical analog of the monosynaptic stretch reflex and thought to provide insights into the neuromuscular mechanism mediating postural control. H-Reflex modulation is reduced in CAI patients and correlated to self-reported functional limitations. Thus, improvements in spinal reflexive excitability (increased H-Reflex values) may represent an underlying neuromuscular mechanism responsible for improved postural control following ankle joint mobilization and plantar massage. We

will assess spinal reflexive excitability in the soleus and fibularis longus using our established methodology. While lying supine, a stimulating electrode will be positioned over the sciatic nerve in the popliteal space. Peak-to-peak Hoffmann reflexes (H-reflex) will be measured and the stimulus intensity increased until a maximal H-reflex is observed. Three H-reflexes for each muscle will be recorded and normalized to the maximal M-response, representing the ratio of the motor neuron pool reflexively activated to the amount of the motor neuron pool available (H:M ratio). Higher H-reflex values and H:M ratios indicate greater excitability.

Supraspinal Level Mechanisms:

The corticospinal motor system plays a critical role in controlling movement by optimizing muscle activation. Abnormal facilitation or inhibition from the corticospinal pathway is associated with impairments of the ankle joint musculature and hypothesized to contribute to the postural instability associated with CAI. As such, cortical excitability may represent a plausible neuromuscular mechanism underlying improvements following ankle joint mobilization and plantar massage. Corticomotor measures of the soleus and fibularis longus will be assessed using Transcranial Magnetic Stimulation (TMS) methodology previously used by the research team. A Magstim 200 (Magstim Company, Wales, UK) will be used to produce a magnetic stimulus (max 2.0 Tesla) over the motor cortex contralateral to the test limb. Testing will be performed over the area generating the greatest motor evoked potential (MEP) while participants perform mild isometric contractions (20%) on an isokinetic dynamometer. Active motor threshold (AMT) will be determined as the lowest stimulator intensity required to elicit an MEP peak-to-peak amplitude ≥100μV in at least 4 of 8 trials. A higher AMT indicates decreased excitability, as a greater stimulus intensity is required to elicit an MEP. Eight stimuli will be delivered at 120%, 130%, and 140% of AMT, and peak-to-peak MEP amplitudes will be recorded for each trial. The cortical silent period (CSP) will be measured as the distance from the end of the MEP to a return of the mean EMG signal plus two times the standard deviation of the baseline (pre-stimulus) EMG signal. A longer CSP indicates a greater corticospinal inhibition.

Corticomotor output mapping provides further insight into the function of the motor cortex by identifying the size of an area within the motor cortex associated with a select muscle. Improved postural control following manual therapies may be the result of a reorganization of the corticomotor output in CAI patients (i.e. an increased map area and/or volume of a given muscle). Corticomotor mapping of the soleus and fibularis longus muscle will be assessed using TMS methods consistent the literature and our own protocols. After AMT is quantified, a 6x6 cm grid (3cm lateral-medial and 3cm anterior-posterior) will outline the hotspot for each muscle and a stimulator intensity of 100% AMT will be used. Three consecutive stimuli will be delivered at each grid location in a random order in order to produce reliable and reproducible maps. Average peak-to-peak MEP amplitudes for each grid site will be normalized to M-max. Cortical representation of the soleus and fibularis longus will be calculated using map area and map volume. Map area is the number of stimulus positions whose stimulation evoked an average MEP ≥MEP threshold and an increase would suggest an expansion of the

cortical representation of a selected muscle. Map volume will be calculated as the sum of the mean normalized MEPs recorded with an increase suggesting greater cortical excitability.

Alterations in cortical activation could represent an underlying cause of postural control improvements following manual therapies as postural control improves following the application of manual therapies and balance is controlled, at least in part, cortically. To assess changes in cortical activity, participants will complete single limb balance assessments with eyes open and closed while cortical activation is simultaneously assessed using electroencephalography (EEG). A V-Amp 16 active channel EEG system (BrainVision LLC, Morrisville, NC) will be used to acquire the EEG data from three channels (Fz, Cz and POz) based on a 10-20 system. The impedance of each electrode will be kept below 40 kW. Bandpass filters of 0.1 Hz and 65 Hz at 3 dB attenuation will be used to remove environmental artifacts. Post-processing will include identifying and decontaminating artifacts as previously described. The primary mechanisms of interest are the power spectral densities (PSD) of the alpha (8-12 Hz), beta (13-19Hz), and sigma (30-40Hz) bandwidths which will be computed for each condition to create a relative PSD. Changes in the relative PSD will be compared among the interventions and control group.

Sensory Organization Strategies [Primary Mechanism of Interest] represents a plausible neuromuscular mechanism as evidence indicates that in lieu of reliable somatosensory information, CAI patients increase reliance on visual information. Further, an increased reliance on visual information is hypothesized to explain the repeated ankle sprains and episodes of giving way associated with CAI. Changes in sensory organization strategies may represent the underlying neuromuscular mechanism of ankle joint mobilizations and plantar massage and these manual therapies improve postural control and reduce giving way episodes in CAI patients. Changes in our primary mechanism of interest will be calculated using the % Modulation measure used previously by our group. This measure estimates the weight given to visual information during eyes open stance based on the magnitude of postural instability that occurs when vision is removed. Raw ground reaction force data will be collected at 200Hz using an Accusway Plus Balance force platform (AMTI, Watertown, MA). Raw data will be filtered appropriately before the % Modulation for center of pressure velocity is calculated from eyes open and eyes closed stance data. Additional postural control measures such as time-to-Boundary (TTB) will also be calculated.[0]

Secondary Measures

Both walking gait and jump landing biomechanics will be assessed. Three-dimensional kinematics (sampled at 100Hz) and kinetics (sampled at 1000Hz) will be obtained during both tasks using a 10-camera Vicon motion capture system. During gait trials, participants will walk at a self-selected speed over multiple embedded force plates. Speed will be enforced with timing gates centered over the force plates during the five test trials. Jump landing biomechanics will be assessed with a drop vertical jump protocol that requires participants to jump from a 30cm platform placed at a

distance of 50% of the participants' height away from the edge of the force platform, with an immediate rebound jump for maximum height. Five test trials will be completed. Both discrete variables and profile plots of the kinematic and kinetic data will be calculated for the ankle, knee, and hip in the sagittal, frontal, and transverse planes. All secondary measure methodology is consistent with those previously used by our research team.

Tertiary Measures

All participants will also be asked to stand barefoot on one leg with eyes closed and hands on hips on the floor for 20 seconds to quantify their balance. Each participant will perform up to 5 trials on each leg. During each trial, the investigator will count the amount of balance errors the participant commits. Errors include any of the following: (1) lifting the hands off the iliac crests; (2) opening the eyes; (3) stepping, stumbling, or falling; (4) moving the hip into more than 30 degrees of flexion or abduction; (5) lifting the forefoot or heel; or (6) remaining out of the test position for longer than 5 seconds. The *Weight Bearing Lunge Measure (WBLT) is a* method of measuring dorsiflexion range of motion and is completed barefoot by placing the participant's great toe in line with their heel on top of a tape measure on the floor. While keeping the heel firmly on the ground, participants are asked to bend their supporting knee to touch the wall in front of them. This is completed through a slow and controlled lunging action. Using the tape measure on the floor, the maximum distance each participant can place their foot away from the wall while keeping both the heel flat on the floor and knee touching the wall will be recorded. This test will be repeated 6 times during each laboratory session. All tertiary measure methodology is consistent with those previously used by our research team.

9.c Study Treatments

Sensory-Targeted Rehabilitation Strategies. This intervention will consist of 6, 5-minute treatments the following over a 2-week period:

Ankle Joint Mobilization: The joint mobilization treatment will consist of 2 sets of Grade III anterior-to-posterior ankle joint mobilizations and one minute between sets. This mobilization will be operationally defined as large-amplitude, 1-s rhythmic oscillation from the joint's mid-range to end range with translation taken to tissue resistance. The objective of this therapy technique is to glide the ankle into the area which restricts range of motion and gently stretch the restricted area. To begin this treatment, a mild traction to the ankle joint to lightly distract the bones of the ankle joint. Then two sets of joint mobilizations, each for two minutes, will be applied. Each repetition will consist of gently gliding the ankle joint in the backward direction until an area of restriction is reached. We will mobilize the joint into the restriction and then glide the ankle back to the starting position. This grade of joint mobilization was selected because it attempts to increase the capsular endpoint and the oscillation spans the length of the joint providing the greatest stimulation of joint receptors. This manual therapy technique is commonly used in athletic training practice and presents minimal risk to participants.

Plantar Foot Massage: The plantar foot massage treatment will consist of 2 sets of 2 minutes of plantar foot massage. This massage will be operationally defined as two minutes of light petrissage (similar to kneading bread) and effleurage (gentle stroking motions) to the plantar surface of the foot from the ball of the foot to the heel. The objective of this therapy technique is to provide stimulation to the plantar cutaneous receptors of the foot. To begin this treatment, we will place our hands on the participant's foot with his thumbs on the plantar surface and his fingers of both hands on the dorsal surface of the foot. We will then apply two sets of massage, each for two minutes. Each set will consist of gently massaging the plantar surface of the foot to the comfort of the participant. This manual therapy technique is commonly used and presents minimal risk to participants.

10 Definition of Evaluable Patients

Evaluable patients will be operationally defined in the following ways:

1) Baseline Evaluation: Any person eligible for the study.

2) 2nd Test Session: All enrolled participants in the intervention groups who completed all 6 sessions of the intervention and all participants in the control group who maintain normal daily activities during the intervention period.

3) 3rd Test Session: All enrolled participants who completed the 2nd test session.

11 Blinding / Unblinding Issues

Based on the study roster and planned data collection methods, blinding of the assessors will be used in the current investigation.

12 Statistical Plan

To achieve Aim 1 and quantify changes caused by the ankle joint mobilization and plantar massage interventions, neuromuscular mechanisms will be submitted to separate 2-way repeated measures (Group × Time) ANOVAs. MANOVAs may be used based on inter-item correlation coefficients found during the preliminary analysis of the data. Pairwise comparisons, when appropriate, will determine the location of significant interactions. An alpha level of 0.05 will be used to assess changes in the primary mechanism of interest (% modulation). An exploratory alpha level (0.10) will be used on all other peripheral, spinal, and supraspinal mechanisms and secondary measures to reduce the chance that possible changes would be overlooked in this initial R21 investigation. Hedge's G effect sizes and confidence intervals based on the pre-to-post change scores[42] will also be calculated and interpreted as follows: less than 0 as small, 0.31–0.7 as moderate, and greater than 0.71 as large. Finally, control group data will be used to calculate the minimal detectable change (MDC) scores for all mechanisms

and secondary measures.[42, 98, 134] The MDC allows us to evaluate the interventions effects relative to the stability of the measures over time. This 3-pronged approach affords us multiple criteria on which to base the interpretation of our results and power future clinical trials.

To achieve Aim 2 and determine the associations among sensory organization strategies, neuromuscular mechanisms, and secondary measures following ankle joint mobilization and plantar massage interventions, we will calculate associations at baseline, at the post-test, and among change scores. These associations will be calculated using Pearson Correlation Coefficients that will be interpreted as: ≤0.29 as negligible, 0.30-0.49 as low, 0.50-0.69 as moderate, 0.70-0.89 as high, and ≥0.9 as a very high correlation.[135] The models will then be adjusted for identified covariates using a general linear model and an exploratory alpha level of 0.10. We anticipate associations that will provide insights about how to specifically leverage the manual therapies mechanisms to target specific neuromuscular impairments and biomechanical deficits associated with CAI.

All experimental conditions are detailed to ensure reproducibility and the proposed analytic plan ensures unbiased treatment and interpretation of the data. We are committed to full transparency in reporting the results and to making the data available upon request for unbiased review.

To explore how individual response variability influences plausible neuromuscular mechanisms, we will use a Bayesian statistical approach.[71, 94144, 145] More specifically, we will determine how patient characteristics (e.g. age, height) and baseline measures influence the probability of having a meaningful change in % Modulation and other neuromuscular mechanisms. Predicting treatment response with only demographic and baseline data would suggest that the neuromuscular mechanism(s) of ankle joint mobilization and plantar massage may be modulated by the patient's sensorimotor constraints.

13 Data Management

Data will be collected both in hard copy & electronically. All computers in the research laboratories are password protected. As soon as feasible, the PIs will transfer the, already de-identified, electronic data to Sharepoint. In order to protect the integrity of the original data files, copies will be made to be used for data manipulation. Any data file that is amended, cleaned, or updated will be given a new name with the corresponding name of the original file followed by _modified and dated with the month_, day_, and 2-digit year it was modified (i.e. IC01_trial_1_modified_10_11_18).

Additionally, data collected in hard copy will be de-identified and transferred to electronic data on Sharepoint as soon as possible. All offices are locked and the personal computers in the PI's respective offices are password protected. Additionally, hard copy files that have yet to be transferred will be stored in a locked cabinet. The

Sharepoint data will only consist of de-identified data. Further details can be seen in the Confidentiality section below.

Data Entry, Procedures, Flow, and Checks

1. The programs and data entry sequence that will be used to record the data entered into an electronic database system are as follows:
    i. The research team will electronically record the data from the hard copy forms collected from the participants.
    ii. Upon completion of data entry, the data will then be transferred to Sharepoint. The website account will be maintained at the University of North Carolina Chapel Hill and only the PIs will have access to the site using a unique user name and password.
2. All hard copy data will be transferred to electronic files and a secure electronic database (Sharepoint) by members of the research team. The data will be entered in/transferred to the electronic databases within 5 business days of data capture.
3. Process for data checks.
    i. Based on data entry plan, this will be a single data entry check. In order to ensure consistency of data entry, the research team will discuss and inspect data entry in the web-based electronic database in their monthly meetings.
    ii. Any issues associated with data entry will be resolved during these meetings.
    iii. In order to ensure consistency of changes, the research team will also modify the files and denote the change in the title of the spreadsheet (e.g. UNC_STARS_database_revised_11_1_18).
4. Audit and tracking system for evaluating data flow and data entry.
    i. The research team will discuss the flow of the database and any data entry issues that they may have in their meetings.
    ii. In the event that the investigators run into an item that does not produce the desired results (e.g. a question that could be worded more clearly for participants on a form), the PIs will discuss it, come up with a strategy to address it, implement the strategy, and ensure that only the most revised version of the item in question is used.
5. Description of data transmission from the databases to the statistical analysis package IBM SPSS Statistics (SPSS).
    i. All data from the secure web-based electronic database (Sharepoint) will be formatted to transfer directly into SPSS via copy and paste.

ii. Electronic trials, when appropriate, will be analyzed using MatLab. The analyzed output in MatLab has been designed to be directly pasted into an Sharepoint database.

    1. During MatLab analyses, all results will be immediately pasted into the Sharepoint database.

iii. The research team will discuss and review the SPSS database in their monthly phone meetings to ensure consistency of data.

14 Safety Issues

Expected risks to the subject are as follows:

- Rare (<1%) of mild skin irritation due to taping the kinematic markers sensors to the skin. This risk will be minimized by a member of the research team removing the tape with care.
- Rare (<1%) of seizure. Overall estimate is that seizure risk is < 1:1000 (0.1%) and this risk is associated with Repetitive TMS, which will not be conducted in this investigation.
- Infrequent (5%) of head and neck aches, hearing shifts, and fainting during and/or immediately after TMS. The research team will disclose this information to the participant prior to enrollment and remind them prior to testing. This is attributed to local stimulation of muscles and nerves near the stimulating coil, a tapping of the scalp by the coil during discharge, and wearing a tight-fitting swim cap. Other stimulation-related effects include teeth aches, facial twitches, odd taste in mouth, and discomfort from blinking and twitches of scalp muscles. All symptoms resolve after cessation of the TMS protocol. TMS may induce fainting or feelings of lightheadedness or dizziness. If symptoms of dizziness, lightheadedness, or feeling faint occur, the TMS protocol will be stopped. The subject will be allowed to lay down or put their head down to prevent fainting. If subjects faint, they must not be allowed to leave the laboratory until fully recovered. TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud click can result in temporary ringing in the ear and subclinical auditory threshold shifts. To prevent transient hearing threshold shifts due to TMS, subjects and investigators will be wear earplugs during TMS.
- Infrequent (10%) of itching/scratching of the scalp during EEG testing. Care will be taken during the application of the EEG cap, electrodes to measure brain wave activity, and the insertion of the gel.

  These risks are considered to be minimal and are addressed in the protocol and consent form."

  Because the manual therapies can cause mild discomfort (<1%), all participants will be monitored at each treatment session during the study. The manual therapies are designed to be pain free and are commonly applied in clinical

scenarios but because of the rare risk of discomfort, participants will be monitored for expected and unexpected AEs related to the manual therapies.

For the protocol, all AEs will be reported promptly based on the requirements of the IRB. Dr. Wikstrom will follow the procedures for reporting AEs. Dr. Wikstrom will report the AE to the UNC IRB as well as the IMC and NCCIH within the required reporting periods.

15 Confidentiality

All participants will be coded upon entry into the investigation. The master sheet (listing names with code numbers) will be stored on a password protected computer in the primary investigator's personal office for each site. Coded data sheets will be kept in a locked filing cabinet in the office of the primary investigator. As data sheets are transfer to electronic files for data analysis, the electronic records associated with the investigation will also be coded and de-identified, and kept on the password protected computed in a separate folder/location. All documents and data collected from participants in this study must be retained for three years in accordance to IRB protocol.

16 IRB Approval Procedures

IRB approval (Appendix 19) will be maintained. The PI will prepare the respective documentation to document consent (Appendix 6 and 18) in consultation with NCCIH.

17 Informed Consent Procedures

Participants interested in the study will contact the primary investigator to learn more about the study and set up an initial meeting. During that meeting, potential participants will be given eligibility questionnaires to complete (based on partial waiver of consent as approved by the IRB). If eligible, participants will be schedule to come in and meet with the PI to review the informed consent document and begin the first test session. Any questions will be answered before any data collection begins.

If a participant is determined to be ineligible for the investigation then the data collected (to determine eligibility) will be immediately destroyed. Specifically, the AII, FAAM, FAAM-S and treatment expectation data sheets will be shreeded. No other data will be collected prior to determining eligibility and the potential participant reading and signing the informed consent document.

18 Plans for and Responsibilities of the Independent Monitoring Committee

An Independent Monitoring Committee (IMC) will be appointed prior to the initiation of the study in consultation with the NCCIH.

18.a Independence of the IMC

To remain objective, the IMC must maintain independence from the study. Accordingly, the IMC will not be directly or indirectly involved in the conduct of the study and does not have scientific, proprietary, financial or other interests that may affect independent decision-making.

Annually the IMC will report to the NCCIH Program Officer that no conflict of interest exists between them, the PIs or any study personnel. Such a statement may also be required prior to each review.

18.b Executive Secretary

Dr. Wikstrom will serve as the executive secretary to facilitate the distribution of reports. All communication between the study staff and the IMC will be facilitated by Dr. Wikstrom with NCCIH copied on the correspondence.

18.c Safety Monitoring Plan

This protocol will be continuously monitored in real-time by the principal investigator for adverse events (AEs). Participants will be discharged from the initial treatment session with specific self-monitoring guidelines (See appendix #21) and instructed to call immediately for any concerning signs or symptoms throughout the rest of the treatment period.

The full data and safety monitoring plan can be seen in Part M of the MOOP.

18.d Safety Reports

At predetermined intervals, Dr. Wikstrom will prepare adverse event reports to be reviewed by the IMC. The adverse events are reported in aggregate by treatment groups, as requested. Serious adverse events are generally reported as they occur. The tables for reporting to the IMC are attached to this document. See Appendix 23.

18.e Roles and Responsibilities of the IMC

The IMC provides independent safety monitoring in a timely fashion to assure patient safety and study quality.

At the beginning of the trial, the IMC will review the manual of operating procedures, containing the study protocol, study forms, and safety monitoring plan, for scope and comprehensiveness. The monitoring plan should delineate data preparation functions, the review process, and the role of the IMC. The monitoring plan also specifies the contents and format of the reports, their frequency, and triggers for ad hoc reviews. Stopping rules, if appropriate, should outline the conditions under which a study may be stopped prematurely. The IMC may suggest modifications to the protocol, the monitoring plan and the reports that will routinely be prepared by the PI.

The primary focus of the IMC's activity is participant safety. The IMC reviews adverse event reports prepared by the PI.

Serious adverse events are generally reviewed as they occur. The IMC will notify the NCCIH if a pattern of events occurs and will suggest prevention measures (e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event).

For unexpected and/or related serious adverse events, the IMC will contact the NCCIH Program representative. In addition, the IMC may request individual participant records, including objective data, subjective questionnaires, and other study related data, to evaluate these events against the known safety profile of the study treatment and the disease.

The IMC may recommend actions including modifying or terminating the study.

In addition to safety monitoring, the IMC may review enrollment data, demographic information, retention status, and other reports prepared by Dr. Wikstrom that describe study performance and progress. The IMC will provide a report to NCCIH that describes study safety, progress and performance and provides recommendations regarding safe continuation or early termination of the trial.

The monitoring plan may require the IMC to evaluate the general performance of the study, including periodic assessment of participant recruitment, accrual and retention, protocol adherence, and data quality and timeliness. The IMC may also review any interim analyses to ensure that once the objectives of the study are met, outcome differences are detected or stopping rule thresholds are reached, the study will conclude.

Confidentiality must be maintained throughout all phases of the trial, including monitoring, preparation of interim results, review, and response to monitoring recommendations. Thus, the IMC should not receive participant identifiers, will maintain study confidentiality and will not share data.

After review and evaluation of the specified periodic reports prepared by the PI, the IMC prepares a summary cover letter, according to pre-specified criteria, for submission to the NCCIH. The letter provides comments on the report, discusses any concerns or suggestions for change, and recommends to NCCIH continuation or cessation of the trial.

IMC Review Instructions

1. The IMC Report will be distributed to the designated IMC by the PI.
2. The IMC will review the report and use the below checklist to review performance, safety and efficacy of the study, and/or provide any additional comments pertaining to his/her review. In addition, the IMC should specify their recommendation to continue or stop the study no later than 2-weeks after the report has been delivered.
3. The IMC will return the checklist to the NCCIH for distribution to the PI.
4. Dr. Wikstrom will distribute the IMC's comments to the NCCIH (Appendix 23).

Appendix 2: Balance Questionnaire

Participant Number_____ Date_____

Balance History Questionnaire (Version 1, Dec 2017)

1. Have you injured your foot, ankle, knee or hip of either leg in the past six months?
   _____ YES _____ NO

2. Have you ever had surgery on either leg?
   _____ YES _____ NO

3. Have you had an injury or illness that affects your ability to balance in the past six months?
   _____ YES _____ NO

4. Do you presently have a head cold or sinus problems that affect your ability to balance?
   _____ YES _____ NO

5. Do you have any history of Vertigo or balance problems?
   _____ YES _____ NO

6. Do you have any vision problems that affect your ability to balance?
   _____ YES _____ NO

7. Do you have any nerve problems in your legs or any decrease or increase of sensation in your legs or feet?
   _____ YES _____ NO

8. Do you have any history of circulation problems in your legs?
   _____ YES _____ NO

9. Do you have Diabetes?
   _____ YES _____ NO

Appendix 3: Ankle Instability Instrument

Participant Number: _____ Date: _____

Ankle Instability Instrument (Version 1, Dec 2017)

Instructions

This form will be used to categorize your ankle instability. Please fill out the form completely. If you have any questions, please ask the administrator of the survey. Please mark the ○ completely. Thank you for your participation.

1. Have you ever sprained an ankle?	Right	○Yes	○ No	
	Left	○ Yes	○ No	
2. Have you ever seen a doctor for an ankle sprain?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	
3. Did you ever use a device (such as crutches) because you could not bear weight due to an ankle sprain?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	

If yes,

3a. In the most serious case, how long did you need the device?

Right: ○ 1-3 days ○ 4-7 days ○ 1-2 weeks ○ 2-3 weeks ○ >3weeks

Left: ○ 1-3 days ○ 4-7 days ○ 1-2 weeks ○ 2-3 weeks ○ >3weeks

4. Have you ever experienced a sensation of your ankle "giving way"?	Right	○ Yes	○ No	
If yes,	Left	○ Yes	○ No	

4a. When was the last time your ankle "gave way"?

Right: ○ <1 month ○ 1-6 months ago ○ 6-12 months ago ○ 1-2 years ago ○ >2 yrs

Left: ○ <1 month ○ 1-6 months ago ○ 6-12 months ago ○ 1-2 years ago ○ >2 yrs

5. Does your ankle ever feel unstable while walking on a flat surface?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	
6. Does your ankle ever feel unstable while walking on uneven ground?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	
7. Does your ankle ever feel unstable during recreational or sport activity?	Right	○ Yes	○ No	○ N/A
	Left	○ Yes	○ No	○ N/A
8. Does your ankle ever feel unstable going *up* stairs?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	
9. Does your ankle ever feel unstable going *down* stairs?	Right	○ Yes	○ No	
	Left	○ Yes	○ No	

	Right	**Left**
How many times have you sprained your ankle in the past?	_____	_____
How long has it been since your last significant ankle sprain (in months)?	_____	_____
How many times in the past 3 months has your ankle felt like it "gives way"?	_____	_____

Appendix 4: Foot & Ankle Ability Measure

Participant Number: _____ **Date:_____**

Foot and Ankle Ability Measure (FAAM) (Version 1, Dec 2017)

Please answer **every question** with one response that most closely describes to your condition within the past week. If the activity in question is limited by something other than your foot or ankle mark not applicable (N/A).

	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking on Even Ground	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking on even ground w/o shoes	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking up hills	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking down hills	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Going up stairs	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Going down stairs	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking on uneven ground	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Stepping up and down curbs	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Squatting	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Coming up on toes	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking initially	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□

Walking <5 mins	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking about 10 minutes	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Walking 15 minutes or greater	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□

Because of your **foot and ankle** how much difficulty do you have with:

Standing	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Activities of daily living	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Personal Care	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Light to moderate work	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Heavy work (push/pulling, climbing, carrying)	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Recreational activities	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□

How would you rate your current level of function during your usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

Right: .0 % Left: .0 %

Total FAAM ADL Score: Right: _____ Left: _____ **(Investigators Only)**

FAAM Sports Scale (Version 1, Dec 2017)

Because of your **foot and ankle** how much difficulty do you have with:

	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Running	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Jumping	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Landing	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Starting and stopping quickly	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Cutting/lateral movements	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Low impact activities	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Ability to perform activity with your normal technique	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□
Ability to participate in your desired sport as long as you would like	Right	□	□	□	□	□	□
	Left	□	□	□	□	□	□

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

Right: .0 % Left: .0 %

Overall, how would you rate your current level of function?
Right: □ Normal □Nearly normal □ Abnormal □ Severely abnormal
Left: □ Normal □Nearly normal □ Abnormal □ Severely abnormal

Total FAAM Sport Score: Right: _____ Left: _____

(Investigators Only)

Appendix 5: Treatment Expectations Questions

Manual therapies will improve my CAI related impairments?

1	2	3	4	5
No Confidence		Neutral		Very Confident

Ankle joint mobilizations will improve my CAI related impairments?

1	2	3	4	5
No Confidence		Neutral		Very Confident

Plantar massage will improve my CAI related impairments?

1	2	3	4	5
No Confidence		Neutral		Very Confident

Appendix 6: Informed Consent Documents

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: 10-4-2017
IRB Study # 17-2655
Title of Study: Neuromuscular Mechanisms of Manual Therapies in Chronic Ankle Instability Patients
Principal Investigator: Erik Wikstrom
Principal Investigator Department: Exercise and Sport Science
Principal Investigator Phone number: (919) 962-2260
Principal Investigator Email Address: ewikstro@email.unc.edu
Funding Source and/or Sponsor: National Institutes of Health: National Center for Complimentary and Integrative Health

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What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary.
You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
Lateral ankle sprains are the most common injury experienced by those who are physically active and recurrent disability, defined as chronic ankle instability, associated with these injuries is extremely common. In this study, we aim to determine the neuromuscular mechanisms responsible for the benefits that chronic ankle instability patients experience after receiving ankle joint mobilization and plantar massage manual therapy treatments. By understanding the mechanisms responsible for the observed improvements, we hope to optimize treatment protocols for chronic ankle instability patients and subsequently reduce the long-term negative consequences and slow the development of the early onset post-traumatic osteoarthritis associated with the condition.
The purpose of this research study is to determine what neuromuscular changes occur following a 2-week treatment of ankle joint mobilization and plantar massage in people with chronic ankle instability (CAI).

You are being asked to be in the study because you have chronic ankle instability, based on the answers you provided to the eligibility questionnaire.

Are there any reasons you should not be in this study?

You should not be in this study if you do not have chronic ankle instability. You should also not be in this study if you have known vestibular and vision problems, acute lower extremities and head injuries (<6 weeks), chronic musculoskeletal conditions known to affect balance (e.g., ACL deficiency) and a history of ankle surgeries to fix internal derangements. You should also not be in this study if you have metal implants anywhere in the head (except in the mouth), pacemakers, implantable medical pumps, ventriculo-peritoneal shunts, intracardiac lines, a history of seizures, have had a stroke, or had a serious head trauma.

How many people will take part in this study?

There will be approximately 60 people in this research study.

How long will your part in this study last?

In addition to our previous interactions, you will be asked to complete three testing sessions that will last approximately 3.0 hours each. Between the first and second test session, you will attend 5 treatment sessions that are 5-minutes each.

What will happen if you take part in the study?

The following test will be completed once before and twice after the intervention.

■ Ankle joint position sense. You will sit at the edge of a table and be asked to move your ankle to two different positions. Each position will be shown to you before you will be asked to return to that position with your eyes closed. You will return to each position 3 times.

■ Plantar light-touch threshold. You will sit at the edge of the table with your eyes closed. We will apply a device, much like fishing line, to determine how sensitive specific points on the bottom of your foot are. We will repeatedly ask you if you can feel the device we have applied to your foot. We will continue to do this until we determine the sensitivity of both points on your foot.

■ Hoffman reflex (H-Reflex). You will lie on a table and the research team will place electrodes over several muscles on your lower leg and on the back of your knee. To apply these electrodes, we will need to clean specific areas of your leg and we may have to shave a small portion of leg hair in each area, if applicable. We will then apply an electrical stimulus to the back of your knee to cause a small muscle contraction in your muscles. Some people find this to be slightly uncomfortable. We will continue to apply these stimuli until we can determine can maximize the muscle contraction. This usually takes about 7-10 stimuli.

■ Transcranial Magnetic Stimulation (TMS). You will be seated in a chair and have your foot resting on a platform. This test, is similar to the H-Reflex test except that we deliver the electrical stimulus to a specific portion of your brain that tells the muscles to contract. We will first map your brain to determine the area that causes the strongest reaction while you perform a small muscle contraction. We will then deliver several more electrical stimuli (8-10) to determine the lowest level of stimuli that can still elicit a strong muscle contraction. Each stimuli will produce a loud click/pop and thus we will ask you to wear ear plugs. For this test, we will also place several electrodes on your muscles and will have to clean and potentially shave those areas. Some people get mild head and neck aches during this testing procedure but those go away shortly after the procedure is over. If you have a history of fainting, please tell the research team as we will want to monitor you more closing during testing as there is a slight risk of faintly during TMS, especially if you have a history of fainting.

■ Cortical Activity. You will be asked to complete single limb balance assessments with eyes open and closed while wearing an EEG cap which measures your brain waves. Each trial will last no more than 20 seconds and you will complete 3 trials with eyes open and 3 trials with eyes closed. While preparing for this test, we will place a cap on your head and then place a gel in each of the cap's electrodes. Placing the gel may result in some light scratching of the scalp and may be itchy during and for a short time after the testing.

■ Biomechanics. You will be asked to complete a walking and jump landing task. For both, we will put a series of small spheres on various landmarks on your body (e.g. hip, knee, shoulder, etc). During walking trials, you will walk at a comfortable speed over a 15 foot space in the lab at least 5 times. For the jump landing you will jump down from a 12 inch box that is 50% of your height away from the target landing area. As soon as you land, you will immediately jump as high as you can. At least five trials will be completed. You will be able to see demonstrations and practice each task.

■ Balance & Range of Motion. . To examine ankle range of motion, you will be barefoot, face a wall, and place the leg being tested slightly in front of the opposite ankle. You will then lunge forward until your knee touches the wall while your heel remains in contact with the ground. You will gradually be moved back from the wall until your knee is no longer able to make contact with the wall or your heel is no longer making contact with the ground. This test will be repeated 6 times, 3 times per leg. During this test you will have a small device strapped to your lower leg to measure range of motion. To examine your balance, you will complete three balance trials per leg. For this test, you will stand on a single leg for 20 seconds with your eyes closed and your hands on your hips. While balancing, you should stand quietly and make any necessary adjustments (if balance is lost) and return to the initial testing position as quickly as possible.

After completion of baseline testing, you will be placed into one of three groups: ankle mobilization, plantar massage, control. Assignment is random, so no one will know what your group assignment will be ahead of time. All interventions are to a single limb and require 6, 5-minute treatments over the next 2-weeks. The first treatment session will be today, after completing the baseline testing. If you are assigned to the mobilization group will receive 2, 2-minute bouts during each session with a one minute break. We will grasp your ankle and lower leg. Then we will move your ankle back and forth (front to back) while holding your lower leg still. If you are assigned to the massage group, you will receive 2, 2-minute bouts with a 1-minute break between sets during each session. The massage will be to the entire bottom of your foot. If you are assigned to the control group, you will receive no treatment during the entire 2-week intervention period. Please continue regular physical activity habits and daily routines over the course of 2-week intervention. At the end of the two weeks, we will schedule another test session were we will repeat the baseline testing. Finally, one month after the final treatment session, we will schedule the final test session and again repeat the same tests.

The research would also like to keep your contact information, without links to your study ID, in case you are eligible for future investigations. You do not need to let us keep your contact information to participate in this study.

Can we keep your contact information (Circle one)? YES NO

If you later change your mind and wish to withdraw your contact information, please contact Dr. Erik Wikstrom at ewikstro@email.unc.edu and your contact information will be removed from the database.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. The benefits to you from being in this study may be an improvement in range of motion at the ankle, better balance, and better function because of decreased ankle instability symptoms if you are assigned to the mobilization or massage groups. These benefits may last at least a month after the intervention.

What are the possible risks or discomforts involved from being in this study?

The risks associated with participation in this research study are minimal and highly unlikely. While the potential exists for you to be mildly sore after the treatments, this is highly unlikely because you are a young individual. You may experience some itching and scratching at the scalp while we assess cortical activity (EEG testing). You may also experience some irritation on your skin where we place the sphered to do the biomechanics testing but this would be rare. Seizure is a very rare (0.01%) during the TMS testing. This risk is associated

with a test protocol that we will not be undertaking in this investigation but please let the research team know if you have a history of seizures, or serious head trauma. There is also a chance that you will have a mild head/neck ache, may become faint, or having a mild temporary hearing shift during the TMS testing. Please let the research team know if you have a history of fainting. To prevent hearing shifts, we will ask that you wear earplugs. The head and neck aches fade quickly after the testing session is done.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

If you choose not to be in the study, what other treatment options do you have?
None. This study is not part of medical care. Therefore, if you do not wish to be in this study, you will not receive the treatments.

What if we learn about new findings or information during the study?
You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about you be protected?
Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

What will happen if you are injured by this research?
All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. You do not give up any of your legal rights by signing this form.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?
You will be compensated a total of $250 for participating in this study. At the conclusion of the first post test (after treatment), you will receive $100. At the conclusion of the second post-test, you will receive $150. Withdrawal from the study prior to these time points will result in the forfeiture of the scheduled compensation.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the National Institutes of Health. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

Appendix 7: Documenting the Consent Process Form

Protocol Number and Title:_____

PI/Site Name:_____

Participant/Subject Name:_____

Date:_____

Consent Forms (CFs) reviewed:

- ☐ Main Study CF, Version/Date:_____
- ☐ Other CF, Specify:_____ Version/Date:_____
- ☐ Other CF, Specify:_____ Version/Date:_____

Language of CF(s) reviewed:

☐ English ☐ Spanish ☐ Other, Specify:_____

Study Staff Member(s) Conducting CF discussion:_____

Was time allowed to ask/answer questions? ☐ Yes ☐ No

If not, please explain:_____

Was a copy of the signed CF(s) provided to the study subject? ☐ Yes ☐ No

If not, please explain:_____

Was/were the CF(s) signed prior to initiation of study procedures? ☐ Yes ☐ No

If not, please explain:_____

Was/were a copy of the signed CF(s) provided to the subject? ☐ Yes ☐ No

If not, please explain:_____

Additional Notes:

_____ _____

Signature of person obtaining consent Date

Appendix 8: Protocol Deviation Form & Log

Protocol ID/Number:					**Site Name/Number:**				
Protocol Title (Abbreviated):									
Principal Investigator:					**Page number [1]:**				
Ref No.	**Subject ID**	**Date of Deviation**	**Date Identified**	**Deviation Description**	**Dev. Type [2]**	**Resulted in AE?**	**Did Subject Continue in Study?**	**Meets IRB Reporting Req. (Yes/No)**	**IRB Reporting Date**
1									
2									
3									
4									
5									
6									
7									

Investigator Signature: _____ **Date:** _____

Form Instructions:

[1] Each page should be separately numbered to allow cross-referencing (e.g., deviation #2 on p. 7)

[2] Deviation Type: (A-J) See codes below—enter the appropriate deviation code from the list.

Protocol Deviation Codes:

A – Consent Procedures
B – Inclusion/Exclusion Criteria
C – Concomitant Medication/Therapy
D – Laboratory Assessments/Procedures
E – Study Procedures
F – Serious Adverse Event Reporting/Unanticipated Adverse Device Effect
G – Randomization Procedures/Study Drug Dosing
H – Visit Schedule/Interval
I – Efficacy Ratings
J – Other

Appendix 9: AE & Serious AE Reporting

The UNC-Chapel Hill policy is based on this guidance. "*Adverse events"* that are not UPIRSOs are not required to be reported to the IRB. Therefore, it is important to delineate the definitions that inform reporting requirements. (See Appendix U, Decision Algorithm for Unanticipated Problems)

Required Reporting of UPIRSOs

Reporting is required of all UPIRSOs, including those which may occur after the participant has completed or is withdrawn from the study, or following study closure. Reporting is completed via IRBIS, UNC's online IRB information system.

Timing of Reports

Events that meet the criteria for an UPIRSO and are also serious adverse events should be reported to the IRB within one (1) day of the investigator becoming aware of the event.
Any other events that meet the criteria for a UPIRSO should be reported to the IRB within one (1) week of the investigator becoming aware of the problem.
If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

Definitions:

"Unanticipated problems involving risks to subjects or others" (UPIRSO) refers to any incident, experience, or outcome that:

- is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- is related or possibly related to a subject's participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events that satisfy all three criteria are reportable to the UNC-Chapel Hill IRB. See SOP 19.4 for additional information.

"Related to the research" refers to an incident, experience or outcome that is likely to have resulted from participation in the research study.

"Possibly related to the research" refers to the reasonable possibility that the adverse event, incident, experience or outcome may have been associated with the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

An "adverse event" or "adverse experience" (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical

exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

Adverse events that meet all three criteria set forth in 19.1.1 (above) and are therefore an UPIRSO are reportable to the IRB. If investigators are unsure whether an AE is an UPIRSO, the event should be reported. The IRB will review the report and make a final determination as to whether the event constitutes an UPIRSO.

"Serious Adverse Event" (SAE) is any adverse event temporally associated with the subject's participation in research (whether or not considered related to the subject's participation in the research) that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Serious adverse events that meet all three criteria set forth in 19.1.1 (above) and are therefore an UPIRSO are reportable to the IRB. If the investigator is unsure whether an SAE is an UPIRSO, the event should be reported. The IRB will review the report and make a final determination as to whether the event constitutes an UPIRSO.

"Unexpected Adverse Event" as defined by the FDA, is any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Serious Adverse Event (SAE): A serious adverse event will be considered any undesirable sign, symptom, or medical condition with one or more of the following outcomes:

- is fatal, is life-threatening,
- requires or prolongs inpatient hospitalization,

- results in persistent or significant disability/incapacity,
- constitutes a congenital anomaly or birth defect,
- is medically significant and which the investigator regards as serious based on appropriate medical judgment.
- any serious psychological and emotional distress resulting in study participation (suggesting need for professional counseling or intervention).

Unexpected Event: Any adverse experience, event, incident, interaction or outcome that is **not** identified in nature, severity or frequency in the study documentation (protocol, consent, Investigator Brochure, package insert etc) is considered an unexpected adverse event. Any event that is previously **not** known or anticipated to result from an underlying disease, disorder, or condition of the human subject or the study population may also be considered an unexpected event. For Cancer Center Studies the DSMP tables A, B, or C have additional defining information regarding "unexpected" that is based on AE grade.

Expected Event: Any adverse experience, event, incident, interaction or outcome that is identified in nature, severity or frequency in the study documentation (protocol, consent, Investigator Brochure, package insert etc) is considered an expected adverse event. Any event that is previously known or anticipated to result from the underlying disease, disorder, or condition of the human subject or the study population may also be considered an expected event. For Cancer Center Studies the DSMP tables A, B, or C have additional defining information regarding "unexpected" that is based on AE grade.

Unrelated Event: Any adverse experience, event, incident, interaction or outcome for which a causal relationship with the study article, study intervention or study participation is not suspected.

Related/Possibly Related Event: Any adverse experience, event, incident, interaction or outcome for which a causal relationship with the study is suspected.

IRB Reporting Criteria For Serious Adverse Events:

Internal events: The IRB-HSR requires that all Internal, Serious, Unexpected adverse events be reported to the IRB-HSR using the IRB Online program within 7 days of the time the study team
receives knowledge of the event.

External events: External, Serious, Unexpected Adverse Events must be reported to the IRB-HSR using the IRB Online program **ONLY** if the event results in a change to the risk section of the consent and/or modification to the protocol.
External, Serious, Unexpected Adverse Events that **DO NOT** result in change to the risk section of the consent and/or modification to the protocol do not need to be submitted to the IRB unless the sponsor requires submission.

Reporting Timeline: Internal, unexpected SAEs and External SAEs resulting in modification to the protocol/consent must be submitted to the IRB-HSR within 1 days from the time the

study team received knowledge of the event. This includes the electronic submission and the hard copy of the signed AE reporting form.

If the internal SAE resulted in harm or death to the subject that was definitely caused by study participation the SAE should be reported to IRB-HSR, appropriate Dean and Office of Risk Management **within 24-hours**.

The IRB-HSR will make a Late Reporting notation to all internal, serious, unexpected adverse event reported greater than 7 days from the time the study team received knowledge of the event.

Appendix 10: Adverse Event Form

STUDY NAME

Site Name:_____ **Pt_ID:_____**	**This form is cumulative and captures adverse events of a single participant throughout the study.**

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious Adverse Event (SAE)
1 = Mild 2 = Moderate 3 = Severe 4 = Life-Threatening	0 = Not related 1 = Unlikely related 2 = Possibly related 3 = Probably related 4 = Definitely related	0 = None 1 = Dose modification 2 = Medical Intervention 3 = Hospitalization 4 = Intervention discontinued 5 = Other	1 = Resolved 2 = Recovered with minor sequelae 3 = Recovered with major sequelae 4 = Ongoing/Continuing treatment 5 = Condition worsening 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (if yes, complete SAE form)

At end of study only: Check this box if participant had no adverse events ☐
None

Adverse Event	Start Date	Stop Date	Severity	Relationship	Action Taken	Outcome of AE	Expected?	SAE?

Appendix 11: Unanticipated Problem (UP)

Protocol Name and Number:	Site Name:	Subject ID Number or List of Affected Subjects:
_____ _	_____ _	_____ _

1. Date UP Identified: __ __/ __ __ __/ __ __ __ __ (dd/mmm/yyyy)
2. Identify UP:_____
3. The Unanticipated Problem was unexpected in terms of nature, severity, or frequency: ☐ Yes ☐ No
4. The Unanticipated Problem is possibly related to participation in the research: ☐ Yes ☐ No
5. The Unanticipated Problem suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized: ☐ Yes ☐ No

   If the answers to questions 3–5 are ALL "YES," report event as an Unanticipated Problem to NCCIH and the institutional review board (if applicable).

6. Briefly describe the UP. Attach additional pages or supplementary information as necessary. Include date of incident and date of discovery. Describe harm or potential harm that occurred to subject(s), whether the incident is resolved, and whether the subject(s) remains in the study:

7. What action was taken with the study as a result of the Unanticipated Problem? (Check all that apply.)

   ☐ No action
   ☐ Revise protocol to eliminate apparent immediate hazards to subjects
   ☐ Modification of inclusion or exclusion criteria to mitigate newly identified risks
   ☐ Implementation of additional procedures for monitoring subjects
   ☐ Suspension of enrollment of new subjects
   ☐ Notify currently enrolled subjects
   ☐ Suspension of research procedures in currently enrolled subjects
   ☐ Modification of consent documents to include a description of newly recognized risks (site and/or study wide)
   ☐ Provision of additional information about newly recognized risks to previously enrolled subjects
   ☐ Other: _____

8. Is the Unanticipated Problem a serious adverse event? ☐ Yes ☐ No

If the Unanticipated Problem is a serious adverse event, submit this form and complete the Serious Adverse Event form.

Statement of Principal Investigator: *I have personally reviewed this report and agree with the above assessment.*

_____ __ __/ __ __ __/ __ __ __ __
Signature of Principal Investigator Date

_____ __ __/ __ __ __/ __ __ __ __
Name of Person Completing the Form Date

Appendix 12: Serious Adverse Event Form

STUDY NAME

Protocol Number:_____

Site Name:_____

Pt ID:_____

Date Participant Reported:

__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

1. SAE onset date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
2. SAE stop date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
3. Location of SAE:_____
4. Was this an unexpected adverse event? ☐ Yes ☐ No
5. Brief description of participants with no personal identifiers:
   Sex: ☐ F ☐ M Age: _____
   Diagnosis for study participation:_____
   _____
6. Brief description of the nature of the SAE (attach description if more space is needed):
   _____
   _____
7. Category of the SAE:
   - ☐ Date of death___/_____/_____ (dd/mmm/yyyy)
   - ☐ Life threatening
   - ☐ Hospitalization – initial or prolonged
   - ☐ Disability/incapacity
   - ☐ Congenital anomaly/birth defect
   - ☐ Required intervention to prevent permanent impairment
   - ☐ Other:_____

8. Intervention type:
   - ☐ Medication or nutritional supplement (specify):_____
   - ☐ Device (specify):_____
   - ☐ Surgery (specify):_____
   - ☐ Behavioral/lifestyle (specify):_____

9. Relationship of event to intervention:
   - ☐ Unrelated (clearly not related to the intervention)
   - ☐ Possible (may be related to intervention)
   - ☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event? ☐ Yes ☐ No

11. What medications or other steps were taken to treat the SAE?

    _____

12. List any relevant tests, laboratory data, and history, including preexisting medical conditions:

    _____

13. Type of report:
    - ☐ Initial
    - ☐ Follow-up
    - ☐ Final

Signature of principal investigator: _____ Date: _____

Appendix 13: Participant Eligibility Checklist

Participant Name _____ Date: _____

Please check the box for all inclusion criteria satisfied.

Inclusion Criteria Satisfied:

- ☐ Male or female 18-45 years of age
- ☐ History of ankle sprain with at least two episodes of "giving way" within the past six months
- ☐ Score of ≥ 5 on the Ankle Instability Instrument (AII)
- ☐ Score of ≤ 90% on the FAAM-ADL
- ☐ Score of ≤ 80% on the FAAM-S.

Notes about inclusion criteria:

Exclusion Criteria Triggered:

- ☐ Younger than 18 or older than 45 years
- ☐ No history of ankle sprain or episodes of "giving way" in the past six months
- ☐ Score of ≤ 5 on the Ankle Instability Instrument (AII)
- ☐ Score of ≥ 90% on the FAAM-ADL
- ☐ Score of ≥ 80% on the FAAM-S.
- ☐ An acute ankle sprain within the past 6 weeks.
- ☐ Previous history of lower extremity surgery with internal derangements, reconstructions, or repair
- ☐ Lower extremity injury within the past 6 months (other than ankle sprains)
- ☐ Presence of balance deficits or conditions known to affect balance as noted on the Balance Questionnaire including diabetes and/or vertigo.

Notes about exclusion criteria:

If all inclusion criteria are satisfied (all boxes checked) and none of the exclusion criteria are triggered, then the participant can be enrolled in the study. If not all inclusion boxes are checked or one or more of the exclusion boxes are checked, participation in this study is no longer allowed.

Screener Name: _____

Screener Signature: _____ Date: _____

PI Signature: _____ Date: _____

Gender and Racial/Ethnic Categories of participant if eligible for inclusion into the study:

Please circle the gender and racial/ethnic categories of the potential participant:

Gender: Male Female

Ethnicity: Hispanic/Latino Not Hispanic/Latino

Race: Asian Black/African American White

American Indian/Alaska Native Native Hawaiian or Other Pacific Islander

Appendix 14: Screening Log

Screening Log Table							
Number	Date	Race	Ethnicity	Eligible for Study	Date Enrollment Confirmed	Ineligible for Study	Reason

Appendix 15: Master Subject List

Master Enrolled Subject List		
Number	Name	Concomitant Medications (if any)

Appendix 16: Training Log

Training Log

IRB #: _____

Protocol #: _____

Protocol Title: Neuromuscular Mechanisms of Manual Therapies

Sponsor: NCCIH

PI Name:_____

Trainee Name:_____Date training completed:

Role: ☐ Co-Investigator
☐ Data Management
☐ Participant Recruiter

☐ Protocol Training including informed consent, study enrollment log, inclusion/exclusion, CRF and data collection sheet.

☐ CRF/eCRF Training (if applicable)

☐ Evaluation Procedures

☐ AE's/SAE's

☐ IP Overview

☐ Data/Query Management (if applicable)

☐ IVRS (if applicable)

☐ Regulatory

☐ Other _____

Trainee Signature:_____ Date Signed:_____

Trainer Name:_____

Trainer Signature:_____ Date Signed:_____

PI Signature:_____ Date:_____

Appendix 17: Data Collection Sheet

Participant Number: _____ Date: _____ Time: _____

Age:____(years) Height: _____(cm) Weight:_____(kg) Gender: _____

Treatment Group: CONTROL MASSAGE MOBILIZATIONS

Treatment/Test Limb: Right Left

SL BESS ERRORS

Trial 1	Trial 2	Trial 3

All errors are counted and include:

1. Lifting the hands off the iliac crest
2. opening the eyes
3. stepping, stumbling, or falling
4. moving the non-stance hip into more than 30° of abduction
5. lifting the forefoot or heel
6. Remaining out of the test position for more than 5 seconds.

WBLT in cm (to the nearest 0.5cm)

Practice 1	Practice 2	Practice 3	Trial 1	Trial 2	Trial 3

GAIT BIOMECHANICS (check if completed

Trial 1	Trial 2	Trial 3	Trial 4	Trial 5

JUMP LANDING BIOMECHANICS (check if completed

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Right					

LIGHT TOUCH THRESHOLD

	Trial 1	Trial 2	Trial 3
1st Metatarsal			
5th Metatarsal			

JOIINT POSITION SENSE

	Trial 1	Trial 2	Trial 3
Plantar Flexion			
Inversion			

TTB

Foot Length: _____(cm) Width: _____(cm)

Force Plate Coordinates

Single Leg	Coordinate (cm) (+X, -X)	Coordinate (cm) (+Y, -Y)
Single Left		
Single Right		

TTB FAILED TRIALS (mark failed trials, zero for no fails)

SINGLE LEG LEFT:

EO: TRIAL I _____ TRIAL II _____ TRIAL III _____

EC: TRIAL I _____ TRIAL II _____ TRIAL III _____

H-REFLEX

	Trial 1	Trial 2	Trial 3
PL			
Soleus			

CORTICOMOTOR MAPPING / EXCITABILITY

	Trial 1	Trial 2	Trial 3
MAPPING			
EXCITABILITY			

Appendix 18: IRB Protocol

IRB Number: 17-2655	Initial	Principal Investigator: Erik Wikstrom

Application Cover Memo

Cover memo prepared by Erik Wikstrom on 10/05/2017 at 03:00 PM

This proposal is in response to a just in time request from NIH. The proposal is new and unrelated to previous proposals but the included methodology is been used by the research team in multiple previous investigations.

General Information

1. General Information

1. Project Title

   Neuromuscular Mechanisms of Manual Therapies in Chronic Ankle Instability Patients

2. **Brief Summary**. Provide a **brief non-technical description** of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

   This proposal will focus on elucidating plausible neuromuscular mechanisms associated with novel and effective manual therapies that target sensory neural pathways in chronic ankle instability (CAI) patients.

   Participants: Sixty participants with chronic ankle instability.

   Procedures (methods): Neuromuscular mechanisms will be quantified before and immediately after a 2-week intervention that consists of 6, 5-minute treatment sessions. Mechanisms will include a comprehensive group of peripheral (ankle joint position sense, plantar light-touch discrimination thresholds), spinal (H-reflex of the soleus and fibularis longus), and supraspinal measures (cortical activity during stance using electroencephalography [EEG], corticomotor excitability and mapping of the soleus and fibularis longus via transcranial magnetic stimulation [TMS], and sensory organization strategies during stance).

3. Is this new study similar or related to an application already approved by a UNC-Chapel Hill IRB? Knowing this will help the IRB in reviewing your new study.

   No

2. Project Personnel

1. Will this project be led by a STUDENT (undergraduate, graduate) or TRAINEE (resident, fellow, postdoc), working in fulfillment of requirements for a University course, program or fellowship?

   No

2. List all project personnel beginning with principal investigator, followed by faculty advisor, co-investigators, study coordinators, and anyone else who has contact with subjects or identifiable data from subjects.

   - List ONLY those personnel for whom this IRB will be responsible; do NOT include collaborators who will remain under the oversight of another IRB **for this study**.
   - If this is Community Based Participatory Research (CBPR) or you are otherwise working with community partners (who are not functioning as researchers), you may not be required to list them here as project personnel; consult with your IRB.
   - If your extended research team includes multiple individuals with limited roles, you may not be required to list them here as project personnel; consult with your IRB.

   The table below will access campus directory information; if you do not find your name, your directory listing may need to be updated.
   If a change to the Principal Investigator is requested during the course of the study, a PI Change Form must be submitted.

Full Name	Role	Department Name	IRB Training	COI WebID	COI Number	Initial COI Disclosure	Potential Conflict	COI Review Process	COI Review Result
University of North Carolina at Chapel Hill (UNC-CH)									
Erik Wikstrom	Principal Investigator	Exercise and Sport Science	✓	235634	17-47235	✓		Completed	No Conflict
Troy Blackburn	Co-investigator	Exercise and Sport Science	✓	235630	17-47231	✓		Completed	No Conflict
Jason Franz	Co-investigator	Biomedical Engineering - Undergraduate	✓	235633	17-47234	✓		Completed	No Conflict
Feng-Chang Lin	Co-investigator	Biostatistics Operations	✓	235631	17-47232	✓		Completed	No Conflict
Brian Pietrosimone	Co-investigator	Exercise and Sport Science	✓	235632	17-47233	✓		Completed	No Conflict
Kyeongtak Song	Research Assistant	Exercise and Sport Science	✓		n/a	n/a			n/a

IRB Number: 17-2655	Initial	Principal Investigator: Erik Wikstrom

NOTE: The IRB database will link automatically to UNC Human Research Ethics Training database and the UNC Conflict of Interest (COI) database. Once the study is certified by the PI, all personnel listed (for whom we have email addresses) will receive separate instructions about COI disclosures. The IRB will communicate with the personnel listed above or the PI if further documentation is required.

3. If this research is based in a center, institute, or department (Administering Department) other than the one listed above for the PI, select here. Be aware that if you do not enter anything here, the PI's home department will be AUTOMATICALLY inserted when you save this page.

Department	Exercise and Sport Science

3. Funding Sources

1. Is this project funded (or proposed to be funded) by a contract or grant from an organization EXTERNAL to UNC-Chapel Hill?

Yes

Is UNC-CH the **direct** recipient of any Federal funding for this study? You should answer 'yes' *only* if you are the grantee. You should answer 'no' if you are the recipient of a sub-award or contractor under the grant.

Yes

Funding Source(s) and/or Sponsor(s)

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number	Detail
NIH National Center for Complementary and Integrative Health (NCCIH)	17-2975	Federal				view

2. Is this study funded by UNC-CH (e.g., department funds, internal pilot grants, trust accounts)?

No

3. Is this research classified (e.g. requires governmental security clearance)?

No

4. Is there a master protocol, grant application, or other proposal supporting this submission (check all that apply)?

- ✔ Grant Application
- ✘ Industry/Federal Sponsor Master Protocol
- ✘ Student Dissertation or Thesis Proposal
- ✘ Investigator Initiated Master Protocol
- ✘ Other Study Protocol

4. Screening Questions

The following questions will help you determine if your project will require IRB review and approval.

The first question is whether this is RESEARCH (click for details)

1. Does your project involve a systematic investigation, including research development, testing and evaluation, which is designed to develop or contribute to generalizable knowledge? PLEASE NOTE: You should only answer yes if your activity meets all the above.

Yes

The next questions will determine if there are HUMAN SUBJECTS (click for details)

2. Will you be obtaining information about a living individual through direct intervention or interaction with that individual? This would include any contact with people using questionnaires/surveys, interviews, focus groups, observations, treatment interventions, etc. PLEASE NOTE: Merely obtaining information FROM an individual does not mean you should answer 'Yes,' unless the information is also ABOUT them.

Yes

3. Will you be obtaining identifiable private information about a living individual collected through means other than direct interaction? This would include data, records or biological specimens that are currently existing or will be collected in the future for purposes other than this proposed research (e.g., medical records, ongoing collection of specimens for a tissue repository).
OR
Will you be using human specimens that are not individually identifiable for FDA-regulated in vitro diagnostic (IVD) device investigations?

No

The following questions will help build the remainder of your application.

4. Will subjects be studied in the Clinical and Translational Research Center (CTRC, previously known as the GCRC) or is the CTRC involved in any other way with the study? (If yes, this application will be reviewed by the CTRC and additional data will be collected.)

   No

5. Does this study directly recruit participants through the UNC Health Care clinical settings for cancer patients or does this study have a focus on cancer or a focus on a risk factor for cancer (e.g. increased physical activity to reduce colon cancer incidence) or does this study receive funding from a cancer agency, foundation, or other cancer related group? (If yes, this application may require additional review by the Oncology Protocol Review Committee.)

   No

6. Are any personnel, organizations, entities, facilities or locations in addition to UNC-Chapel Hill involved in this research (e.g., is this a multi-site study or does it otherwise involve locations outside UNC-CH, including foreign locations)? You should also click "Yes" if you are requesting reliance on an external IRB, or that UNC's IRB cover another site or individual. See guidance.

   No

Exemptions

Request Exemption

Some research involving human subjects may be eligible for an exemption which would result in fewer application and review requirements. This would not apply in a study that involves drugs or devices, involves greater than minimal risk, or involves medical procedures or deception or minors, except in limited circumstances.

Additional guidance is available at the OHRE website. Exemptions can be confusing; if you have not completed this page before, please review this table with definitions and examples before you begin.

1. Would you like your application evaluated for a possible exemption?

   No

Scientific Review

Scientific Review

All biomedical research conducted at the University of North Carolina at Chapel Hill involving procedures that pose greater than minimal risk must undergo scientific review. Scientific review is a process that evaluates the scientific merit of a protocol ensuring that only scientifically sound protocols are submitted for IRB review. Scientific review ensures that the research uses procedures consistent with sound research design and the research design is sound enough to reasonably expect the research to answer its proposed question.

For example, research that involves experimental drugs or devices or invasive procedures requires scientific review. Additional examples can be found here.

At UNC, the Protocol Review Committee provides scientific review for oncology studies. For all other studies, scientific review can be conducted:

1. *Externally, by an independent organization that has no conflict of interest with the submitted research activity or;*
2. *Internally by the UNC Scientific Review Committee (SRC).*

Examples:

1. *An investigator-initiated study (with greater than minimal risk) regardless of the funding source must undergo scientific review by the UNC SRC unless it has been reviewed and approved by a protocol review committee empaneled for this purpose by Federal-funding agency (e.g., NIH, CDC, DOD) or a national foundation.*
2. *A multicenter industry/foundation sponsored protocol does not require scientific review by the UNC SRC.*

Note: Study section or FDA IND/IDE review is not adequate review to supplant review by the UNC SRC.

1. Does your research study require review by the Scientific Review Committee?
   If you are unsure if your project requires SRC review, please contact the OCT at 919-843-2698.

   Respond "no" if your research methods are limited to:

   - the collection and/or use of existing data, documents or specimens and/ or,
   - administering surveys; conducting interviews or focus groups, and/or
   - prospective collection of biological specimens by non-invasive means (hair and nail clippings, sweat, dental plaque and calculus, saliva, sputum).
   - Collection of blood from healthy adults by finger stick.

   No

Select one or more of the following:

✔ This protocol does not involve interaction or intervention that poses greater than minimal risk to subjects. Minimal Risk-the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

✘ This protocol was reviewed by a protocol review committee empaneled for this purpose by Federal-funding agency (e.g., NIH, CDC, DOD) or a national foundation. Please provide evidence of this in the form of a letter from the project office if it is not evident from the protocol. Study section or FDA IND/IDE review is not adequate.

✘ The protocol was developed by an industry sponsor (e.g., pharmaceutical, device or diagnostics trials) and involves multiple research sites.

IRB Number: 17-2655 | Initial | Principal Investigator: Erik Wikstrom

This research project does not require review by the UNC SRC. Please complete the remainder of the application.

Part A. Questions Common to All Studies

A.1. Background and Rationale

A.1.1. Provide a summary of the background and rationale for this study (i.e., why is the study needed?). If a complete background and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive background and literature review, including references.

Lateral ankle sprains are a highly prevalent[1-6] and costly[6, 7] musculoskeletal condition. Erroneously considered a benign injury, more than 40% of lateral ankle sprains result in chronic ankle instability (CAI);[8] a condition characterized by life-long residual symptoms,[9-19] reduced physical activity,[20-22] and recurrent injury.[23, 24] Neuromuscular impairments in the periphery,[15-17, 25] at the spinal level,[26-30] and supraspinally,[11, 31-36] perpetuate a continuum of disability in CAI patients[37] that is linked to post-traumatic ankle osteoarthritis.[38-41] Conventional rehabilitation strategies largely ignore the full spectrum of neuromuscular impairments associated with CAI[37] and thus fail to break the continuum of disability. Targeting sensory neural pathways, via manual therapies, represents a novel and potentially transformative rehabilitation strategy for CAI. Our work shows that ankle joint mobilization and plantar massage treatments have significant albeit unique influences on biomechanical measures in CAI patients.[42] We hypothesize that the underlying mechanism of these manual therapies is the restoration of appropriate sensory organization strategies, a supraspinal impairment in CAI patients[33] that is not improved following traditional interventions.[43] Further, we hypothesize that altering sensory organization strategies is the result of interacting peripheral, spinal, and supraspinal mechanistic pathways. Elucidating neuromuscular mechanisms is vital to developing intervention strategies that break the continuum of disability in CAI patients. The objective of this R21 proposal is to elucidate the neuromuscular mechanisms underlying the significant positive effects observed following 2-weeks of independent ankle joint mobilization and plantar massage interventions in CAI patients.[42]

Included citations can be seen in the attached grant application.

A.1.2. State the research question(s) (i.e., specific study aims and/or hypotheses).

Aim 1: Determine changes in peripheral, spinal, and supraspinal neuromuscular mechanisms after 2-week manual therapy interventions (ankle joint mobilization, plantar massage) relative to a non-treatment control group in CAI patients. Neuromuscular mechanisms will be quantified before and immediately after a 2-week intervention. Mechanisms will include a comprehensive group of peripheral (ankle joint position sense, plantar light-touch discrimination thresholds), spinal (H-reflex of the soleus and fibularis longus), and supraspinal measures (cortical activity during stance using electroencephalography [EEG], corticomotor excitability and mapping of the soleus and fibularis longus via transcranial magnetic stimulation [TMS], and sensory organization strategies during stance). Our primary mechanism of interest is sensory organization strategies. Sixty CAI patients will be randomized into three equal groups (ankle joint mobilization, plantar massage, control) to complete 6 treatment sessions over 2-weeks.

Hypothesis 1. Both interventions, relative to the control group, will result in significant sensory organization strategy changes, representing a reduction in the CAI patient's reliance on visual information during stance.

Hypothesis 2. Each intervention will result in unique combinations of peripheral, spinal, and supraspinal mechanistic pathways relative to the control group.

Aim 2: Determine the associations among peripheral, spinal, and supraspinal neuromuscular mechanisms, secondary biomechanical measures, and sensory organization strategies in CAI patients. These associations will be quantified to elucidate the unique combination of peripheral, spinal, and supraspinal mechanistic pathways thought to contribute to a reducing in the reliance of visual information during stance. Secondary measures which will include jump landing and gait biomechanics will be assessed before and immediately after the 2-week interventions. We will use an analytical approach (see statistical analysis) to determine simple associations at baseline, post-test, and among change scores in neuromuscular mechanisms and secondary measures.

Hypothesis 1. Each intervention will result in unique combinations of changes in peripheral, spinal, and supraspinal mechanistic pathways will be strongly associated with changes sensory organization strategies.

Hypothesis 2. Each intervention will result in secondary measure changes associating with changes in sensory organization strategies as well as peripheral, spinal, and supraspinal mechanistic pathways.

A.2. Subjects

A.2.1. Total number of subjects proposed across all sites by all investigators (provide exact number; if unlimited, enter 9999):

60

A.2.2. Total number of subjects to be studied by the UNC-CH investigator(s) (provide exact number; if unlimited, enter 9999):

60

A.2.3. If the above numbers include multiple groups, cohorts, or ranges or are dependent on unknown factors, or need any explanation, describe here:

No Answer Provided

A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations:
Do not check if inclusion of a group is purely coincidental and has no bearing on the research. For example, you should check "Pregnant women" if you specifically intend to recruit women who are pregnant. Do not check if you are conducting a survey of the general public, not aimed at pregnant women. See SOP 1201: Vulnerable subjects in research.

✗ Children (under the age of majority for their location)

Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

✗ Pregnant women

✗ Nonviable neonates or neonates of uncertain viability

✗ Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

✗ UNC-CH Student athletes, athletic teams, or coaches

A.2.5. Based on your recruitment plan and target sample population, are you likely to include any of the following as subjects? Select all that apply.
Based on your responses, the consent form builder will insert the required text into your consent form template.

✗ Decisionally impaired individuals

(e.g., Mini mental state examination (MMSE), Montreal cognitive assessment (MOCA))

✗ Children who are wards of the State (Foster children)

✗ Non-English-speaking individuals

✓ UNC-CH Students

Some research involving students may be eligible for waiver of parental permission (e.g., using departmental participant pools). See SOP 32.9.1

✓ UNC-CH Employees

✗ People, including children, who are likely to be involved in abusive relationships, either as perpetrator or victim. This would include studies that might uncover or expose child, elder or domestic abuse/neglect. (See SOP Appendix H)

A.2.6. If any of the above populations are checked (excluding 'Decisionally impaired individuals' and 'Children who are wards of the State (Foster children)'), please describe your plans to provide additional protections for these subjects.

In all recruitment materials and in the informed consent document, we will include the following language:

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

A.2.7. Age range of subjects:

Minimum age of subject enrolled	18
	years
Maximum age of subject enrolled	45
» If no maximum age limit, indicate 99	
	years

A.3. Inclusion/exclusion criteria

A.3.1. List required characteristics of potential subjects (i.e., inclusion and exclusion criteria). If not covered, list also characteristics that would preclude their involvement.

CAI will be defined as those individuals who: (1) have sustained at least two lateral ankle sprains; (2) have experienced at least one episode of giving way within the past 6-months; (3) answer 4 or more questions of "yes" on the AII; (5) have self-assessed disability scores of ≤90% on the FAAM; and (6) have self-assessed disability scores ≤80% on the FAAM-S. These criteria are in agreement with the guidelines established by the International Ankle Consortium's recent position statement.

Exclusion criteria for CAI will include known vestibular and vision problems, acute lower extremities and head injuries (<6 weeks), chronic musculoskeletal conditions known to affect balance (e.g., ACL deficiency) and a history of ankle surgeries to fix internal derangements. Participants will also be excluded if they have any of the following which are contraindications to TMS testing: metal anywhere in the head (except in the mouth), pacemakers, implantable medical pumps, ventriculo-peritoneal shunts, intracardiac lines, history of seizures, stroke, and serious head trauma. Given the young age (18-35) of the proposed participants, we do not anticipate encountering these conditions but will screen for them non-the-less. The most likely conditions that will be encountered are a history of serizures and hostory of serious head trauma.

A.3.2. Justify any exclusion based on race, gender or ethnicity

NA

A.3.3. Will pregnant women or women who become pregnant be excluded?

Yes

If yes, provide justification and describe the type and timing of pregnancy testing to be used:

We will exclude subjects that are known to be pregnant but will not perform pregnancy testing. Pregnancy will be excluded by self reporting from the subject. Pregnant women will be excluded due to the fact that later stages pregnancy impairs postural control. If a woman becomes pregnant while enrolled, she will not be excluded.

A.4. Study design, methods and procedures

Your response to the next question will help determine what further questions you will be asked in the following sections.

A.4.1. Will you be using any **methods or procedures commonly used in biomedical or clinical research** (this would include but not be limited to drawing blood, performing lab tests or biological monitoring, conducting physical exams, administering drugs, or conducting a clinical trial)?

Yes

A.4.2. Describe the study design. List and describe study procedures, including a sequential description of what subjects will be asked to do, when relevant.

We plan to use a single-blind randomized study design to quantify changes in the hypothesized neuromuscular mechanisms following ankle joint mobilization and plantar massage.

Methodology Designed to Achieve the Specific Aims: The following neuromuscular mechanisms and secondary measures will be completed at baseline, immediately (within 48-hours) after the intervention and 4-weeks after the intervention.

Peripheral Neuromuscular Mechanisms:

Ankle joint position sense will be used to assess changes in a participant's ability to detect the position of the foot/ankle complex relative to the body. The theoretical premise of this mechanism is that CAI participants have an impaired ability to detect ankle joint position due to altered input from damaged mechanoreceptors. [25, 96, 97] Postural control improvements following manual therapies[42, 98, 99] may be the result of improved input from mechanoreceptors. Ankle joint position sense will be assessed at the mid-range of plantar flexion and inversion as these positions have the greatest sensitivity to CAI associated impairments. Participants will be seated with their foot in neutral (0? of plantar flexion) before an active repositioning technique is used to quantify the absolute and constant error for each movement.

Plantar light-touch thresholds will assess changes in somatosensation on the plantar foot. These thresholds are increased in CAI patients [16, 17] and thought to be the result of repetitive trauma to the mechanoreceptors. The effects of manual therapies[42, 98, 99] may be the result of improved plantar mechanoreceptor sensitivity in CAI patients. To assess this neuromuscular mechanism, we will use a protocol [17, 80, 85] that requires participants to lie prone while thresholds are assessed at the head of the 1st and base of the 5th metatarsal (Right: A). Thresholds will be determined using Semmes-Weinstein monofilaments (Right: B) and a highly reliable 4-2-1 stepping algorithm.[100]

Spinal Level Neuromuscular Mechanisms:

The Hoffman reflex (H-Reflex) is the electrical analog of the monosynaptic stretch reflex[27, 101] and thought to provide insights into the neuromuscular mechanism mediating postural control.[102, 103] H-Reflex modulation is reduced in CAI patients[27] and correlated to self-reported functional limitations.[104] Thus, improvements in spinal reflexive excitability (increased H-Reflex values) may represent an underlying neuromuscular mechanism responsible for improved postural control following ankle joint mobilization and plantar massage. We will assess spinal reflexive excitability in the soleus and fibularis longus using our established methodology.[33, 77, 88, 89] While lying supine, a stimulating electrode will be positioned over the sciatic nerve in the popliteal space. Peak-to-peak Hoffmann reflexes (H-reflex) will be measured and the stimulus intensity increased until a maximal H-reflex is observed. Three H-reflexes for each muscle will be recorded and normalized to the maximal M-response, representing the ratio of the motor neuron pool reflexively activated to the amount of the motor neuron pool available (H:M ratio). Higher H-reflex values and H:M ratios indicate greater excitability.

Supraspinal Level Mechanisms:

The corticospinal motor system plays a critical role in controlling movement by optimizing muscle activation.[105] Abnormal facilitation or inhibition from the corticospinal pathway is associated with impairments of the ankle joint musculature and hypothesized to contribute to the postural instability associated with CAI.[32, 64] As such, cortical excitability may represent a plausible neuromuscular mechanism underlying improvements following ankle joint mobilization and plantar massage. Corticomotor measures of the soleus and fibularis longus will be assessed using Transcranial Magnetic Stimulation (TMS) methodology previously used by the research team.[32, 34, 36, 64, 77, 88, 89] A Magstim 200 (Magstim Company, Wales, UK) will be used to produce a magnetic stimulus (max 2.0 Tesla) over the motor cortex contralateral to the test limb. Testing will be performed over the area generating the greatest motor evoked potential (MEP) while participants perform mild isometric contractions (20%) on an isokinetic dynamometer. Active motor threshold (AMT) will be determined as the lowest stimulator intensity required to elicit an MEP peak-to-peak amplitude ≥100μV in at least 4 of 8 trials. A higher AMT indicates decreased excitability, as a greater stimulus intensity is required to elicit an MEP. Eight stimuli will be delivered at 120%, 130%, and 140% of AMT, and peak-to-peak MEP amplitudes will be recorded for each trial. The cortical silent period (CSP) will be measured as the distance from the end of the MEP to a return of the mean EMG signal plus two times the standard deviation of the baseline (pre-stimulus) EMG signal.[106] A longer CSP indicates a greater corticospinal inhibition.

Corticomotor output mapping provides further insight into the function of the motor cortex by identifying the size of an area within the

motor cortex associated with a select muscle.[36, 107-109] Improved postural control following manual therapies may be the result of a reorganization of the corticomotor output in CAI patients[36, 109] (i.e. an increased map area and/or volume of a given muscle). Corticomotor mapping of the soleus and fibularis longus muscle will be assessed using TMS methods consistent the literature[36] and our own protocols.[93] After AMT is quantified, a 6x6 cm grid (3cm lateral-medial and 3cm anterior-posterior) will outline the hotspot for each muscle and a stimulator intensity of 100% AMT will be used. Three consecutive stimuli will be delivered at each grid location in a random order in order to produce reliable and reproducible maps.[107] Average peak-to-peak MEP amplitudes for each grid site will be normalized to M-max. Cortical representation of the soleus and fibularis longus will be calculated using map area and map volume.[36] Map area is the number of stimulus positions whose stimulation evoked an average MEP ≥MEP threshold and an increase would suggest an expansion of the cortical representation of a selected muscle. Map volume will be calculated as the sum of the mean normalized MEPs recorded with an increase suggesting greater cortical excitability.

Alterations in cortical activation could represent an underlying cause of postural control improvements following manual therapies as postural control improves following the application of manual therapies and balance is controlled, at least in part, cortically.[110] To assess changes in cortical activity, participants will complete single limb balance assessments with eyes open and closed while cortical activation is simultaneously assessed using electroencephalography (EEG).[110, 111] A V-Amp 16 active channel EEG system (BrainVision LLC, Morrisville, NC) will be used to acquire the EEG data from three channels (Fz, Cz and POz) based on a 10-20 system. The impedance of each electrode will be kept below 40 kW. Bandpass filters of 0.1 Hz and 65 Hz at 3 dB attenuation will be used to remove environmental artifacts. Post-processing will include identifying and decontaminating artifacts as previously described.[112, 113] The primary mechanisms of interest are the power spectral densities (PSD) of the alpha (8-12 Hz), beta (13-19Hz), and sigma (30-40Hz) bandwidths which will be computed for each condition to create a relative PSD.[110] Changes in the relative PSD will be compared among the interventions and control group.

Sensory Organization Strategies [Primary Mechanism of Interest] represents a plausible neuromuscular mechanism as evidence indicates that in lieu of reliable somatosensory information, CAI patients increase reliance on visual information.[33, 114, 115] Further, an increased reliance on visual information is hypothesized to explain the repeated ankle sprains and episodes of giving way associated with CAI.[116] Changes in sensory organization strategies may represent the underlying neuromuscular mechanism of ankle joint mobilizations and plantar massage and these manual therapies improve postural control and reduce giving way episodes in CAI patients.[42] Changes in our primary mechanism of interest will be calculated using the % Modulation measure used previously by our group.[33] This measure estimates the weight given to visual information during eyes open stance based on the magnitude of postural instability that occurs when vision is removed.[33] Raw ground reaction force data will be collected at 200Hz using an Accusway Plus Balance force platform (AMTI, Watertown, MA). Raw data will be filtered appropriately before the % Modulation for center of pressure velocity is calculated from eyes open and eyes closed stance data.[12, 117] Additional postural control measures such as time-to-Boundary (TTB) will also be calculated.[12, 117-120]

Secondary Measures

Both walking gait[121-128] and jump landing[129-133] biomechanics will be assessed. Three-dimensional kinematics (sampled at 100Hz) and kinetics (sampled at 1000Hz) will be obtained during both tasks using a 10-camera Vicon motion capture system. During gait trials, participants will walk at a self-selected speed over multiple embedded force plates. Speed will be enforced with timing gates centered over the force plates during the five test trials. Jump landing biomechanics will be assessed with a drop vertical jump protocol that requires participants to jump from a 30cm platform placed at a distance of 50% of the participants' height away from the edge of the force platform, with an immediate rebound jump for maximum height. Five test trials will be completed. Both discrete variables and profile plots of the kinematic and kinetic data will be calculated for the ankle, knee, and hip in the sagittal, frontal, and transverse planes. All secondary measure methodology is consistent with those previously used by our research team.

*Measures of balance and dorsiflexion range of motion will also be quantified.

Balance Error Scoring System (BESS) Postural Control Assessment:

The BESS tests balance during multiple stances: double-leg, single-leg, and tandem stance and on 2 surface conditions: firm and foam. For this study, we will only test participants during the sing-leg stance on a firm surface. To complete this task, participants must balance for 20 seconds with eyes closed and hands on their hips. Participants will be instructed to stand quietly and to make any necessary adjustments and return to the initial testing position within 5 seconds if balance is lost. Participants will be scored based upon the errors recorded during each of the 3 trials collected. Errors will include: lifting the hands off the iliac crest; opening the eyes; stepping, stumbling, or falling; moving the non-stance hip into more than 30° of abduction; lifting the forefoot or heel; and remaining out of the test position for more than 5 seconds.

Weight Bearing Lunge Measure:

This method of measuring dorsiflexion range of motion is completed barefoot by placing the participant's great toe in line with their heel on top of a tape measure on the floor. While keeping the heel firmly on the ground, participants are asked to bend their supporting knee to touch the wall in front of them. This is completed through a slow and controlled lunging action. Using the tape measure on the floor, the maximum distance each participant can place their foot away from the wall while keeping both the heel flat on the floor and knee touching the wall will be recorded. This test will be repeated 6 times during each testing session.*

Intervention Delivery: After completion of baseline testing, participants will be randomized into 3 groups to receive interventions identical to our previous work.[42, 71] All interventions are to a single limb and require 6, 5-minute treatment sessions over 2-weeks. The first group (n=20) will receive 2, 2-minute bouts of Grade III anterior-to-posterior talocrural joint mobilization with 1-minute between sets during each session. Mobilizations will be large-amplitude, 1-s rhythmic oscillations from the mid- to end range of arthrokinematic motion. The second group (n=20) will receive 2, 2-minute plantar massage bouts with 1-minute between sets during each session. The massage will be a combination of petrissage and effleurage to the entire plantar surface. The third group (n=20), a control condition, will receive no treatment during the entire 2-week intervention period. All groups will be instructed to continue regular physical activity habits and daily routines over the course of 2-week intervention.

A.4.3. If subjects are assigned or randomized to study "arms" or groups, describe how they are assigned.

- *Describe the methods of computing the randomization schedule (if any) and maintaining blinding (if any).*
- *Who will perform these computations?*
- *How will you verify each subject's eligibility prior to randomization?*

Participants will be randomized and allocated in a 1:1:1 ratio within blocks (n=6) using sealed envelopes generated by the study biostatistician.

Eligibility will be determined by questionnaire, consistent with best practices research within the field of chronic ankle instability.

A.4.4. Describe any follow up procedures.

A 4-week follow up after the intervention will be conducted. This assessment is identical to those conducted immediately before and after the intervention and is described above in A.4.2.

A.4.5. Once this study has been approved by the IRB, for how many months or years will this study be active (you are collecting data or have access to identifiers)?

36-months.

A.4.6. Will this study use any of the following methods?

✗	Audio Recording
✗	Video Recording
✗	Behavioral observation - (e.g., Participant, naturalistic, experimental, and other observational methods typically used in social science research)
✗	Pencil and paper questionnaires or surveys
✓	Electronic questionnaires or surveys
✗	Telephone questionnaires or surveys
✗	Interview questionnaires or surveys
✗	Other questionnaires or surveys
✗	Focus groups
✗	Diaries or journals
✗	Photovoice
✗	Still photography

A.4.7. If there are procedures or methods that require specialized training, describe who (role/qualifications) will be involved and how they will be trained.

Conducting H-Reflex, EEG, and TMS procedures require training but not specialized training. Members of the research team (Pietrosimone & Blackburn) has extensive experience with H-Reflex and TMS testing while Franz and Wikstrom have experience with EEG procedures. All research assistants will be trained in this procedures prior to enrollment of participants.

A.4.8. Are there cultural issues, concerns or implications for the methods to be used with this study population?

No

A.4.A. Biomedical methods and procedures

A.4.A.1. Is this an interventional study?

Yes

Distinguish what is being done specifically for this research from procedures that would be done anyway for clinical care:

Participants in this investigation are not actively seeking healthcare for their ankle instability. Therefore everything done in this study is for research.

The included therapies are commonly deployed in clinical practice to care for both acute lateral ankle sprains as well as chronic ankle instability.

A.4.A.2. Is this a Clinical Study?
Check YES if this study involves research using human volunteers that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials and observational studies. Do NOT check yes merely because you are conducting research in a clinical setting or using clinical data.
Click here for additional definition of "Clinical Study"

Yes

Will this clinical trial be listed in ClinicalTrials.gov, either by you or the sponsor?

Yes

Choose the appropriate Phase designation for this clinical trial.

✗	Pilot Study

IRB Number: 17-2655 Initial Principal Investigator: Erik Wikstrom

- ✗ Phase I
- ✗ Phase I/II
- ✓ Phase II
- ✗ Phase III
- ✗ Phase IV
- ✗ Other

A.4.A.3. If the study involves the use of placebo control, provide justification

A control group is being used to establish stability of the outcome measures and allow us to better quantify the changes due to the active therapies.

A.4.A.4. Will this study involve drugs, biologics or other substances (such as a botanical or dietary supplement)?
For guidance on dietary supplements, see Section VI, C FDA guidance document UCM229175.pdf

No

A.4.A.5. Is there an Investigational New Drug application (IND) for this study?

No

Please check below:

- ✓ This study does not involve drugs, biologics or other substances.
- ✗ I am using a U.S. commercially available agent, consistent with labeling.
- ✗ I am studying a botanical substance or dietary supplement intended to affect the structure and/or function of the body; it is **not** intended to cure, treat, mitigate, prevent or diagnose disease, including its associated symptoms.

A.4.A.6. When the intent of a clinical investigation is to collect information about the safety or effectiveness of a device, the need for an Investigational Device Exemption (IDE) must be evaluated. Please review the Investigational Device Guidance document prior to completing this section. Your response to the following questions will determine if an IDE is needed.

A. Select the response that best describes your investigation:

5. None of the above.

A.4.A.7. Does your study involve any of the following? (check all that apply)

- ✗ Embryonic stem cells
- ✗ Fetal tissue
- ✗ Genetic testing (see GINA and GWAS)
- ✗ Clinical laboratory tests

If McLendon Labs will do the testing, you must complete the appropriate form found at UNC Health Care and submit to them for review.

- ✗ Testing for communicable diseases that have mandated reporting requirements (link to state guidance)
- ✗ Point of Care Testing (POCT), which is CLIA-approved testing done at the "bedside" or site of care by hospital or clinic personnel (not by subject). Examples include urine pregnancy testing, glucose monitoring, etc.

If McLendon Labs will do the testing, you must complete the POCT form found at UNC Health Care and submit to them for review.

- ✗ If your study utilizes **radiopharmaceuticals** to address basic science questions, an IND is not necessary.
Instead, your study will be reviewed/approved by the Radioactive Drug Research Committee (RDRC); approval by the Radiation Safety Subcommittee (RSS) is not required.
If you have questions about the RDRC approval process, please contact Dede Corvinus.
- ✗ Diagnostic or therapeutic ionizing radiation, or radioactive isotopes (not covered under 21 CFR 361.1), which subjects would not receive otherwise if not participating in this research study. Do not check if all radiation is administered as standard of care. Do check if your study includes views/scans that represent no greater than minimal risk as determined by the Radiation Safety Sub-committee.
Application for Human Use of Radiation in Research.
- ✗ Gadolinium administered as a contrast agent
- ✗ Recombinant DNA or gene transfer to human subjects
- ✗ Any research activities conducted in the UNCHC Perioperative areas. This includes Pre-care, Pre-op, Operating room and PACU.
You must complete the Checklist for Perioperative Services and return it to Susan.Phillips2@unchealth.unc.edu and to richard_feins@med.unc.edu.

A.4.A.8. Will your study involve storage of specimens for future unspecified research?

No

A.5. Benefits to subjects and/or society

A.5.1. Describe how this study will contribute to generalizable knowledge that will benefit society.

This investigation is significant because it will elucidate the neuromuscular mechanisms responsible for the significant benefits seen in CAI patients following prevalent but understudied manual therapies. The results will then allow us to better leverage the underlying mechanisms of these manual therapies in clinical practice to improve patient outcomes.

A.5.2. Does this study have the potential for direct benefit to individual subjects in this study?

Yes

Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form, if there is a consent form. Do not cite monetary payment or other compensation as a benefit.

Explain

Previous research has demonstrated that these commonly used manual therapies can improve ankle dorsiflexion range of motion, postural control, and self-reported function. Further, these benefits are retained for at least 1-month following the interventions. It is unknown if these benefits are permanent or not.

A.5.3. Are there plans to communicate the results of the research back to the subjects?

No

A.6. Risks and measures to minimize risks

For each of the following categories of risk you will be asked to describe any items checked and what will be done to minimize the risks.

A.6.1. Psychological

- ✗ Emotional distress
- ✗ Embarrassment
- ✓ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.2. Describe any potential psychological risks checked above and what will be done to minimize these risks

Though there is a risk of breach of confidentiality, we have taken steps to minimize this risk. Each subject and his/her associated information will be identified by a subject identification number. Code lists linking the subject's identification number and his/her name and email address will be viewed by the research team only, and will be secured in the Sports Medicine Research Laboratory (Fetzer Hall) on a password-protected computer. Email addresses will be obtained for the purpose of contacting subjects to schedule testing and to contact participants for future research investigations, if allowed by the participant. Hard copies of data will be kept in a locked filing cabinet in the principal investigator's personal office (Woollen Gymnasium). Electronic data, and transferred hard copy data will be stored on both the data collection computer and the principal investigator's personal computer, as well as backup storage devices. Computer access will be protected via confidential passwords, and backup devices will be stored in the Sports Medicine Research Laboratory, which is secured via keycard entry. Code lists identifying subjects will be destroyed following completion of the study.

A.6.3. Social

- ✗ Loss of reputation or standing within the community
- ✗ Harms to a larger group or community beyond the subjects of the study (e.g., stigmatization)
- ✓ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.4. Describe any potential social risks checked above and what will be done to minimize these risks

See response to A.6.2.

A.6.5. Economic

- ✗ Loss of income
- ✗ Loss of employment or insurability
- ✗ Loss of professional standing or reputation
- ✗ Loss of standing within the community

- ✗ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.6. Describe any potential economic risks checked above and what will be done to minimize these risks.

No Answer Provided

A.6.7. Legal

- ✗ Disclosure of illegal activity
- ✗ Disclosure of negligence
- ✗ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.8. Describe any potential legal risks checked above and what will be done to minimize these risks

No Answer Provided

A.6.9. Physical

- ✗ Medication side effects
- ✓ Pain
- ✓ Discomfort
- ✓ Injury
- ✗ To a nursing child or a fetus (either through mother or father)

A.6.10. Describe any potential physical risks checked above, including the category of likelihood and severity, and what will be done to minimize these risks. Where possible, describe the likelihood of the risks occurring, using the following terms:

- Very Common (approximate incidence > 50%)
- Common (approximate incidence > 25 - 50%)
- Likely (approximate incidence of > 10 - 25%)
- Infrequent (approximate incidence of > 1 - 10%)
- Rare (approximate incidence < 1%)

Describe severity of risks using the following grading scale:

- Mild- No disruption to the subject's ability to perform daily activities; may include non-prescription intervention only
- Moderate- Temporary interference with daily activities; may include prescription intervention
- Severe- Interference with daily activities; medically significant but not life threatening
- Life threatening

Examples:

Rare (Rare (

If you are using these terms differently than described above, please provide your study-specific definitions.

Phase 1 trials: Due to limited experience, incidence may be better described as the number of events that have occurred in the total number of animals/humans studied.

Rare (<1%) of pain / mild discomfort during and/or following a treatment session. Any such discomfort dissipates quickly and does not impact the participant more than 5-10 minutes. Both treatments, which are commonly employed in clinical practice, are designed to be pain free at all times. If pain presents, treatment will be immediately stopped.

Rare (<1%) of mild skin irritation due to taping the kinematic markers sensors to the skin. This risk will be minimized by a member of the research team removing the tape with care.

Rare (<1%) of seizure. Overall estimate is that seizure risk is < 1:1000 (0.1%) and this risk is associated with Repetitive TMS, which will not be conducted in this investigation.

Infrequent (5%) of head and neck aches, hearing shifts, and fainting during and/or immediately after TMS. The research team will disclose this information to the participant prior to enrollment and remind them prior to testing. This is attributed to local stimulation of muscles and nerves near the stimulating coil, a tapping of the scalp by the coil during discharge, and wearing a tight-fitting swim cap. Other stimulation-related effects include teeth aches,facial twitches, odd taste in mouth, and discomfort from blinking and twitches of scalp muscles. All symptoms resolve after cessation of the TMS protocol. n subjects with history of fainting. TMS may induce fainting or feelings of lightheadedness or dizziness.If symptoms of dizziness, lightheadedness, or feeling faint occur, the TMS protocol should be stopped. The subject will be allowed to lay down or put their head down to prevent fainting. If subjects faint, they mustnot be allowed to leave the laboratory until fully recovered. TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loudclick can result in temporary ringing in the ear and subclinical auditory threshold shifts. To prevent transient hearing threshold shifts due to TMS, subjects and investigators will be wear earplugs during TMS.

Infrequent (10%) of itching/scratching of the scalp during EEG testing. Care will be taken during the application of the EEG cap, electrodes to measure brain wave activity, and the insertion of the gel.

Any safety concerns would likely be recognized immediately during testing, but subjects will be instructed via the informed consent document that they should inform UNC Student Health Services or their personal physician in the event that they experience lingering issues after leaving the laboratory. All members of the research team are trained in emergency care (i.e. CPR/First Aid). These

individuals will monitor subjects for adverse events during testing, and will refer any individuals who experience adverse events to Student Health Services, or Emergency Medical Services depending on the nature and severity of the adverse event.

A.6.11. Unless already addressed above, describe procedures for referring subjects who are found, during the course of this study, to be in need of medical follow-up or psychological counseling

See above.

A.6.12. Are there plans to withdraw or follow subjects (or partners of subjects) who become pregnant while enrolled in this study?

No

A.7. Data and safety monitoring

A.7.1. When appropriate, describe the plan for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based data and safety monitoring board or committee (DSMB, DSMC, DMC), depending on the study. For studies that do not raise obvious safety concerns, you may still describe your plans for monitoring the study as it progresses.

Adverse events would occur "in real time" as subjects perform the assessments and undergo the intervention. As such, these adverse events would be readily observed by the research team. As such, our safety monitoring plan exclusively involves observation of the subjects as they perform the assessments. In the unlikely event that a subject experiences an adverse event during the investigation, these events will be documented by the research team on the subject's de-identified data collection sheet as per the DSMP submitted to the sponsor and outlined below.

Monitoring the progress of trials and the safety of participants:

The investigators are attempting to identify the mechanisms of ankle joint mobilizations and plantar massage in those with chronic ankle instability. The investigators are relying on the participants to truthfully report any concerns, problems, or increases in pain or disability so that the tests and interventions may be appropriately altered or discontinued. Participants will be encouraged to contact the PI if they experience any additional problems or have any questions. As part of the study procedures, the entire research team will meet at least quarterly to help improve compliance with participant recruitment and research procedures as well as to determine if any participants are experiencing harm/injury. To help ensure that no harm/injury is occurring to the participants, Dr. Wikstrom (PI) will work with the North Carolina Translational and Clinical Sciences Institute (NC TraCS) to identify an independent Data and Safety Officer. The PI, will directly monitor participant's reports of injury or harm and complete progress reports per completed block of randomization. Cumulative data will be presented to the Data and Safety Officer as needed and at a minimum of every six months. No investigators have a biased interest in the success of any particular test or intervention.

Assuring compliance with the requirements regarding the reporting of unanticipated problems or adverse experiences:

Any life-threatening adverse events that occur will be reported to the IRB within 24-hours of the occurrence. Any non-life-threatening adverse events will be reported to the IRB within 72-hours. The Data Safety Officer will also be notified as described above so that trends in injury and/or harm can be identified quickly. The investigators have no other entities to which they will need to report any adverse events.

Assuring that any action resulting in a temporary or permanent suspension of the study is reported to the appropriate entities (i.e., funding agency):

The NIH will be notified within seven days of any changes in the study or suspension of the study by the Institutional Review Board of UNC Chapel Hill.

Assuring data accuracy and protocol compliance:

The PI will be responsible for ensuring the accuracy of data and protocol compliance. Any deviations from the proposed protocol will be immediately reported to the IRB and the need to retraining the research team, and/or specific members of the team will be determined.

Assuring communication among multi-center sites adequately protects the participant (if this is a multi-center study in which the lead PI or UNC is the coordinating institution):

NA

A.7.2. If not already addressed above, describe the plans for aggregate review of unanticipated problems (including but not limited to adverse events) across all sites, in order to monitor subject safety.

See above. A safety officer has not yet been identified as we wanted to wait until the sponsor approves the proposed plan.

A.7.3. What are the criteria that will be used to withdraw an INDIVIDUAL SUBJECT from this study or halt the research intervention (e.g., abnormal lab tests, allergic reactions, failure or inability to comply with study procedures, etc.)?

Individuals will be withdrawn from the study if they experience any of the following:
1) signs of seizure or greater than expected discomfort while completing assessments or intervention
2) failure or inability to comply with the study procedures

A.7.4. Are there criteria that will be used to stop the ENTIRE STUDY prematurely (e.g., safety, efficacy, unexpected adverse events, inability to recruit sufficient number of subjects, etc.)?

Yes

Please explain

Recommendation from the data safety officer.

IRB Number: 17-2655 Initial Principal Investigator: Erik Wikstrom

A.7.b. Will this study involve a data and safety monitoring board or committee?

No

A.8. Data analysis

A.8.1. Summarize the statistical analysis strategy for each specific aim.

To achieve Aim 1 and quantify changes caused by the ankle joint mobilization and plantar massage interventions, neuromuscular mechanisms will be submitted to separate 2-way repeated measures (Group × Time) ANOVAs. MANOVAs may be used based on inter-item correlation coefficients found during the preliminary analysis of the data. Pairwise comparisons, when appropriate, will determine the location of significant interactions. An alpha level of 0.05 will be used to assess changes in the primary mechanism of interest (% modulation). An exploratory alpha level (0.10) will be used on all other peripheral, spinal, and supraspinal mechanisms and secondary measures to reduce the chance that possible changes would be overlooked in this initial R21 investigation. Hedge's G effect sizes and confidence intervals based on the pre-to-post change scores[42] will also be calculated and interpreted as follows: less than 0 as small, 0.31–0.7 as moderate, and greater than 0.71 as large. Finally, control group data will be used to calculate the minimal detectable change (MDC) scores for all mechanisms and secondary measures[42, 98, 134]. The MDC allows us to evaluate the interventions effects relative to the stability of the measures over time. This 3-pronged approach affords us multiple criteria on which to base the interpretation of our results and power future clinical trials.

To achieve Aim 2 and determine the associations among sensory organization strategies, neuromuscular mechanisms, and secondary measures following ankle joint mobilization and plantar massage interventions, we will calculate associations at baseline, at the post-test, and among change scores. These associations will be calculated using Pearson Correlation Coefficients that will be interpreted as: ≤0.29 as negligible, 0.30-0.49 as low, 0.50-0.69 as moderate, 0.70-0.89 as high, and ≥0.9 as a very high correlation.[135] The models will then be adjusted for identified covariates using a general linear model and an exploratory alpha level of 0.10. We anticipate associations that will provide insights about how to specifically leverage the manual therapies mechanisms to target specific neuromuscular impairments and biomechanical deficits associated with CAI.

A.8.2. If this is a pilot study, please describe the future study and say how its study design, aims, sample size, and methods differ from the pilot study you are proposing.

NA

A.8.3. Provide a compelling justification for the proposed sample size in terms of the likelihood of achieving each aim.

Changes in sensory organization strategies has been chosen as the primary mechanism of interest and will be assessed by calculating the % Modulation of the resultant center of pressure velocity between eyes open and eyes closed stance.[33]

To achieve Aim 1, 18 participants per group are needed to ensure significant changes in the primary mechanism of interest following both interventions relative to the control group. Between group (i.e. massage vs. control [d=0.53] & mobilization vs. control [d=0.69]) pre to post effect sizes from our preliminary data (See Preliminary Studies) were used to calculated the needed sample size. Using GPower (3.1), a repeated measures, between factors ANOVA model for three groups and two time points was used. Parameters included a purposefully conservative intra-measure correlation=0.90, α=0.05, and 1-β=0.90. To achieve Aim 2, 16 participants per group are needed to identify significant correlations. This value was calculated based on previously established correlations between neuromuscular mechanisms and biomechanical measures of postural control.[16, 95] Parameters for this analysis included a correlation of r=0.5 (range from literature: 0.50 to 0.58), an α=0.05, and 1-β=0.90. Thus, we will recruit 20 participants per group and plan for a 10% dropout rate, which would leave 18 subjects per group. Our previous work[42] had a 98.75% (79/80) retention rate using the same intervention protocol and all participants completed 100% of the treatment sessions.

A.8.4. Summarize the plans for data management.

Data entry will be confirmed by at least two members of the research team.

The research team will use REDCap to maintain their database.

The PI will be responsible for database management.

A.9. Identifiers

A.9.1. Check which of the following identifiers you already have or will be receiving, or select "None of the above."

- ✔ Names (this would include names/signatures on consent forms)
- ✔ Telephone numbers
- ✘ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- ✘ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes (e.g. GPS coordinates), except for the initial three digits of a zip code
- ✘ Fax numbers
- ✔ Electronic mail addresses
- ✘ Social Security numbers
- ✘ Medical record numbers
- ✘ Health plan beneficiary numbers

- ✗ Account numbers
- ✗ Certificate/license numbers
- ✗ Vehicle identifiers and serial numbers (VIN), including license plate numbers
- ✗ Device identifiers and serial numbers (e.g., implanted medical device)
- ✗ Web universal resource locators (URLs)
- ✗ Internet protocol (IP) address numbers
- ✗ Biometric identifiers, including finger and voice prints
- ✗ Full face photographic images and any comparable images
- ✗ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher
- ✗ None of the above

A.9.2. For any identifiers checked, how will these identifiers be stored in relationship to the research data?

- ✗ with the research data (i.e., in the same data set and/or physical location)
- ✓ separate from the research data (i.e., coded with a linkage file stored in a different physical location)

Provide details about the option you selected above:
Identifying information will be used to contact participants for the purpose of scheduling treatments and data collection. This information will be maintained until data collection is collected. Participants will also be asked if the research team can keep their contact information in case they may be eligible for future investigations. None of the identifiers noted above will be linked to any participant's data for this investigation.

A.9.3. Are you collecting Social Security Numbers to be used as a unique identifier for study tracking purposes for national registry or database? (Do not check yes if collecting SSN *only* for payment purposes; this will be addressed later.)

No

A.10. Confidentiality of the data

A.10.1. Describe procedures for maintaining confidentiality of the data you will collect or will receive (e.g., coding, anonymous responses, use of pseudonyms, etc.).

Each subject and his/her associated information will be identified by a subject identification number. Code lists linking the subject's identification number and his/her name and email address will be viewed by the research team only, and will be secured in the Sports Medicine Research Laboratory (Fetzer Hall) on a password-protected computer. Email addresses will be obtained for the purpose of contacting subjects to schedule testing and to contact participants for future research investigations, if allowed by the participant. This list will be keep electronically on the PI's password protected computer in their personal office (Woollen Gymnasium). Hard copies of data will be kept in a locked filing cabinet in the principal investigator's personal office. Electronic data and transferred hard copy data will be stored on both the data collection computer and the principal investigator's personal computer, as well as backup storage devices. Computer access will be protected via confidential passwords, and backup devices will be stored in the Sports Medicine Research Laboratory, which is secured via keycard entry. Code lists identifying subjects will be destroyed following completion of the study.

A.10.2. Describe how data will be transmitted among research team (i.e., personnel listed on this application).

De-identified data will be transmitted to members of the research team via email, printed materials, and portable electronic storage devices. In all instances, these materials will consist of raw data and will be stripped of all identifiers.

A.10.3. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?

No

A.10.4. Do you plan to obtain a federal Certificate of Confidentiality for this study?

No

A.10.5. If this study is limited to data collection by survey or interview, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

NA

A.10.6. Will any of the groupings or subgroupings used in analysis be small enough to allow individuals to be identified?

No

A.11. Data sharing and transmission

A.11.1. Check all of the following who will receive identifiable data (contains any of the 18 identifiers listed above) outside the immediate research team (i.e., not listed as personnel on this application)? *

- ✔ No one
- ✘ Coordinating Center
- ✘ Statisticians
- ✘ Consultants
- ✘ Other researchers
- ✘ Registries
- ✘ Sponsor and/or its designee(s)
- ✘ External labs for additional testing
- ✘ Journals
- ✘ Publicly available dataset
- ✘ Other

A.11.2. For any recipients checked above, explain the confidentiality measures to be taken

NA

A.12. Post-study disposition of identifiable data or human biological materials

A.12.1. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. If you plan to destroy linkage codes or identifiers, describe how and when this will be done.

The code list identifying participant names with study data will be destroyed following completion of the study (i.e. completion of primary data analysis).

Part B. Direct Interaction

B.1. Methods of recruiting

B.1.1. Check all the following means/methods of subject recruitment to be used:*

- ✔ In person
- ✘ Participant pools
- ✔ Presentation to classes or other groups
- ✘ Letters
- ✔ Flyers
- ✘ Radio, TV recruitment ads
- ✘ Newspaper recruitment ads
- ✘ Website recruitment ads
- ✘ Telephone script
- ✔ Email or listserv announcements
- ✘ Follow up to initial contact (e.g., email, script, letter)
- ✘ Other

B.1.2. Describe how subjects will be identified

The sample for this investigation will consist of volunteers from the faculty, staff, and student populations at UNC-CH and the surrounding area. Potential participants will be recruited verbally from various classes, particularly – but not exclusively – in the Department of Exercise & Sport Science, following approval by individual course instructors. Potential participants will be read a standard recruitment script detailing the inclusion criteria, procedures, duration, benefits, and potential risks associated with participation, and will be allowed to ask any questions pertaining to the investigation. Interested individuals will be scheduled to determine eligibility. Flyers posted on and off campus will also be used.

B.1.3. Describe how and where subjects will be recruited and address the likelihood that you will have access to the projected number of subjects identified in A.2.

Recruitment will occur on the UNC-CH campus (verbal and flyer) as well as various locations off campus (TBD) via flyers. The proposed project is scheduled to occur of 24-months (primary data collection) and we regularly recruit and enroll CAI participants at a rate of 30-40 per semester in other investigations using identical recruitment techniques.

B.1.4. Describe how you will protect the privacy of potential subjects during recruitment

As there are no risks associated with the recruitment process, no additional measures will be taken to protect potential subjects' privacy.

B.1.5. Describe how subjects will be contacted, if not addressed above

See above.

B.1.6. Describe who (by role) will do the recruiting

Recruiting will be performed only by those listed as study personnel on the protocol.

B.1.7. Describe efforts to ensure equal access to participation among women and minorities

Each of the recruiting methods listed above permits probabilities of recruitment of women and minorities which are consistent with the distributions of these groups within the population.

B.2. Protected Health Information (PHI)

Protected Health Information (PHI) is any identifiable information about the subject's health that relates to their participation in this research and is obtained from sources other than the subject, such as medical records, health care providers, insurance plans, etc. more

B.2.1. Are you requesting a limited waiver of HIPAA authorization?
If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a limited waiver of HIPAA authorization (see SOP 29.3). This does not apply to situations where you will never contact subjects directly (e.g., retrospective chart review), in which case you should request a full waiver under section D.

No

B.2.2. Will you need ongoing access to PHI (e.g., medical records) to conduct the study, beyond the identification of potential subjects as addressed above? In this case you will need to obtain a signed HIPAA Authorization from each subject.

No

B.3. Subject Contact, Duration and Privacy

B.3.1. Number of contacts per subject (contacts includes in-person, telephone, email, mailings, etc.)

11

B.3.2. Duration of each contact. If multiple contacts, provide the range or average time for each contact.

1- 10 minute recruitment 2-email of eligibility link (questionnaire takes about 10 minutes) 3- email to schedule assessment (2 minutes) 4- baseline and first treatment (~3 hours) 5-9 5 minutes each 10- post test (~3 hours) 11- follow up (~3 hours)

B.3.3. Total duration of individual subject's participation, including follow up evaluation, if applicable

10 hours

B.3.4. Where are you studying subjects or obtaining their data?

Non-healthcare setting

B.3.5. Provide more information about the location(s) where research will be conducted (e.g., if UNC Medical Center is checked in #4 above and study visits will be conducted in the CTRC, enter "CTRC" here.)

The Sports Medicine Research Lab (Fetzer Gymnasium)

B.3.6. Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope)

As no interviews or physical examinations are to be conducted as part of this investigation, all data will be de-identified, and private information will not be collected, no additional measures will be taken to ensure privacy beyond secured access to code lists linking subject names and identification numbers. The code list will only exist until data collection is complete.

B.4. Incentives for participation

B.4.1. Are there incentives (monetary or non-monetary) for subjects to participate or are you reimbursing subjects for study-related costs (e.g., travel, parking, hotel accommodations or childcare)?

Yes

A. Please describe any incentives and/or reimbursements for study-related costs separately below.

$250

B. Specify the schedule for incentives and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it.

Compensation distribution will be $100 after the immediate post-test and $150 after completion of the 4-week follow up. If a participant

withdraws or is withdrawn prior to a milestone listed above, the compensation will not be awarded.

C. For compensation in foreign currency, provide a US dollar equivalent.

NA

D. Discuss the potential for coercion, given factors like the amount of the incentive, the age of the subjects, the purchasing power in foreign countries, the time involved and complexity of procedures, etc.

Given the small amount of the compensation ($250) for a total of almost 11 hours of time, we believe that the potential for coercion is very low. Particularly since participants must meet specific eligibility criteria.

E. If the subjects are children who will receive the compensation, i.e., the child, the parents or both?

NA

B.4.2. Are you collecting Social Security numbers for payment and/or tax-related purposes?

No

B.5. Costs to be borne by subjects

B.5.1. Will there be any costs that subjects will incur related to participation in the study? Do not include costs for standard care for which patients would be billed if they were not in this study. Also do not include the time spent participating in the study.

No

Part C. Existing Data, Records, Specimens

C.1. Data Sources

C.1.1. What existing records, data or human biological specimens will you be using? (Indicate all that apply or select 'None of the above'):

- ✘ Medical records in any format.

  ALERT: You must check both boxes: 1) Medical records in any format and 2) Electronic medical record using Epic, or you/your study team will not be granted access to Epic for research purposes.

- ✘ Electronic medical records using Epic, WebCIS or other electronic system
- ✘ Carolina Data Warehouse for Health (CDW-H) (for UNC and its affiliates only)
- ✘ Carolinas Collaborative Data Request and Review Committee (DRRC)
- ✘ Paper medical records

If you access the records of fewer than 50 patients under a full or limited waiver of HIPAA, submit a copy of your IRB approval letter and a completed Research Disclosure Form to Health Information Management (HIM). Do not submit this information to the IRB. For additional information about this process, you should contact HIM directly at : 919-595-5591 or 919-966-1225 or 919-595-5580.

- ✘ Data already collected from another research study

Were the investigators for the current application involved in the original collection? --

- ✘ Patient specimens (tissues, blood, serum, surgical discards, etc.)

Has the clinical purpose for which they were collected been met before removal of any excess? --

- ✘ Data already collected for administrative purposes
- ✘ Student records (You will need to satisfy FERPA requirements: see SOP 2301, section 1.1 for guidance)
- ✘ UNC Dental Records
- ✘ Data coming directly from a health plan, health care clearinghouse, or health care provider?
- ✘ Publicly available data
- ✘ Other
- ✔ None of the above

For EACH data source checked above, provide a description of the data, proposed use, how data were collected (including consent procedures), and where data currently reside.

--

C.1.2. Describe your plans for obtaining permission from the custodians of the data, records or specimens (e.g., pathology dept, tissue bank, original researcher):

No Answer Provided

C.1.3. Do the custodians of the data, records or specimens require a data use agreement?

No

C.2. Coding and Data Use Agreements

C.2.1. When you receive these data, records or human biological specimens will they be coded? Coded means identifying information that would enable the research team to readily ascertain the individual's identity has been replaced with a number, letter, symbol, or combination thereof (i.e., a code). If you will not be using existing materials, check "No."

No

Answer the questions below to identify the mechanism which precludes your access to the codes and include a copy of any agreements or documents that explain these protections:

Data use agreement with custodian of data (agreement prohibiting the release of the key to decipher the code to the applicant under any circumstances)?	--
Note: For Data Use Agreements, Non-Clinical Agreements, or Clinical Agreement Amendments, please submit the New OIC RRF and draft materials via email to OIC@unc.edu	--
Data are publicly available?	--
Honest broker (centralized custodian who controls data and will not release codes or IDs)?	--
Other	--

Part D. The Consent Process

D.1. Obtaining informed consent from subjects

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances. If you will be requesting a waiver answer "not applicable" for any of the following questions that will not pertain to this study. You will be asked to provide relevant information in the section below on waivers.

D.1.1. Will children under the age of majority in their locale (18 years in NC) be enrolled?
(Note: Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.)

No

D.1.2. Will adult subjects be enrolled in your study?

Yes

Explain the process for obtaining consent from the subject.

Phase 1: Prior to completion of the electronic eligibility survey, potential participants will read a description of the information that will be gathered in the surveys and the purpose of that information. Potential participants will then be asked to provide consent for this element (screening for eligibility) of the study. If consent is not provided, they will be thanked for their time and interest and told that they are not eligible for the remaining parts of the investigation. Phase 2: Once deemed eligible, potential participants will be contacted to schedule the testing session. Upon reporting to the Sports Medicine Research Center and prior to data collection, all subjects will be required to read and sign the approved informed consent form. Individuals will be asked if they have any questions pertaining to the study procedures prior to signing the consent form and initiating data collection.

D.1.3. Will decisionally-impaired subjects be enrolled in your study? (includes unconscious patients, some psychiatric disorders, others who lack the capacity to give consent)

No

D.1.4. Are you planning to obtain consent from any Non-English speaking subjects?

No

D.1.5. Describe who (by role) will be obtaining consent or parental permission.

Consent will be obtained only by those personnel listed on the protocol.

D.1.6. Discuss the potential for influencing the subject's decision to participate. Describe steps that will be taken to minimize undue influence during the consent process. These might include a waiting period between the initial consent discussion and obtaining consent, or obtaining consent by someone other than a person with perceived authority (e.g., professor, employer, treating physician).

As the PI teaches courses in which potential subjects may be currently enrolled or enrolled in the future, these individuals will be informed that their participation or the lack thereof will not influence their grade in a given course or their academic standing.

The following language will also be placed on the informed consent and discussed during recruitment.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

D.1.7. Has the sponsor of this study provided a model consent form?

No

D.2. Waiver of written documentation of informed consent

The default is for subjects to sign a written document that contains all the elements of informed consent. Under limited circumstances, the requirement for a signed consent form may be waived by the IRB. For example, this might occur for phone or internet surveys, when a signed consent form is either impractical or unnecessary, or in circumstances where a signed consent form creates a risk for the subject.

D.2.1. Are you requesting a waiver of any aspect of written (signed) documentation?

Yes

Choose which of the following consent approaches apply and attach the relevant document: *

- ✗ Full consent form minus the signature lines

You will be provided with a system built consent form when you reach the Consent Form section. This can be edited to remove the signature lines.

- ✗ Information or fact sheet (streamlined unsigned consent form)
- ✓ Online consent form with electronic agreement
- ✗ Consent statement incorporated into a survey itself
- ✗ Verbal consent obtained in person or via the phone
- ✗ Short form (for subjects with limited ability to read full consent form)

Choose which one of the following justifies the waiver of written documentation: *

- ✗ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form. Note: This justification cannot be used in FDA-regulated research.
- ✓ The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. (e.g., many phone or mail surveys, "man in the street" interviews, etc.).

Explain

The study is broken into two phases. The first is an online survey to determine eligibility. Participants are informed of what will be collected in the survey and that they do not have to complete the survey (elements of consent are present) but participants cannot give a written consent. Therefore, we are requesting a partial waiver for pre-screening of potential participants. The text that includes some elements of consent can be found in the eligibility packet submitted with this application.

If your request for a waiver of written documentation applies to some but not all of your subject groups and/or consent forms, please describe and justify

No Answer Provided

D.3. Full or partial waiver of consent

The default is for subjects to give informed consent. A waiver might be requested for research involving only existing data or human biological specimens. More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

D.3.1. Are you requesting any of the following:

- ✗ a waiver of informed consent in its entirety
- ✗ a waiver or alteration of some of the elements of informed consent
- ✗ a waiver of HIPAA authorization (If you are accessing patient records for this research, you must also request a waiver of HIPAA authorization)

D.3.2. If your request for a waiver applies to some but not all of your subject groups and/or consent forms, please describe and justify
No Answer Provided

D.3.3. Does this request for waiver support a study design that involves deception or withholding of information?
No

Consent Forms

This submission requires the following consent forms

Template Type
Adult Consent Form
Text for Online Consent Form **I am not using this template because:** Waiver of written consent requested in application (Section D.2.)

This submission includes the following consent forms

File Name	Document Type
Adult_Consent_Form-1_BIO of MT_R1.docx	Adult Consent Form

view consent forms

Attachments

This submission requires the following attachments

Document Type
Grant Application
Electronic Questionnaire Survey
Script for Class Recruitment
Flyer for Recruitment
Email or Listserv Recruitment

This submission includes the following attachments

File Name	Document Type
COMBINED GRANT_NO CITATION FIELDS.docx	Grant Application
Class Recruitment_Bio of MT.docx	Script for Class Recruitment
Email Recruitment_Bio of MT.docx	Email or Listserv Recruitment
Flyer_Bio of MT.docx	Flyer for Recruitment
Eligibility Packets_Bio of MT.docx	Electronic Questionnaire Survey
RE R21AT009704-01 clarification letter.txt	Email Correspondence (convert to PDF or TXT)

view attachments

Addenda

Data Security Requirements

view addenda

IRB Number: 17-2655	Initial	Principal Investigator: Erik Wikstrom

If Principal Investigator of this study is a Student or Trainee Investigator, the Faculty Advisor certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

Certifying Signatures:

Signature: Electronic Signature Received **Date:** 10/05/2017 03:00:51 PM
Erik Wikstrom

The expectation is that this approval is being given on behalf of the head of the Department, Division, or Center. If the chair or director is an investigator on this project or otherwise conflicted in approving it, the Vice-Chair or Chair's designee should review it. By approving, you are certifying the following on behalf of your department, division or center:

- This research is appropriate for this Investigator and our department
- The investigator(s) are qualified to conduct the research
- There are adequate resources (including financial, support and facilities) available
- For units that have a local review committee for pre-IRB review, this requirement has been satisfied
- I support this application, and hereby submit it for further review

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

If you are approving for other purposes (e.g., CTRC, DSMB, IBC, PRC, RSC, or other review committees), you affirm the following:

- The proposed submission is approved and may be forwarded for IRB review.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

Department Approval Signatures:
By signing in the appropriate space, the Department Chairperson(s) is indicating only that he/she has seen and reviewed this submission

Department: Exercise and Sport Science
Signature: Electronic Signature Received **Date:** 10/05/2017 08:52:38 PM
Name & Title: Ed Shields, Associate Professor, Director of Graduate Studies

Appendix 19: IRB Approval Forms

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
720 Martin Luther King, Jr. Blvd.
Bldg. 385, 2nd Floor
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: Erik Wikstrom
Exercise and Sport Science

From: Biomedical IRB

Approval Date: 11/07/2017
Expiration Date of Approval: 11/06/2018
RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Initial
Expedited Category: 4.Noninvasive clinical data,7.Surveys/interviews/focus groups
Study #: 17-2655

Study Title: Neuromuscular Mechanisms of Manual Therapies in Chronic Ankle Instability Patients

This submission has been approved by the IRB for the period indicated. It has been determined that the risk involved in this research is no more than minimal.

Study Description:

This proposal will focus on elucidating plausible neuromuscular mechanisms associated with novel and effective manual therapies that target sensory neural pathways in chronic ankle instability (CAI) patients.

Participants: Sixty participants with chronic ankle instability.

Procedures (methods): Neuromuscular mechanisms will be quantified before and immediately after a 2-week intervention that consists of 6, 5-minute treatment sessions. Mechanisms will include a comprehensive group of peripheral (ankle joint position sense, plantar light-touch discrimination thresholds), spinal (H-reflex of the soleus and fibularis longus), and supraspinal measures (cortical activity during stance using electroencephalography [EEG], corticomotor excitability and mapping of the soleus and fibularis longus via transcranial magnetic stimulation [TMS], and sensory organization strategies during stance).

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/index.cfm?event=home.dashboard.irbStudyManagement&irb_id=17-2655.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at http://irbis.unc.edu.

Please be aware that additional approvals may still be required from other relevant authorities or "gatekeepers" (e.g., school principals, facility directors, custodians of records).

The current data security level determination is Level II. Any changes in the data security level need to be discussed with the relevant IT official. If data security level II and III, consult with your IT official to develop a data security plan. Data security is ultimately the responsibility of the Principal Investigator.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Troy Blackburn, Exercise and Sport Science
Jason Franz, Biomedical Engineering - Undergraduate
Feng-Chang Lin, Biostatistics Operations
Brian Pietrosimone, Exercise and Sport Science

Appendix 20: Participant Payment Log

Payment Log Table		
Number	Payment 1 Date & Subject Initials	Payment 2 Date & Subject Initials

Appendix 21: Participant Self-Monitoring Guidelines

If, after receiving your treatment, you experience any of the following symptoms that may or may not affect your normal daily activity listed below, please contact your research coordinator immediately.

1. Muscle soreness
2. Pain
3. Spasm
4. Swelling
5. Fever or redness of your ankle
6. Altered sensation of your foot or ankle
7. Increased feelings of instability
8. Anything else that feels abnormal with your foot and/or ankle

The University of North Carolina Research Coordinator is Erik Wikstrom. He can be reached at 919-962-2260 or by email at wikstrom@unc.edu

Appendix 22: Study Completion Form

Pt_ID: _____

1. Date of final study visit: __ __ / __ __ __ / __ __ __ __
   d d m m m y y y y

2. Date of last-known study intervention: __ __ / __ __ __ / __ __ __ __
   d d m m m y y y y

3. Primary reason for terminating participation in the study:

   ☐ Completed study

   ☐ Participant was determined after enrollment to be ineligible (provide comments): _____

   ☐ Participant withdrew consent

   ☐ In the principal investigator's opinion, it was not in the participant's best interest to continue (provide comments): _____

   ☐ Adverse event (If checked, complete the AE form.)

   ☐ Death

   ☐ Lost to followup

   ☐ Other (specify): _____

   ☐ Unknown

Comments:

_____

_____

PI Signature: _____ Date: _____

Appendix 22: IMC Report Template

Tool Summary Sheet

Tool:	Independent Monitoring Committee (IMC) Report Template
Purpose:	MS Word template to be used as a starting point for preparing a IMC report
Audience/User:	Statisticians and Principal Investigators responsible for preparation of IMC reports
Details:	This template includes a proposed structure for a IMC report as well as draft language and other guidance
Best Practice Recommendations:	• Review this template several months prior to the date of the first IMC meeting, and customize to the specific needs and requirements of the study. • In the template, the instructions and explanatory text are indicated by *{blue italics}* Instructional text will also be enclosed in braces to signify this text for screen-readers used by the visually impaired. • Text enclosed with <> is a placeholder for a specific detail (e.g., <protocol title>); replace as appropriate. • Delete template-specific *instructional text* as well as this Tool Summary Sheet during the report development process. • Leave the template version information in the lower left hand corner of the document. • It is easiest and cleanest to use the styles that are embedded in the document, rather than to create your own. (In MS Word 2007: From the Home menu, select the bottom right arrow key to bring up the styles box, select "Options", under "Select Styles to Show" select "in current document".) • Ensure that all placeholder and example text is replaced with the study specific information.

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made:
1.0	13Apr2016	First approved version

INDEPENDENT MONITORING COMMITTEE REPORT

PROTOCOL TITLE: <Insert title of the protocol>

PROTOCOL NUMBER: <Insert protocol number>

PROTOCOL VERSION: <Insert version number and date of current protocol>

PRINCIPAL INVESTIGATOR: <Name of PI
PI's Title
Institution
Address>

MEETING DATE: <Insert date of the scheduled meeting>

DATE REPORT ISSUED: <Insert date that the report is being issued>

DATA CUTOFF DATE: <Insert the date of the data snapshot for the analyses in this report>

DATE OF LAST DATA REVIEW: <Insert date of last IMC meeting>

PREPARED BY: <Name of person who prepared the report
Person's Title
Place of employment
Address>

Table of Contents

{This table uses the Table of Contents function in Microsoft Word that will automatically update headings and page numbers used in the body of the report. In the body of the report, add, delete, or modify headings as needed in order to best reflect your study.}

Executive Summary

{Add, delete, or modify summary topics as needed.}

Report Overview	*{Example text:}* This report reviews enrollment and safety data available in the study database as of April 19, 2015. Summary tables are provided in the body of the report. Additional tables and figures referenced in the report are provided in the Appendices.
Study Site Status	*{Example text:}* Two of the 3 study sites have been activated. The third will be activated this month.
Enrollment Status	*{Example text:}* • 100 subjects have been screened for this study. • 20 subjects have been enrolled.
Subject Status	*{Example text:}* • 5 subjects are awaiting dosing. • 5 subjects have completed Month 1 follow-up. • 5 subjects have completed Month 2 follow-up. • 5 subjects have completed the protocol. • No treated subjects have been discontinued (withdrawn) from the study.
Stopping Rules **<or Halting Rules or Suspension Guidelines>** *{Use terminology that matches the protocol throughout this report}*	*{Example text:}* No stopping rules have been met since the previous IMC review. Or There are no new “Alerts” since the previous IMC review.

Safety Summary	*{Example text:}* • 100 adverse events have occurred in 7 subjects. • 50 adverse events were reported in the previous IMC report. • There have been no additional serious adverse events since the last IMC meeting. • Of the 50 adverse events, all were considered either mild or moderate.
Protocol Deviations	*{Example text:}* • 50 protocol deviations associated with 5 subjects have been reported. • None of the deviations has impacted subject safety. • 5 deviations have impacted scientific integrity
Quality Management	*{Example text:}* Quality management reviews are performed quarterly and were last completed on July 8, 2015 and October 7, 2015.

Protocol Synopsis

{Add, delete, or modify protocol headings as required. Enter appropriate information in second column; some clarification guidance has been provided.}

Protocol Title	<Insert protocol title>
Principal Investigator	<Insert name of Principal Investigator>
Study Sites	<List name of each study site>
Study Activation Date	<Insert activation date of first site>
Planned Accrual	<Insert planned number of participants to be enrolled>
Planned Accrual Period	<Insert time (months, years, etc.)>
Planned Duration	<Insert time from first participant-first visit to last participant-last visit (months, years, etc.)>
Study Design	<Briefly describe study design>
Study Objectives	<Briefly describe study objectives>
Treatment Description	<Briefly describe study treatment(s)>
Inclusion Criteria	<List inclusion criteria>
Exclusion Criteria	<List exclusion criteria>
Study Outcomes	<Briefly describe study outcomes>
Study Stopping Rules **<or Halting Rules or Suspension Guidelines>** *{Use terminology that matches the protocol throughout this report. Replace headings as appropriate.}*	<Clarify stopping rules or suspension guidelines>

{Add, delete, or modify headings as needed in order to best reflect your study. Place summary tables, listings, and figures within the body of the report; however, if the tables, listings, or figures are long, place them in the Appendices. For small numbers of subjects, listings may be more appropriate than summary tables.}

Report Overview

{Example text:}

The purpose of this report is to review cumulative enrollment and safety data for the subjects enrolled in the Excellent study. This report reflects data from the study database as of April 19, 2015. Within the body of the report are summary tables of enrollment, demographic characteristics, and adverse events. Additional tables, listings, and figures referenced in this report are provided in Appendices A-C. There have been five IMC meetings for this study, and the last review was on April 10, 2014. At that time, the IMC concluded that the available safety data supported the continuation of the trial. Readers of this report are asked to maintain the confidentiality of the information provided in this report.

Response to Most Recent IMC Recommendations/Requests

{Identify IMC recommendations/requests from the last meeting and clarify how those requests have been handled in the report and/or elsewhere. If this is the first IMC meeting for this protocol or no previous recommendations/requests were made, indicate as such in this section. Doing so will provide a future reminder to the author who is likely to use the previous report as a starting point for the subsequent report.}

Enrollment Status

{Describe enrollment and provide a summary table (see example below). Provide enrollment statistics by site if the study involves multiple sites. If the study is enrolling, provide the subject accrual target and estimated time to completion of enrollment. A figure showing expected/planned versus actual enrollment is helpful (see example on next page).

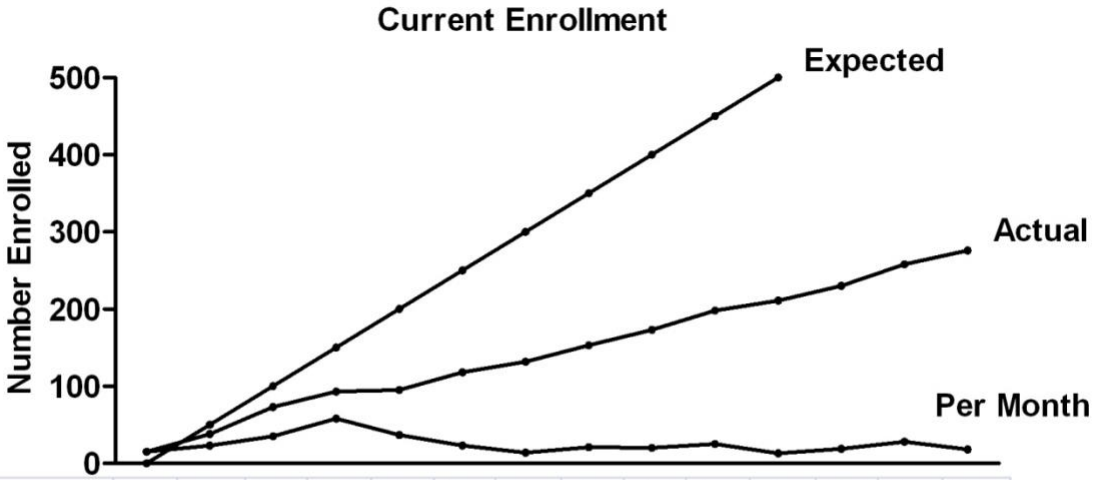
Sample Table:}

Table #. Subject Enrollment Status for All Subjects

Type	Site A	Site B	Total
Pre-Screened	100	100	200
Consented and Screened	50	50	100
Eligible	35	40	75

{Sample Figure:}

Figure #. Expected versus Actual Accrual



	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Expected	0	50	100	150	200	250	300	350	400	450	500			
Actual	15	38	73	93	95	118	132	153	173	198	211	230	258	276
Per Month	15	23	35	58	37	23	14	21	20	25	13	19	28	18

Subject Status

{Describe where patients are in the study in relation to major milestones, such as the number of subjects who have completed the baseline visit, the dosing visit, year 1 follow-up, and the final study visit. A summary table providing the study milestones and the number of subjects who have completed those milestones is recommended.

Also, provide the number of subjects who were terminated and the reason for their termination, such as voluntary withdrawal, death, lost to follow-up, adverse event, or completed the protocol. A summary table of subject disposition is also recommended. For some protocols, it is important to distinguish between subjects who withdrew early from the study and those who discontinued treatment but may or may not still be followed.}

Demographics (and Baseline Characteristics if Appropriate)

{Describe the demographic characteristics (age, race, and ethnicity) and key baseline characteristics of enrolled subjects (if appropriate). Provide a summary table (see example on the next page) or a listing of the data. Listings are preferable over summary tables if only a few subjects have been enrolled. However, avoid listing any information that could potentially lead to the identification of a participant.

Sample Listing:}

Listing #. Listing of Demographic Information for All Consented Subjects

Subject ID	Age (yrs)	Gender	Race	Ethnicity
001	60	Female	Black	Not Hispanic or Latino

Subject ID	Age (yrs)	Gender	Race	Ethnicity
002	65	Female	Black	Not Hispanic or Latino
003	64	Male	White	Hispanic or Latino
004	72	Male	White	Not Hispanic or Latino
005	45	Male	Alaskan Native	Not Hispanic or Latino
006	70	Male	White	Not Hispanic or Latino

Safety Summary

Stopping Rules

{List and describe any stopping rules that have been triggered since the previous IMC report and over the course of the study.}

Deaths

{List and describe any deaths that have occurred since the previous IMC report and over the course of the study.}

Unanticipated Problems

{Summarize or list unanticipated problems. The Office for Human Research Protections (OHRP) considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

1. *Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document, and (b) the characteristics of the subject population being studied;*
2. *Related or possibly related to participation in the research (in this guidance document, 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.*

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 subjects or others.}

Adverse Events

{Summarize or list the adverse events (AEs) that have occurred since the previous IMC report and over the course of the trial. Provide information on severity and relatedness to treatment and study procedures (see an example of a summary table below). Please

ensure that categories summarized match those in the protocol. For instance related/unrelated vs. the 5 category delineation.

In addition, a summary table or listing of subjects experiencing adverse events by treatment group, system organ class, and preferred term should be considered. Extensive listings may be placed in the Appendix.

Sample Table:}

Table #. Summary of All Adverse Events for Consented Subjects

Topics	Site A	Site B	Total N=12
Number of AEs reported	38	30	68
Number of Subjects with AEs [1]	4	3	7
Number of SAEs reported	1	0	1
Number of Subjects with SAEs [1]	1	0	1
Number of AEs by Severity*	**Site A**	**Site B**	0
Mild	31 (81.1%)	24 (80.0%)	55 (80.9%)
Moderate	7 (18.9%)	3 (10.0%)	10 (14.7%)
Severe	0 (0.0%)	3 (10.0%)	3 (4.4%)
Subjects with AEs by Severity [2]**			
Mild	4 (100.0%)	3 (100.0%)	7 (58.3%)
Moderate	3 (100.0%)	2 (66.7%)	5 (41.7%)
Severe	0 (0.0%)	1 (33.3%)	1 (8.3%)

Number of AEs by Relatedness to Treatment*	**Site A**	**Site B**	**Total N=12**
Unrelated	25 (64.9%)	23 (76.7%)	48 (70.6%)
Unlikely	9 (24.3%)	4 (13.3%)	13 (19.1%)
Possible	4 (10.8%)	3 (10.0%)	7 (10.3%)
Probable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with AEs by Relatedness to Treatment [2]**	**Site A**	**Site B**	**Total N=12**
Unrelated	4 (100.0%)	3 (100.0%)	7 (58.3%)
Unlikely	3 (100.0%)	2 (66.7%)	5 (41.7%)
Possible	2 (66.7%)	2 (66.7%)	4 (33.3%)
Probable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of AEs by Relatedness to Study Procedures	**Site A**	**Site B**	**Total N=12**

Topics	Site A	Site B	Total N=12
Unrelated	26 (67.6%)	21 (70.0%)	47 (69.1%)
Unlikely	5 (13.5%)	4 (13.3%)	9 (13.2%)
Possible	4 (10.8%)	4 (13.3%)	8 (11.8%)
Probable	1 (2.7%)	1 (3.3%)	2 (2.9%)
Definite	2 (5.4%)	0 (0.0%)	2 (2.9%)
Subjects with AEs by Relatedness to Study Procedures [2]**	**Site A**	**Site B**	**Total N=12**
Unrelated	4 (100.0%)	3 (100.0%)	7 (58.3%)
Unlikely	2 (66.7%)	2 (66.7%)	4 (33.3%)
Possible	3 (100.0%)	3 (100.0%)	6 (50.0%)
Probable	1 (33.3%)	1 (33.3%)	2 (16.7%)
Definite	2 (66.7%)	0 (0.0%)	2 (16.7%)

[1] Subjects who experience one or more AEs or SAEs are counted only once.
[2] Subjects are counted only once within a particular severity grade or relatedness category.
*** Percentages are based on number of AEs reported for each treatment group.**
**** Percentages are based on N for each treatment group.**

Serious Adverse Events

{Summarize or list all serious adverse events (SAEs) that have occurred since the previous IMC report and over the course of the trial. Provide information on expedited reports, and include MedWatch forms in the Appendix if applicable.}

Laboratory Findings

{Summarize results from any clinical laboratory tests that are being monitored for subject safety. Laboratory results may be presented as summary tables, listings by subject, or plots. Depending on the study, identify by subject any significant changes from baseline, results that are clinically significant, or results that are considered adverse events.}

Other Clinical Tests

{You may list types of tests, such as imaging or physical examinations, as separate headings.

Summarize any other clinical tests that are being monitored for subject safety. Depending on the study, identify by subject any significant changes from baseline, results that are clinically significant, or results that are considered adverse events.}

Protocol Deviations

{Summarize or list protocol deviations that have occurred since the previous IMC report and over the course of the study.}

Quality Management

{Provide details regarding quality management activities completed since the last IMC review, including frequency. Summarize or list findings and identify measures or corrective actions taken to address the findings or issues.}

Outcomes Data

{As a general rule, interim results should not be performed or presented unless interim analyses are described in the protocol or the IMC has requested an interim analysis to assess a safety concern or study futility. The decision whether or not to present interim or final results in this report, or to present results in an open or closed session, should be discussed with the IMC and the study sponsor.}

Appendix A: Additional Summary Tables

{It is likely that these Appendices will originate as separate electronic files created by SAS or some other statistical software. If you are creating an electronic version of the full report, use Adobe pdf (or equivalent) to combine the files with this document in a "published" Adobe report. It is very useful to include a Table of Contents or, at a minimum, a list of items contained within each Appendix (e.g., a list of table numbers and names).

Page numbering of the contents of the Appendices are at the discretion of the document owner. Each Appendix file can 1) begin at page 1 or 2) can be numbered contiguously with this document. The second option is advantageous but more difficult to achieve.

A subset of these items may also have been inserted into the report. It is acceptable to also include those items in the corresponding appendix. All other displays that are not inserted into the body of the report should be included herein. It is good practice to ensure that all post-text displays are referenced somewhere in the body of the report.

Include post-text Summary Tables here.}

Appendix B: Additional Figures

{Include post-text Figures here.}

Appendix C: Additional Data Listings

{Include post-text Data Listings here.}