Study Title

The effect of Cranial Laser Reflex Technique on hamstring function: a pilot study

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MASTER PROTOCOL

THE EFFECT OF CRANIAL LASER REFLEX TECHNIQUE ON HAMSTRING FLEXIBILITY, STRENGTH AND PAIN PRESSURE THRESHOLD: A PILOT STUDY

PROTOCOL

Title: The Effects of Cranial Laser Reflex Technique (CLRT) on Hamstring Flexibility, Strength and Pain Pressure Threshold: a pilot study

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PRÉCIS

Title: The Effects of Cranial Laser Reflex Technique (CLRT) on Hamstring Flexibility, Strength, and Pain: a pilot study.

Objectives: To assess the acute effect on hamstring flexibility, strength, and pain pressure threshold of a novel laser therapy intervention (CLRT) compared to sham.

Design and Outcomes

This is a randomized, blinded crossover trial with 44 healthy young adults that will compare the acute effects of CLRT to sham laser on hamstring flexibility, strength, and pain pressure threshold (PPT). The primary outcome is hamstring flexibility, which will be assessed by independent examiners using the standard Knee-Extension-Angle (KEA). As secondary outcomes, hamstring strength will be measured using handheld dynamometry (HHD), and PPT with digital algometry. The intervention will consist of low-level-laser stimulation of the hamstring cranial reflex points for an average total treatment time of 30 seconds. A one-week washout period will occur between visits, and participants will have access to usual care throughout the research study. The research study will be conducted at the Neurophysiology Lab at the University of North Carolina and in UNC Medical School, Wing D.

Specific Aim 1: To examine the acute effect of CLRT on hamstring flexibility as measured by the standard 90-90 Knee Extension Angle (KEA) test.

Hypothesis 1: CLRT will increase mean hamstring flexibility immediately after treatment.

Specific Aim 2: To examine the acute effect of CLRT on hamstring strength as measured by handheld dynamometry (HHD).

Hypothesis 2: CLRT will have a neutral to positive effect on hamstring strength.

Specific Aim 3: To examine the acute effect of CLRT on hamstring pain pressure threshold as measured by digital algometry.

Hypothesis 3: CLRT will increase PPT in the hamstrings.

LIST OF ABBREVIATIONS

ADL	Activity of Daily Living
AE	Adverse Event/Adverse Experience
ATP	adenosine triphosphate
CLRT	Cranial Laser Reflex Technique
Co-I	Co-Investigator
CRF	Case Report Form
CRP	Cranial Reflex Point
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DSMC	Data and Safety Monitoring Committee
EXSS	Exercise and Sport Science
FDA	Food and Drug Administration
HHD	Handheld Dynamometry
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Insitutional Review Board
KEA	Knee extension angle
LLLT	Low level laser therapy
LTrP	Latent trigger point
mtNO	mitochondrial nitric oxide
mW	miliwatt
NC TraCS	North Carolina Translational and Clinical Sciences Institute
NIH	National Institutes of Health
nm	nanometer
NRS	Numerical Rating Scale
OHRP	Office for Human Research Protections
PBM	Photobiomodulation
PI	Principal Investigator
PID	Participant ID
PPT	Pain Pressure Threshold
PS	Potential subject
SAE	Serious Adverse Event/Serious Adverse Experience
tcPBM	Transcranial Photobiomodulation
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
UP	Unexpected Problem
US	United States

2. BACKGROUND AND RATIONALE

2.1: Background

Hamstring injuries are a common occurrence in many sports that involve sudden or explosive movements, such as jumping and sprinting. Soccer and lacrosse players are especially at risk for these frustrating injuries that have the highest rate of recurrence (12-31%) in sports(1) making prevention and rehabilitation important areas of study. Static stretching is widely performed, even though it may cause a significant loss of strength(2), endurance(3), and explosive performance for 24 hours(4). Latent myofascial trigger points (LTrPs) are typically asymptomatic neuromuscular lesions that are associated with muscle overload and decreased contractile efficiency and are highly prevalent in the lower extremity(5). Currently no clear consensus exists on the most effective protocols for prevention of hamstring injuries(6), but decreased flexibility and reduced strength are known risk factors for hamstring strain(1) and other musculoskeletal lesions such as lower back pain(7).

Low Level Laser Therapy (LLLT) aka Photobiomodulation (PBM) is the application of low doses of monochromatic coherent light from low powered laser devices to induce a biostimulatory effect in the target tissue. PBM has been shown to be effective for musculoskeletal pain relief and wound healing(8), as well as many other applications (9-14). PBM is anti-inflammatory and reduces oxidative stress, working primarily on the mitochondria in stressed or ischemic tissues. The mitochondria produce nitric oxide (mtNO) that binds to the chromophore cytochrome c oxidase, competitively displacing oxygen leading to oxidative stress and reduced ATP production. Light of suitable wavelength, sufficient irradiance and time when applied to injuries is absorbed by cytochrome c oxidase, displacing mtNO and thereby reducing oxidative stress and increasing ATP production. A cascade of downstream metabolic effects leads to a reduction in inflammatory markers including prostaglandin E2, interleukin 1β, interferon (α, β, γ), and tumor necrosis factor-α (15-17). Anti-inflammatory and immune-modulatory markers are also upregulated, such as TGF-β1, IL-4, and IL-10 (18, 19).

Lasers have a long history of use in acupuncture in lieu of needles (20-23). Typically, lower doses (1-4 J/cm^2) of laser light are used on specific points to induce a non-local or systemic effect. Laser acupuncture has been shown to be effective in a variety of musculoskeletal conditions such as low back pain and knee pain, and has been shown to have significant effects on brain activation in fMRI studies (24, 25)

Cranial Laser Reflex Technique (CLRT) is a novel complementary and alternative (CAM) medicine intervention for musculoskeletal conditions that incorporates principles of laser acupuncture with chiropractic cranial reflexology(26). Developed in 2006 by Dr. Nick Wise (PI), CLRT has been incorporated into clinical practice by hundreds of practitioners around the world. It involves non-invasive laser stimulation of a distinct cranial microsystem discovered by chiropractors(27). It was postulated that these cranial reflexes are similar in nature to acupuncture points and would likewise respond to

photobiomodulation (PBM) from a low level laser (28, 29) (30). Clinical experience by the PI and others confirmed that cranial reflexes are indeed responsive to low doses (0.5-5 J/cm2) of laser light: the length, strength, and pain in a specific muscle could be improved rapidly, even in cases of chronic post-stroke muscle spasms(31). This pilot study will examine the acute effect of this promising intervention on hamstring flexibility and strength in healthy young adults.

2.2: Study Rationale

Preliminary Findings

The Principal Investigator, Dr. Nicholas Wise, has 16 years of clinical experience in conservative care of musculoskeletal conditions, specializing in manual manipulation and laser therapy. Since developing CLRT in 2006, he has amassed clinical data and presented numerous case reports from clinical practice demonstrating that CLRT has the ability to modulate muscle tone, strength, and pain. This is the first clinical trial to directly examine these effects of CLRT in human subjects.

Environment and Capabilities of the Research Team

This project will take place at the University of North Carolina School of Exercise and Sports Science Neurophysiology Lab. Dr. Nicholas Wise, the PI of this proposed project, is a board-certified chiropractor and postdoc research fellow in the Program on Integrative Medicine in The Department of Physical Medicine and Rehabilitation.

Dr. Pietrosimone is an assistant professor in the Department of Exercise and Sports Science at UNC. His research has evaluated the neuromuscular mechanisms related to disability following lower extremity joint injury. Additionally, he has sought to develop novel intervention strategies to treat neuromuscular impairments and improve clinical outcomes.

Providing guidance to the project are senior statistician, Dr. Mark Weaver, and Dr. Susan Gaylord, PhD, research psychologist and director of PIM, who has expertise in project design and CAM modalities for pain management. Jacob Hill is a postdoc researcher in Physical Medicine and Rehabilitation and has been trained in the physical assessment tests used in this study.

3. STUDY DESIGN

This is a randomized, assessor-blinded, sham controlled crossover study with repeated measures.

First Visit. The research staff will schedule all study visits in the Neurophysiology Lab or other appropriate site in the UNC Healthcare system or medical school. The baseline phase of the first visit will include review of inclusion/exclusion criteria and the components of the study. Those who wish to sign the consent will complete a brief questionnaire on their activity level, history of hamstring injuries, and perceived hamstring tightness.

Randomization/Random Allocation. Subjects who meet the inclusion criteria and give consent will be randomized to one of the following for the first treatment period: 1) active CLRT; or 2) sham laser. At the first intervention visit, the research assistant will enter the subject's assigned ID into an online computer program (selected by study biostatistician) to determine assignment to one of the two periods. The study biostatistician will use computer-generated random numbers to generate the allocation sequence using random blocks of random sizes. The program documents treatment assignment in an un-editable form including a date stamp.

Post Randomization. After randomization, subjects will be asked to complete the three functional hamstring tests: KEA, HHD, and PPT. Subjects will have direct contact with the investigator and research assistant at each visit to facilitate adverse event reporting.

Assessments. KEA: The 90-90 Knee Extension Angle test is a functional assessment designed to assess lower extremity flexibility and is considered the gold standard for hamstring length (32) The participant will be in the supine position on a treatment table. The tested extremity (the right leg in each subject) will be placed in a 90° hip and 90° knee position with the contralateral lower extremity placed flat on the table. A digital inclinometer will be consistently placed at the level of the medial malleoli and the superior pole of the patella. The examiner will maintain 90° of hip flexion. Pelvic position will be monitored by palpation of the anterior superior iliac spine and lumbar spinous processes to maintain a neutral pelvic position. The examiner will passively extend the knee to the point of a ''strong, but tolerable stretch," as reported by the subject. The examiner will read the angle of the inclinometer and record the mean value of three attempts. A greater angle indicates greater degree of flexibility.

Hand held Dynamometry (HHD) is currently considered a reliable and valid measurement of peak muscle contraction(33). The subject will be prone on the table with right leg bent to 90°. The tester will place the dynamometer (microFET2; Hoggan Health Industries, Salt Lake City, UT) at the heel of the participant and apply force to the heel, gradually increasing in 3 to 5 seconds. Participants will be instructed to resist the applied force and maximally contract the hamstring muscle against the HHD device. The test ends once they are no longer able to resist the force and the leg begins to move (break point). The investigator will record the mean value of three attempts.

Pain Pressure Threshold (PPT) is a reliable, accurate and valid method for measuring muscle pain sensitivity and response to treatment(34). The digital algometer (FDX, Wagner Instruments, Greenwich, CT) is a hand-held muscle tester with a range of 0–100 lbf that consists of a padded disc with a diameter of 0.5" attached to a microprocessor-control unit that measures peak force (pounds or kilograms). The unit has a digital readout for peak-applied pressure and provides a built-in calibration routine that verifies a valid calibration. In order to determine PPT, the researcher will apply the tip of the algometer to a tender spot in the participant's hamstrings and increase the amount of pressure until the participant verbally informs the researcher when the sensation of pressure became pain. At this point

the algometer is removed and the peak force recorded. The mean of three repeated measures will be reported.

Intervention: **CLRT**. Subject will don protective eyewear and remain in the prone position. The hamstring reflexes are two lines on the posterior portion of the top of the head, approximately 2 cm long and 2 cm apart, running parallel to the sagittal suture (fig. 1). The posterior end of the reflexes can be located by finding the vertex, or CZ point in the standardized 10-20 EEG system, and moving laterally approximately 1 cm.

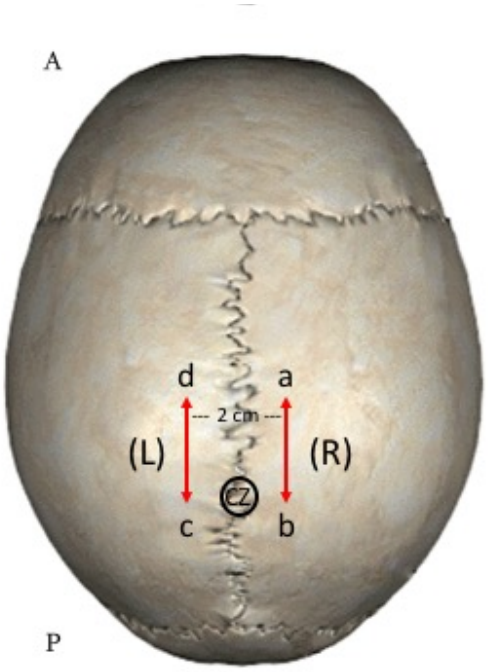

Fig.1 Location of bilateral cranial reflexes for hamstrings

Sequence:

The aperture of the laser probe will be placed at point (a), turned on and moved to point (b) at a speed of approximately 2 cm/s. The laser will be turned off and quickly returned to point (a), turned on and moved to point (b) again. This will be repeated for a total of 30 times. The probe will make light contact with the scalp during the powered laser pass, moving aside as much hair as possible.

Device: The treatment device to be used in this study is a Class IIIB 810nm 200mW near-infrared GAAlAS diode laser (THOR Photomedicine Ltd, Great Britain) that is currently marketed in the US. The laser probe is FDA-cleared and classified as a non-significant risk device. The spot size is 0.0364 cm^2, and the treatment time is 30 seconds. Current best-practice recommendations for laser acupuncture(35) recommend a dosage between 1-4 J/cm^2 per point. Since the cranial reflex point (CRP) is a line of 2 cm, for the purposes of calculating dosage, we will treat it as a series of 10 connected points each with a diameter of 2mm. With the scanning rate of 2cm/s, each "point" on the line will receive 1/10 of each pass, totaling 3s (out of 30s total) exposure time per point. The dose per point for this intervention is calculated to be approximately **1.65 J/cm^2**.

$$Power\ Density\ \left(\frac{J}{cm^2}\right) = \frac{end\ power(W) * Time\ (s) * energy\ loss\ factor\ (\frac{1}{cm})}{area\ (cm^2)}$$

$$= \frac{0.2\ W * 3s * 1}{0.0364\ cm^2} = 1.65\ \frac{J}{cm^2}$$

Random Allocation. At the first intervention visit, the research assistant will enter the subject's assigned ID into an online computer program that will determine assignment to one of the two treatment periods. Using a random number sequence to generate a permuted block of 2-4, the program ensures

equal numbers of subjects in each arm. The program documents treatment assignment in an un-editable form including a date stamp.

Masking. The research coordinator and treating investigator will be unmasked. All research assistants performing the assessments will be masked. Masking will be maintained in the random allocation procedure. The treating investigator will not indicate to subjects or assessor to which period the participant is assigned.

Remuneration. Subjects will receive an Amazon gift card worth $25 upon completion of the second visit. If the subject completes only the first visit, they will be compensated a prorated amount with a card worth $15.

The following patient-reported variables will be assessed:

1) **Expectation of benefit:** Measured with a modified Borkovec and Nau scale(36). This instrument provides an assessment of credibility of each intervention using an adaptation of a validated credibility scale previously developed for psychological studies for purposes of comparing the two treatment arms. This instrument has been successfully adapted for use in other conditions such as chronic pain and migraine headache. It will be administered after each subject completes the second visit.
2) **Perceived value of the intervention** is measured at the end of the active intervention via questionnaire. At the end of the post-intervention phase, subjects will be invited to participate in a brief post-study interview to assess their overall impressions of the treatment.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1: Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study. Criteria include:

1) Between 18-35 years of age
2) All genders
3) Willing to complete two study visits over 2-3 weeks
4) Able to read and communicate in English

4.2: Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation. Exclusion criteria include:

1) Current lower back condition with pain, numbness or tingling that radiates down the legs
2) Active treatment for a major medical illness, such as heart disease, uncontrolled diabetes or hypertension, malignancy, autoimmune, or immune deficiency disorder

3) History of vasculitis, intracranial mass, clotting disorder (including medication-induced, e.g., warfarin)
4) Current skin malignancy on scalp
5) Cognitive dysfunction preventing informed consent
6) Pending or currently receiving benefits from personal injury litigation, including worker's compensation
7) Chronic long-term disability related to lumbosacral injury/symptoms
8) Epilepsy

4.3: Study Enrollment Procedures

Sample Size and Population

Target Population. The target population will be healthy young adults between the ages of 18-35. Healthy young adults are chosen as the target population because this is a) a pilot study and b) the expectation of rapid subject recruitment and excellent retention.

Recruitment Estimates. Approximately 60 healthy young adults will be screened to achieve a pre-intervention sample size of 44 subjects. We expect at least 38 of the 44 to complete the 2-week intervention, which will provide adequate power to test Aim 1.

Sources of Subjects

The primary source for recruitment will occur through the Exercise and Sports Science Department. Additional recruitment for potential subjects will occur at other sites around UNC. The study will be listed on the NC TraCS research recruitment website *www.jointheconquest.com*.

Consenting

All subjects will be assessed for eligibility on the basis of their medical condition by the PI, Dr. Wise, a board certified chiropractor specializing in conservative care of musculoskeletal conditions. Interested individuals will sign a permission to contact form. Prior to the initial visit with a study team member, the subject will complete a telephone screen with telephone consenting. If the potential participant remains eligible, a study team member will schedule an appointment for the first study visit.

Consenting Process

Informed consent forms (ICFs) will be reviewed with the patient by either the study coordinator, the project supervisor, or the co-investigator. The study team member will read the ICFs to the patient as they follow along. Any questions the patient may have will be answered accordingly. After reviewing the consent, a patient may decline to participate, sign to participate at the time of the meeting, or take the ICFs home with them to be signed at a later time. The patient will be considered to be a subject at the time of signing the consent. Persons who cannot sign for themselves will not be recruited.

Documentation

Documentation of each study visit will include a visit checklist signed by the study team personnel completing the visit.

Randomization

The study coordinator randomizes eligible subjects into one of the two arms at the time of their first visit using a computer-generated blocked randomization process. Please see Section 9.2 for details.

5. STUDY INTERVENTION

5.1: Intervention, Administration, and Duration

CLRT is a complementary or alternative intervention that incorporates principles of laser acupuncture with chiropractic cranial reflexology. Instead of acupuncture points derived from TCM, CLRT involves low level laser stimulation of two distinct cranial microsystems discovered by chiropractors. The first map of cranial reflex points/pathways (CRP) was originally discovered by a doctor named Jack Elvidge using Applied Kinesiology, and each CRP corresponds to a major muscle or group. These soft-tissue CRPs are either points or directional lines on the skull, and they appear to have an influence on the particular muscle's tonus and strength. It was originally found that stimulating a linear reflex with digital pressure in one direction relaxed the muscle's tone, and stimulating it in the opposite direction increased the tonicity.

The second set of CRPs used in CLRT were discovered by David Denton, D.C., and consists of points that relate to each vertebra of the spine, rib, sacroiliac joint, sacrum and coccyx. Denton found that subtle manipulations of these points affected the position and function of misaligned vertebra in manner similar to adjusting them directly. Dr. Nicholas Wise developed CLRT after postulating that the CRP's had similar optical properties to the acupuncture meridians, and would respond to coherent light in a similar manner. Upon clinical experimentation, he found that the cranial reflexes were in fact extremely responsive to low doses of laser light. The major goal of CLRT is to quickly decrease in pain, increase joint range of motion, and achieve lasting functional improvements. CLRT can be performed with a range of laser powers from 5milliwatts (mW) to 500mW with similar results, and wavelengths from 405nm-840nm have been used successfully.

The first visit will last approximately 1 hour and the second visit will take 30 minutes.

5.2: Concomitant Interventions

5.2.1: Allowed Interventions

Subjects will be allowed to partake in their usual exercise and physical activities.

5.2.2: Required Interventions

Participation in both study arms of the crossover trial.

5.2.3: Prohibited Interventions

None.

5.3: Adherence Assessment

We will define study adherence as completion of both study visits.

6. STUDY PROCEDURES

6.1: Schedule of Evaluations

Activity	Visit 1 (Week 1)	Visit 2 (Week 2)	Check-in Call (Week 3)
People involved in visit/activity:	Study Coordinator, Investigator and Research Assistant	Investigator and Research Assistant	Research Assistant
Location:	Neurophysiology Lab	NL	Phone
Eligibility Criteria Review	**X**		
Informed Consent Review	**X**		
Randomization	**X**		
Musculoskeletal History	**X**		
Hamstring Tightness Questionnaires	**X**	**X**	
90-90 KEA	**X**	**X**	
Handheld Dynamometry	**X**	**X**	
Intervention	**X**	**X**	
Expectation of Benefit	**X**		
Perceived value of the intervention		**X**	
Follow up			**X**

6.2: Description of Evaluations

6.2.1: Screening Evaluation and Consenting

Screening

A brief telephone call by the research assistant that will cover inclusion/exclusion criteria and components of the study will be completed. If subject is interested, they will be invited to consent and enroll in the study.

Consenting

Interested participants will travel to UNC Neurophysiology Lab at Fetzer Hall to meet with a Study Coordinator or Research Assistant to review consent forms and sign and date (in a private room).

After participants sign the consent, their musculoskeletal history questionnaire will be reviewed by the PI to ensure that the patient has no outlying medical issues that would exclude participation.

6.2.2: Enrollment, Baseline, and/or Randomization

Enrollment

Subjects are enrolled at time of signing the consent form. The analysis will be done under an Intention to Treat.

Baseline Assessments

Age, gender, hamstring injury questionnaire, perceived hamstring tightness scale, activity level.

Randomization

Randomization occurs at the end of the baseline and screening phase immediately prior to starting the intervention.

6.2.3: Blinding

Subjects and assessors will be blinded to treatment allocation. The subject will be face down, eyes closed, and wearing protective eyewear that blocks the specific wavelength of the laser light during the intervention.

Individuals authorized to break the blind include the PI and study statistician.

Circumstances for breaking the blind include the development of a Serious Adverse Event (SAE) or recurrent Adverse Event (AE) apparently related to the research interventions.

The procedure for breaking the blind is to have the research assistant inform the PI or the study statistician of the allocation of the subject.

After each treatment session, the participants will complete a de-blinding questionnaire administrated by the assessor providing a dichotomous 'yes' or 'no' answer as to whether active treatment was received. This response will be followed by a second question regarding how certain they were that active treatment was received on a 0–10 numeric rating scale (NRS), where 0 represents absolutely uncertain and 10 represents absolutely certain.

6.2.4: Study Visits

Study visits will ideally be one week apart. (See Section 6.1 for Schedule of Evaluations table.)

- ***Visit 1:***
  - Inclusion / Exclusion Criteria
  - Consenting: Subject Enrollment
  - Study questionnaires: Hamstring Injury questionnaire
  - Randomization
  - KEA

- HHD
- PPT
- Intervention
- Post KEA
- Post HHD
- Post PPT
- De-blinding questionnaire

- ***Visit 2: Week 2-3***
  - KEA
  - HHD
  - PPT
  - Intervention
  - Post KEA
  - Post HHD
  - Post PPT
  - De-blinding questionnaire

6.2.5: Completion

- Study questionnaires:
  - Expectation of benefit/ Believability scale
- Evaluation for participants who discontinue study intervention early

  Potential reasons for early termination include: subject no longer interested, adverse events, subject not able or willing to follow the protocol, subject moved away from the area or prolonged travel.

  If subjects withdraw early, the PI or his designee will attempt to follow-up by telephone to inquire about health status as it relates to adverse events experienced by the subject leading to early discontinuation of participation.

7. SAFETY ASSESSMENTS

7.1: Specification of Safety Parameters

Low level laser devices used for the purposes of photobiomodulation or acupuncture are designated by the FDA as "non-significant risk" devices (37). After four decades of research, over 4000 peer-reviewed papers and over 150 Phase III clinical trials, there are no known side effects attached to low level laser therapy (LLLT). Animal studies have shown that lasering the head, or transcranial photobiomodulation (tcPBM), is very safe and causes no thermal or neoplastic changes in the cortex(38). The use of tcPBM has been shown to have promise for treating traumatic brain injury(39-41) and stroke(42-44), as well as enhancing mood(45-47) and cognition(48-52) in humans.

CLRT involves principles and laser dosages very similar to laser acupuncture. Laser acupuncture has been extensively studied and deemed to be safe and effective for certain musculoskeletal conditions(21), especially in long-term follow up (29). No known or anticipated serious side effects from CLRT have yet occurred but minor reactions may include mild delayed onset muscle soreness or headache. Due to the intensity of the laser light, subjects will wear proper eye protection that blocks the specific wavelength of light while lasers are in use.

Based on previous research, no serious side effects are anticipated. The PI will closely monitor all subjects for any adverse events and will report them to the IRB if any arise.

Examples of safety measures include: monitoring subjects for any discomfort related to intervention; reports of cramps, spasms, headache or delayed onset muscle soreness.

7.2: Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

1) Timing: each contact with the subject will be an opportunity to inquire about adverse events.
2) Recording: each incidence of an adverse event will be recorded in the case report form in a designated location for this information.
3) Analyzing: the PI will be informed of all adverse events and will forward the information to the IRB.

7.3: Adverse Events (AEs) and Serious Adverse Events (SAEs)

Definitions

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

A serious adverse event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

Classification of AE Severity

Classification of AEs will be based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4, 2009. AEs will be described by symptom or condition/diagnosis, and graded for severity (mild, moderate, or severe), depending on the intensity of the event. Two additional categories will be used based on the CTCAE system, "life threatening" and "death".

Grade 1. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; minimal impact on subject's life; intervention not indicated.

Grade 2. Moderate: medical care sought; significant but limited inconvenience on Activities of Daily Living (ADL) or lifestyle; local or noninvasive intervention indicated.

Grade 3. Severe: medically significant but not immediately life-threatening; disabling; limiting self-care; substantial disruption to the subject's well-being; hospitalization or prolongation of hospitalization indicated.

Grade 4. SAE. Life-threatening consequences; urgent medical intervention indicated.

Grade 5. SAE. Death: related to AE.

An AE that is graded as severe (Grade 3) can be distinct from an SAE (Grades 4 and 5). A subject could experience a severe AE (Grade 3) that does not meet the definition of an SAE (see above). Alternatively, a subject could experience a moderate AE (fever, mild confusion) that meets the SAE definition (example - need for antibiotics to combat a life threatening infection).

AE Attribution Scale

AEs will also be classified on an assessment of relatedness to the study intervention. AEs will be categorized according to the likelihood that they are related to the study intervention. They will be labeled as: 1) definitely related, 2) definitely unrelated, 3) probably related, or 4) possibly related to the study intervention in the opinion of the PI after review of the circumstances and relevant records. Attributions will be made by the PI.

7.4: Reporting Procedures

Those events that will be asked about (solicited) include: delayed onset muscle soreness and pain in the hamstring. Other events that could occur with maximal contraction of the hamstring strength test include fatigue, cramps, spasms, muscle strain, or muscle pain.

Unsolicited events will be captured by query at each visit after enrollment.

Time frames for reporting and collecting AEs are weekly. Reporting of AEs must be to the IRB and OHRE. For SAEs the time frame is daily reporting and capture as soon as possible.

Detection of AEs and SAEs will be the responsibility of each member of the research team at every subject contact. Reporting procedures for unexpected events related to the study intervention will include written documentation of the finding or complaint, which will occur within 5 days for AEs and immediately or as soon as possible for SAEs. The goal of reporting is to inform the PI for a determination of severity, relatedness to the research, and next level of reporting, i.e. IRB, TraCS Institute.

Decisions regarding relatedness and severity will be made by the PI once all available information has been reviewed.

Safety Monitor members will be informed of AEs and SAEs as part of their routine reviews.

Case Report Forms will be used to collect AE and SAE data entered into a secure database.

Reports will be distributed to the PI and Co-I's and Project Manager. These reports will be coded and without identifiers.

7.5: Follow up for Adverse Events

Subjects who have experienced AEs will be followed until resolved or considered stable by the PI. For issues not resolved, a minimum period of follow up is 1 month with contact on a weekly basis by telephone or in person.

7.6: Safety Monitoring

The senior advisors on this study will serve as data and safety monitors and make up the Data and Safety Committee: Dr. Brian Pietrosimone, Dr. Susan Gaylord, and Dr. Mark Weaver. We will record all adverse events and unexpected health problems and review weekly with the study team. Safety monitors will review the adverse events and unexpected health problems after the tenth subject reaches visit 2 in the intervention and every 3 months thereafter.

8. INTERVENTION DISCONTINUATION

Discontinuation of intervention for a participant: Subject may stop their participation for any reason, e.g., the subject is non-compliant with the protocol; subject develops unacceptable side effects; or psychosocial circumstances prevent continuation.

Possible reasons for discontinuation of the whole study: Study closure by NC TraCS; research environment is no longer supportive; multiple Unexpected Problems (UP); insufficient recruitment to answer research hypotheses. If greater than 3 enrolled and randomized subjects develop a grade 3 or greater adverse event due to the intervention, the entire study would be stopped and the safety monitors would reevaluate.

Early discontinuation: Participants will continue to be followed, with their permission, for another 6 weeks if study interventions are discontinued for reasons other than the normal end of the study.

Normal end to the study: Subjects completing the final evaluation will be followed up one week after the final visit by phone call to solicit any possible AEs.

9. STATISTICAL CONSIDERATIONS

9.1: General Design Issues

Primary Outcome

90-90 Knee Extension Angle Test. **KEA** is a functional test designed to assess lower extremity flexibility and is considered the gold standard test for assessing hamstring length (53). Results will be recorded as degrees of knee flexion angle. A clinically significant effect size is an increase of 5 degrees.

Secondary Outcomes

Handheld Dynamometry. HHD is currently considered a reliable and valid measurement of peak muscle contraction. The subject will be prone on the table with right leg bent to 90° and will maximally contract the hamstring muscle for 4-5 seconds against the HHD device. The investigator will record the mean value of three attempts.

Pain Pressure Threshold. PPT is a reliable, accurate and valid method for measuring muscle pain sensitivity and response to treatment(54). In order to determine PPT, the researcher will apply the tip of the algometer to a tender spot in the participant's hamstrings and increase the amount of pressure until the participant verbally informs the researcher when the sensation of pressure became pain. At this point the algometer is removed and the peak force recorded. The mean of three repeated measures will be reported. An increase in PPT signifies an increase in pain tolerance.

Additional Variables

Age, gender, activity level, perceived hamstring tightness, perceived hamstring flexibility and perceived hamstring strength will be assessed at baseline and subsequent follow up visit.

9.2: Sample Size and Randomization

Sample Size and Power: Based on previously published results(55), we would consider a mean increase of 5º on the KEA (e.g., from 135º to 140º) to be clinically meaningful, and we assume a common standard deviation of 15º. We further assume that correlation between repeated measurements from the same individual will be at least 0.75 (likely a conservative assumption). Under these assumptions, enrolling 38 participants would provide at least 80% power using a two-sided test at the 0.05 level. Allowing for up to 10% loss to follow-up, we will enroll 44 participants.

9.3: Definition of Populations

We are defining our intention-to-treat population as all subjects who are randomized. We will retain randomized subjects into the treatment periods to which they were assigned. For a per-protocol analysis (if necessary), we will analyze data from subjects who attend and complete both study visits.

9.4: Interim Analyses and Stopping Rules

We are not planning any pre-specified interim analyses for any reason. The study may be suspended by our PI or the Data and Safety Monitoring Committee (DSMC) if a severe adverse event occurs that is deemed to be secondary to the intervention. The DSMC may also suspend or stop the study or a study arm if reported adverse events are increasing, either across intervention arms or in a particular study arm.

9.5: Outcomes

Outcomes include two functional measures that will be logged into REDCap at the time of the evaluation. The study coordinator will verify complete data entry after each study visit.

9.5.1: Primary Outcome

We define the primary outcome as the change in angle of the KEA test from the time before to the intervention to afterwards.

9.5.2: Secondary Outcomes

We define the secondary outcome as the difference in peak hamstring strength on HHD, and difference in PPT scores between pre and post-intervention time periods.

Subgroup analyses: conduct analyses on the primary outcome stratifying on gender and baseline hamstring subjective tightness, flexibility and strength, number of prior hamstring injuries.

9.6: Data Analyses

To compare mean KEA response between treatment conditions, we will use a linear mixed effect model. The model will include fixed effects for treatment, period, and baseline pre-intervention KEA within each period. The model will include random subject effects to account for correlation between repeated measurements. Given the length of the washout period relative to the treatment period, the primary analysis will assume no carry-over effects and will estimate effect size along with a 95% confidence interval. As a secondary analysis to explore the potential for carry-over, we will include and test a fixed effect for treatment-by-period interaction. If significant carry-over is identified, we will also report comparisons using only the period 1 data. We will use a similar approach to explore intervention effects on HHD and PPT.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1: Data Collection Forms: Data Type & Personnel Collecting Data

Principal Investigator—Nicholas Wise

Co-Investigator- Jacob Hill
Research Assistants—TBD

Data Collection and Contacts with Subjects.

Paper records collected at study visits will be entered into the REDCap database, a secure online research database system. Paper source documents will be locked in a file cabinet under the control of the full-time Study Coordinator.

10.2: Data Management

All data will be collected at the University of North Carolina at Chapel Hill. Online questionnaires will be completed by subjects during study visits. Data collection forms are listed in Table 5 and are attached to this document in appendices.

The research assistant or investigator will verify questionnaire completion after each study visit; data will be input by research assistants. Source documents are identified by a Study Identification (ID). Investigator will compile a data completion report every other month to be reviewed at study meetings.

10.3: Quality Assurance

10.3.1: Training

Current HIPAA and CITI Human Ethics training certificates or their equivalents are required of all study personnel who will be collecting, entering or managing data.

Before participant data is collected, the PI or Project Manager will ensure that staff has completed

training for applicable tasks. A log including dates and type of training will be kept in the Study Regulatory Binder.

The Study Manual of Operating Procedures (MOP) will include detailed procedures for each of the following:

1. Consent forms
2. Functional assessment tests (KEA, HHD, PPT)

REDcap will be used to track recruitment data, questionnaires, and initial and post-intervention evaluations.

The PI will train staff in data entry procedures and report generating options in REDcap database as outlined in the Study MOP.

10.3.2: Quality Control Committee

Quality control will be an agenda item of the research meeting which will include the PI, Research Assistants, and Co-Is as available.

Data will be presented in the meeting from information gathered as described in section 10.3.3 below.

10.3.3: Metrics

Outcome Measures:

Questionnaires designed to be completed on paper (Expectation of Benefit / Credibility survey) will be collected and entered into the REDCap database by a research assistant. The research assistants, under supervision of the PI, will also enter study visit data, including KEA, HHD and PPT scores. The research assistant who will be responsible for data entry will not have contact with enrolled study participants. Double data entry for all paper-based outcome measures will be performed. Corrections will be made using source documents. If a greater than 1% discrepancy in data is found, then additional training will take place.

10.3.4: Protocol Deviations

Staff will be trained to record any protocol deviation that may occur while performing their specific research related activities. Many of the data collection forms include comment sections where protocol deviation information will be captured on the source documents. Deviations will also be documented in REDcap. Training of the research staff will include practices of double checking all demographics, inclusion/exclusion criteria, data collection procedures including capture and secure storage, intervention procedures and data management activities.

Deviations will be documented as a written report submitted to the UNC IRB by the PI or Project Manager or Study Coordinator within 2 weeks. If warranted, corrective action plans will be

developed and submitted to the IRB as part of that reporting process.

10.3.5: Monitoring

Outside monitoring of the study is not required. However, the Regulatory binder will be maintained as if study monitoring were to take place.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1: Institutional Review Board (IRB) Review

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB and the Scientific Review Committee responsible for oversight of research at UNC. The IRB application, modification, and renewal procedures will be adhered to throughout the study.

11.2: Informed Consent Forms

A signed consent form will be obtained from each participant.

The consent form will describe the purpose of the study, the procedures to be followed, reasons not to be in the study, risks and benefits of participation, responsibilities of the participant, incentives and remunerations, privacy and confidentiality measures, and names and contact information for the PI and the study staff.

Procedures for obtaining and documenting informed consent: Interested persons meeting screening criteria of age, inclusion / exclusion will be given a copy of the informed consent form (ICF) in the presence of the Study Coordinator or their designee, who will then read the consent orally with the potential subject (PS), indicating important points in each section and answering any questions at that time. The PS will be given time to re-read any or all of the form, and they may take it home for further review if they so desire for signing at a later time. If they have their questions answered and are willing to participate, the informed consent will be signed at the time of the meeting by the PS and research team member obtaining the consent. The PS is considered to be a subject in the study (enrolled) at the time of the signing. A copy of the IFC will be given to each participant.

Those below age 18, pregnant women, prisoners, and those requiring a legally authorized representative are excluded from participation.

11.3: Participant Confidentiality

Participant confidentiality will be maintained according to the Health Insurance Portability and Accountability Act (HIPAA).

Any data, forms, reports, and other records that leave the site will be identified only by a participant

identification number (Participant ID, PID) to maintain confidentiality.

All records will be kept in a locked file cabinet in Medical School Wing D. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, and the OHRP.

Research records arising from this study will be retained at a secure UNC-maintained locked site for 5 years with access limited to the PI and named designees.

11.4: Study Discontinuation Understanding

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Data and Safety Monitoring Committee. No other committees.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by NC TraCS prior to submission. Publication Committee formation will be contingent on successful data collection.

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15. SUPPLEMENTS/APPENDICES

Appendices List

A. Consent Form

B. Data Collection Forms

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Appendix A: Consent Form

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

Consent Form Version Date: 10/8/2016
IRB Study # 16-0898
Title of Study: The effects of Cranial Laser Reflex Technique on hamstring strength and flexibility: a pilot study
Principal Investigator: Nicholas Wise, D.C.
Principal Investigator Department: Physical Medicine and Rehabilitation
Principal Investigator Phone number: 919-642-3838
Principal Investigator Email Address: nicholas_wise@med.unc.edu
Faculty Advisor: Brian Pietrosimone, Ph.D.
Faculty Advisor Contact Information: 919-962-3617

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 refuse to join, or you may withdraw your consent to be in the study, for any reason, at any time, 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 healthcare 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 your participation 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?

The purpose of this research study is to examine the effects of Cranial Laser Reflex Technique (CLRT), a proposed treatment for musculoskeletal conditions, on hamstring strength and flexibility. Having tight hamstrings is a known risk factor for low back pain and can lead to many types of sports injuries. This is the first study to test the effects of CLRT on hamstring muscle properties.

CLRT is analogous to laser acupuncture, which is an established treatment/technique that uses non-invasive low-level laser therapy (LLLT) to stimulate specific points from Traditional Chinese Medicine. CLRT uses LLLT on cranial reflexes discovered by U.S. chiropractors that correspond to major muscles/muscle groups and specific vertebrae. While many cranial reflexes are singular points, some (like the hamstrings) are lines. This study specifically investigates the effects of low-level laser stimulation along the hamstring cranial reflex on the flexibility, strength, and pain pressure threshold of the hamstring muscle.

Appendix A (cont.): Consent Form

Healthy adults between the ages of 18 and 35 meet the criteria for inclusion in this study.

Are there any reasons you should not be in this study?
You should not be in this study if you have a current lower back condition with pain, numbness, or tingling in your legs; if you have a history of skin cancer or malignancy on the top of your head (a possible contraindication for light therapy); or if you are pregnant or plan to become pregnant during the course of the study.

How many people will take part in this study?
There will be approximately 44 participants in this research study.

How long will your part in this study last?
If you choose to participate in this study, you will be asked to attend two sessions, one week apart. The first session will last approximately one hour. The second session will last approximately 30 minutes. The total time commitment for participation in this study is approximately 90 minutes.

What will happen if you take part in the study?

This is a randomized crossover trial over two sessions. In the first session, you will be assigned by chance to either the real or the sham CLRT group. Neither you nor the researcher performing the functional tests will know which group you are in. In the second visit, you will automatically be assigned to the other group.

In the first session, you will be asked to complete a questionnaire, then perform three tests that assess hamstring function. You will perform each test with your dominant leg 3 times to ensure accurate measurement. The first test is to determine how flexible your hamstrings are. In this test, you will lie on your back, flex your hip to 90°, and the assessor will measure how straight your leg can get. In the second test, for hamstring strength, you will lie face down, bend your knee to 90°, and contract your hamstring as hard as you can against a measuring device. The third test is to see how sensitive your muscle is. In this test, a device that measures force will be slowly pushed into your hamstring muscle until you indicate that the sensation of pressure turns to pain.

After the pre-testing, you will receive either the real or sham CLRT, depending on your randomized assignment. The treating investigator will locate one end of the hamstring reflex point near the crown of your head, place a light therapy device (real or sham) to the point, turn on the device, then move it 2 inches toward the center of your head in a linear fashion, following the hamstring reflex line. This will be repeated briskly 30 times, with each pass lasting one second, for a total of 30 seconds on each side. You will then repeat the hamstring tests three times. The treatment process for both groups will be identical, though the device in the sham laser group will be non-operational.

In the second session one week later, you will again be asked to fill out a questionnaire, and perform the hamstring tests again. Then, you will receive either the real or sham CLRT (as before), in the opposite group assigned in the first session. If you were assigned to the Real CLRT in Week 1, you will be assigned to the Sham CLRT in Week 2, and vice versa.

Appendix A (cont.): Consent Form

**Questionnaires*: You will be asked to fill out a brief questionnaire about your activity level, history of musculoskeletal injuries and perceived hamstring tightness. This should take approximately 10 minutes. You may choose not to answer any question for any reason.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. Besides a possible temporary change in hamstring flexibility, you will not personally benefit from participating in this research study.

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

Although we do not anticipate any, there may be uncommon or previously unknown risks. You should report any problems to the researcher immediately. LLLT devices used for the purposes of photobiomodulation or acupuncture are designated by the FDA as "non-significant risk" devices, therefore deemed exceedingly safe. After almost five decades of research, LLLT has been shown to be effective for pain relief and wound healing with no known side effects.

No known serious side effects from CLRT have occurred through 10 years of clinical experience, and none are expected. Rare minor reactions could include: delayed onset muscle soreness.

Muscle cramps may rarely occur during the maximal contraction of the strength test. In very rare cases, a muscle strain may occur.

Due to the intensity of the laser light, you will wear proper eye protection while lasers are in use. These glasses block out the specific wavelength and protect your eyes from any stray laser light.

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. Your personal information will be secured in a password-protected hard drive accessible only to research staff. All personal information will be kept separate and secure from your research data.

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

Appendix A (cont.): Consent Form

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, you 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 receiving an Amazon gift card worth $25 at the conclusion of the second visit for participating in this study.

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.

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, at any time. 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.

Appendix A (cont.): Consent Form

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	Signature of Research Team Member Obtaining Consent
Printed Name of Research Participant	Printed Name of Research Team Member Obtaining Consent
Date	Date

Appendix B(a): IPAQ (version 1.0)

Subject Number _____ Date_____

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Appendix B(a) cont.: IPAQ (version 1.0)

Subject Number _____ Date_____

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix B(b): Hamstring History (version 1.0)

Subject ID: _____ Date: _____

Hamstring History Form

CLRT Hamstring Study

Please circle YES or NO in response to the following questions:

YES	NO	Have you had an injury to either leg that has altered your function in the past 6 months?
YES	NO	Have you ever had a surgery to either leg (hamstring, knee, ankle, hip)?
YES	NO	Do you have any disc or nerve injuries in your legs or lower back?
YES	NO	Do you have any known muscular abnormalities?
YES	NO	Do you have a heart condition that would stop you from exercising?

The following questions ask about previous injuries to your LEFT and RIGHT hamstring muscles:

Number of previous acute strains in your **LEFT SIDE HAMSTRINGS**: _____

If you answered "0" above, skip the next 3 questions regarding the left hamstring and continue at the next section.

Please circle the best answer to each question (LEFT side only):

How long ago was your most recent LEFT hamstring injury?	0-6 mo.	6-12 mo.	1-2 yr.	> 2 yr.
How long did it affect your ability to perform your normal activities?	1-3 days	4-7 days	1-4 wk.	> 4 wk.
How much has it affected your activities of daily living?	Not at all	A little	Somewhat	A lot

Number of previous acute strains in your **RIGHT SIDE HAMSTRINGS**: _____

If you answered "0" above, skip the next 3 questions regarding the right hamstring and continue at the next section.

Please circle the best answer to each question (RIGHT side only):

How long ago was your most recent RIGHT hamstring injury?	0-6 mo.	6-12 mo.	1-2 yr.	> 2 yr.
How long did it affect your ability to perform your normal activities?	1-3 days	4-7 days	1-4 wk.	> 4 wk.
How much has it affected your activities of daily living?	Not at all	A little	Somewhat	A lot

Please rate the following based on the scale below, ON AVERAGE:

How tight would you say your hamstrings are?	Not at all	A little	Somewhat	Very	Extremely
How strong would you say your hamstrings are?	Not at all	A little	Somewhat	Very	Extremely
How much does hamstring pain/soreness affect you?	Not at all	A little	Somewhat	Very	Extremely

Appendix B.c: De-blinding Questionnaire (Ver. 0.1)

ID #_____ Date: _____

CLRT Hamstring Study
De-blinding Questionnaire

1. Do you believe you received the active treatment (CLRT) today?

   ○ Yes ○ No

2. How certain are you that you received the active treatment today?

Not at all certain				Somewhat certain						Absolutely certain
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

Appendix C.a: Adverse Event Form (version 1.0)

Adverse Event Form

Cranial Laser Reflex Technique for Hamstring Flexibility, Strength and Pain

Pilot trial supported by NC TraCS and NCCIH

Site Name: University of North Carolina-Chapel Hill, Program on Integrative Medicine, Dept. of Physical Medicine and Rehabilitation

Subject 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)

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

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

_____ _____

Signature /Print name Date

Appendix C.b: Serious Adverse Event Form (version 1.0)

Serious Adverse Event (SAE)
Report Form

Nutrition for Migraine Prevention

Protocol Number:_____

Site Number:_____

Pt ID:_____

Visit Date:

__ __/__ __ __/__ __ __ __
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):_____

Appendix C.b (cont.): Serious Adverse Event Form (version 1.0)

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 C.c : Modified Borkovec and Nau Expectation of Benefit/ Credibility Form (version 1.0)

ID: _____ Date_____

Expectation of Benefit / Credibility

INSTRUCTIONS

You have been given details about the treatments you are learning in this study. We are interested in obtaining your impressions about and reactions to the procedures presented to you thus far. Please answer the questions below by first finding the number on the scale that most accurately describes your impressions and then by filling in the oval that corresponds with that number.

1. How logical does this type of intervention seem to you for improving muscle function?

Not logical									Very logical
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

2. How confident are you that this intervention will be successful in improving muscle function?

Not at all confident									Very confident
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

3. How confident would you be in recommending this intervention to a friend who has a problem with their hamstrings?

Not at all confident									Very confident
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

4. How important do you think it is that we make this intervention available to others who experience muscle problems?

Not at all important									Very important
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O