IRB-1 Study Protocol & Statistical Analysis

Title: Physical Activity Interventions To Heal Chronic Low Back Pain
NCT Number: NCT04678297
Document Date: 5/8/2020

Protocol Version # and/or Date: [The protocol version must be revised each time a modification is submitted to the IRB to change the protocol.]
5/8/20

Study Protocol Title for IRB: The Role of Emotion Regulation on Low Back Pain Outcomes

Clinical Trial/GCP Training

Is this a research study in which one or more human subjects are prospectively assigned[1] to one or more biomedical or behavioral interventions[2] (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes[3] (i.e a clinical trial)? Indicate "yes," "no," or "N/A" in the space immediately below.

Yes

Is the study fully or partially funded by the NIH? Indicate "yes," "no," or "N/A" in the space immediately below.

Yes

Have the required key personnel completed Good Clinical Practice (GCP) Training? Indicate "yes," "no," or "N/A" in the space immediately below. (Note that IRB approval will not be given for NIH funded clinical trials until all required key personnel complete the GCP training.)

Yes

Research Plan

Purpose/Introduction: [State the reason for the study, the research hypothesis, and the goals of the proposed study as related to the research question(s). Provide a clear and succinct summary description of the background information that led to the plan for this project. Provide references as appropriate and, when applicable, previous work in animal and/or human studies. Provide previous UConn protocol number, if applicable.]

[1]The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
[2]An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive/behavioral therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.
[3] 3.Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention, behavioral intervention for psychiatric symptoms); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

Back pain is a highly prevalent and poorly managed health problem in the U.S. Chronic low back pain (CLBP) is the most prevalent chronic pain condition, afflicting up to 10% of adults at any given time and 70% of all people during their lifetime (Hartvigsen et al., 2018). In addition to the pain itself, individuals with CLBP are at risk for increased disability, depression, anxiety, and reduced quality of life (Kim et al., 2015; Raby et al., 2016).

More effective treatments for CLBP are desperately needed. Treatment recommendations for CLBP are directed by causal factors (Chou et al., 2017), even though most cases (85%) are not linked to a specific pathology (Foster et al., 2018). When CLBP does not respond to medication or self-care, non-pharmacological treatments are recommended and widely used, despite a lack of empirical evidence and considerable variability in efficacy across individuals (Crawford et al., 2014a, b; Hu et al., 2015). Because patient satisfaction with conventional CLBP treatment is relatively low and most patients report only modest relief (Sanderson et al., 2012; Stewart et al., 2015), research to identify more helpful and acceptable therapies is urgently needed.

Yoga is a widely-used integrative modality for CLPB with demonstrated but modest efficacy. A growing number of high-quality randomized clinical trials (RCTs) (e.g., Highland et al., 2018; Saper et al., 2013, 2017; Bramberg et al., 2017) support yoga's effectiveness for reducing pain and improving function in adults with CLBP. Although some reviews have been hesitant to conclude yoga is an effective treatment for CLBP, most reviews, meta-analyses (Chang et al., 2018; Wieland et al., 2017) and practice guidelines (Chou et al., 2017) support yoga as an evidence-based treatment for CLBP. Yoga generally produces effects roughly equivalent to other well-established treatments like PT and provides an additional treatment option to those with CLBP, which is especially important when many have tried existing treatment options, are being taken off of opiate pain medications, and are in search for other options.

Yoga's mechanisms of action (MOAs) remain poorly understood, but a better understanding can lead to development of more effective and targeted yoga treatment. Because most research on yoga has focused on determining preliminary efficacy or effectiveness, the MOAs by which it exerts clinical improvement on pain remain unknown. Typically, yoga interventions for CLBP use protocols of standard yoga postures, such as those used in this proposal, that seem well-suited to improve functioning and decrease pain through stretching/strengthening, although there is much variation in emphasis on other potentially helpful aspects such as meditation and relaxation. Compared to stretching/strengthening exercise conditions, these studies suggest that the other aspects of yoga (e.g., meditation, breathwork, spirituality) contribute above and beyond stretching/strengthening, adding additional value to the intervention (e.g., Sherman, 2011; Saper et al., 2017). However, studies have not tested *how* yoga as a more integrative mind-body intervention helps people better manage their pain. Only one team of investigators has attempted to examine potential mediators in an RCT of yoga's effects on these outcomes, but lacked a strong theoretical basis for selecting the MOAs tested: A 12-week RCT examined effects of yoga v. intensive stretching v. a self-help book and identified self-efficacy, hours of practice, and sleep quality as mediators of improved function in the yoga group (Sherman et al., 2013), but these assessed mechanisms accounted for only a small portion of the variance in improvement observed in the yoga group (ER was not measured). Variations in the extent to which key mechanisms such as ER are emphasized in the intervention (Park et al., 2017) may account for the generally favorable but mixed effect sizes shown across different yoga interventions for CLBP and other pain conditions (Wieland et al., 2017).

Understanding Yoga's MOAs is Key to Facilitating Optimization and Dissemination. This lack of knowledge regarding *how* yoga reduces pain means interventionists cannot explicitly optimize current yoga interventions to reduce pain based on empirically based MOAs because those MOAs have yet to be identified. Identifying the pathways (such as ER) through which yoga exerts effects on pain can usefully

inform development of interventions that are specifically designed to enhance yoga's effects on the targeted mechanisms, thus improving its effectiveness. For example, if ER, the focus of the present study, is found to be a key driver of reduced pain and improved functioning, dimensions of yoga shown to be particularly helpful in improving ER should be integrated into future interventions.

For EACH Participant Population State the Number of Participants to be Enrolled and Screened and/or the number of participant records reviewed (including, HIPAA covered health records and FERPA covered school records), if applicable: [State the total number of participants/records to be enrolled and, if enrolling more than one participant population, describe the total enrollment for each. Tip: consider attrition and the number of participants who may fail screening. Use of a range may provide flexibility. Note that the range must be justified in the **Justification of Sample Size section below**.]

Study staff will conduct initial screening, and eligible volunteers will be scheduled for a screening exam and data collection visit. Based on study screenings, we will enroll 204 men and women over age 18 diagnosed with nonspecific CLBP. We anticipate conducting approximately 250-500 screening visits to meet this enrollment target.

Justification of Sample Size: [For qualitative and pilot studies, describe how the proposed sample size is appropriate for achieving the anticipated results. For quantitative studies, provide a power analysis that includes effect size, power and level of significance with references for how the sample size was determined. Explain the rate of attrition and possible number who fail the screening, with references as appropriate.]

Our **primary aim** is to demonstrate that the yoga intervention group will achieve superior mean ER (DERS scores) at 6-wks and subsequent time points compared to the stretching/strengthening control group. We estimated power in efforts of detecting a meaningfully sized *t*-statistic between two independent groups for ER at 12-wks. Since literature is generally sparse, prior effect sizes for the present calculation were drawn from studies, which (a) tested ER as an outcome of a yoga-based intervention or (b) tested ER as an outcome of an emotion regulation-based intervention. Based on previous literature, we anticipated a moderate effect size of d= 0.50. Power and alpha were set at 80% and 0.05, respectively.

The estimated mean change in DERS scores, our primary outcome measure, for an effect size of d = 0.50 would be -8.5 ± 1.6 points (-5.9% ± 1.1%; Mennin et al., 2015; Broderick & Metz, 2009; Gratz et al., 2014; Goodman et al., 2014; Niedtfeld et al., 2017; Fox et al., 2007; Harrison et al., 2009; Havinghurst et al., 2009; Keuthen et al., 2012). Imputing parameters into GPower to detect a change of this magnitude, a sample size of 104 will be needed at the 6-wk time-point. To account for a predicted 20% attrition rate at 12-wks, 3- and 6-month follow-up, an additional 26, 33, and 41 participants will be needed, respectively (n's=130, 163, and 204, respectively). Thus, a final baseline sample size of 204 will be needed to power our primary aim.

In consideration of our secondary aims, we also powered detection of paths a and b within pain severity/interference mediation models. This was done using simulation in R (N = 5000). Following simulation methods (N = 5000) presented in Fritz & MacKinnon (2007), sample size was determined by increasing simulation sample size until 90% of simulations significantly detected both paths a and b with estimated effect size magnitudes of d = 0.39 (path a) and d = 0.26 (path b) at alpha = .05. A proposed sample size of 116 was calculated, which was already reached when powering our primary aim.
Enrollment of UConn Students and/or Employees: [Will UConn students be enrolled? If so, describe if these students include those who any key research personnel teaches, or for whom any key research personnel has responsibility. Will UConn employees be enrolled? If so, describe if these employees

report to any key personnel. For each group, explain why this population is *necessary* to the study. Tip: convenience is not sufficient justification.]

We do not plan to specifically recruit UConn students or employees. If any individuals who happen to be students, faculty, or staff members at UConn wish to be screened for the study, we will take great care to remind these individuals that all responses will be kept confidential and their participation will not impact their employment or education status.

Enrollment of Key Personnel, Spouses or Dependents/Relatives: Will study key personnel, spouses of key personnel, or dependents/relatives of any key personnel be enrolled in the study? If so, describe and provide justification.

No, we do not plan to enroll relatives, spouses, or dependents of study personnel.

For EACH Participant Population Describe Screening Procedures, if applicable: [Describe when participants will be screened and how this will occur. Include copies of all screening forms and related documents. Describe procedures to notify participants of the screening result, if applicable. Provide a copy of the screening instrument.]

We will recruit participants using multiple diverse methods, utilizing resources through the University of Connecticut's Center for Advancement in Management Pain (CAMP), Institute for Collaboration, Health Intervention and Policy (INCHIP), the Musculoskeletal Institute, UConn's Urgent Care Center, Emergency Department and Primary Care Centers, Hartford Healthcare's Bone & Joint Institute, and Connecticut Children's Medical Center (CCMC), the Connecticut Convergence Institute, UConn's Center for Aging, and other affiliated centers.

We plan to advertise via social media (e.g., Instagram, Twitter, Facebook), web-based advertisements, listservs, emailing, and paper flyering at local outpatient clinics. We will also rely on word-of-mouth referrals from colleagues at local partner institutions. Dr. Starkweather currently oversees other studies that screen individuals experiencing chronic pain, and will coordinate referrals for people interested in the current trial as indicated. To ensure a diverse sample of participants, we will also target recruitment at minority community agencies and events, as well as local agencies serving women.

Recruitment staff will meet with participants to obtain informed consent before the screening exam to ensure they meet study inclusion/ exclusion criteria and can participate safely. Screening, performed by a trained RA under Dr. Starkweather's supervision, includes a brief interview and a physical examination. Inclusion/ exclusion criteria will be assessed by self-report during the screening interview and physical exam (see detailed criteria below).

Patients who have recently changed any professionally-delivered pain treatment (e.g., medications, chiropractic) are not eligible until their treatment has been stable for 30 days. Participants will be asked to keep all pain treatments stable during the 12-week intervention and to take their lowest usual dose of pain medications within 24 hours of each assessment.

Anticipated Study Time Frame: [Describe the estimated time frame of the study from anticipated start to anticipated finish. If the study will occur in more than phase include these in the time frame. Use of a table is often helpful.]

Both the yoga and stretching intervention groups will meet approximately twice weekly for 12 weeks, 1.25 hours per session; depending on scheduling, some minor adjustments may be made (e.g., due to snow days, holidays). Post-intervention follow-ups will be scheduled approximately one week after

program end. Participants will also be invited back to complete post-12-week (3 month) and post-24-week (6 month) follow-up assessments. Depending on the timing of participants' initial assessment of eligibility (within 3 weeks of intervention start), involvement with the study protocol may last between approximately 9-10 months.

Design, Procedures, Materials and Methods: [Describe the study design, including the sequence of all study procedures. Experimental procedures should be clearly described and labeled as such. If the study uses control or experimental groups, or different treatment arms, clearly describe what participation will be like for each of the groups or study arms. Tip: describe procedures in the order conducted, where they will be conducted and how long they will take to complete. The IRB strongly suggests that investigators incorporate *flexibility* into the study design to accommodate anticipated events (i.e. explain how missed study appointments can be made up by participants). If this study offers treatment for the participants' condition, complete the Treatment Study Supplemental Form (IRB-1C) and attach it to this application for review. Use of a table is often helpful here.

> [Describe study procedures for use of interviews or focus groups if applicable. Include details such as how long each procedure will take to complete, who will be asked to participate in these procedures and where these procedures will be conducted. Provide copies of interview and focus group questions/topic areas.]

All study procedures will be completed in laboratory space at UConn-Storrs and at UConn Health in Farmington. Depending on scheduling requirements, we expect holding classes on the Storrs campus in the Hawley Armory or on the 3rd floor of Arjona (in collaboration with CMHS) and at the UConn Health campus at either the UConn Health Wellness Center or the UConn Health Center of Aging. After a brief phone screening (see attached script), recruitment staff will meet with participants to obtain informed consent before the screening exam to ensure they meet study inclusion/ exclusion criteria and can participate safely. Screening, performed by a trained RA under Dr. Starkweather's supervision, includes a brief interview and a physical examination. Inclusion/ exclusion criteria will be assessed by self-report during the screening interview and physical exam. Participants will not receive any test results produced by the study (including genetic testing), as results are not intended to be diagnostic. During the initial scheduling call for baseline assessments, participants will be asked whether they have a gender preference for the personnel performing sensory testing. Participants' requests for same-gender assessors will be honored.

Eligible participants will be added to a cohort list, with baseline assessments scheduled approximately one month before the start of the treatment protocol including questionnaires, behavioral assessment of ER, and blood draws. Venous blood samples (15 ml) will be collected in one 10-ml PAXgene vacutainer and one 5-ml EDTA vacutainer by a research team member experienced in venipuncture, immediately placed in a biohazard container and transported to the laboratory (adjacent to the Outpatient Pavilion) where they will be processed and stored in a -80ºC freezer for bulk processing of genetic and protein measures. Physiological and quantitative sensory measurements will be conducted by a trained RA. Investigators collecting and analyzing pain sensitivity measures will be blinded to participants' assignment. Post-intervention assessments will be scheduled at least one week after the end of the yoga intervention to avoid capitalizing on immediate post-session changes. We anticipate that each assessment will take approximately one hour or less.

Participants will be asked to keep all pain treatments stable during the approximately 12-week intervention and will be reminded to take their lowest, doctor prescribed dose of pain medications within 24 hours of each assessment.

After baseline assessment, participants will be randomized to either a yoga or stretching/strengthening group using a stratified randomization scheme based on biological sex to ensure balance between groups. We will conduct the interventions with between 4-8 cohorts of patients (up to 34 per cohort, until recruitment target is met), simultaneously running a stretching and a yoga group of approximately equal size.

For both intervention groups, the importance of attending all sessions is stressed during session 1 and throughout all subsequent sessions. Participants who miss a session without notifying the instructor will be contacted to check on the reason for non-attendance and to encourage resuming participation as soon as possible. Participants are encouraged to consult with the instructor individually before or after class about problems or difficulties they are encountering at home or in the formal session. Participants will be asked to practice every day for approximately 20 minutes to maximize the benefit of the intervention. They are encouraged to not push themselves as much when practicing at home and to stop when pain or discomfort becomes noticeable.

Details regarding the yoga and stretching interventions are below:

Yoga. This intervention will be led by certified 500-hour RYTs (Registered Yoga Teachers) trained in working with back pain patients. We will utilize a CLBP protocol developed by Dr. Erik Groessl (Groessl et al., 2016), which relies on classical hatha yoga with influences from vinyasa and Iyengar yoga. These yoga styles are widely used in clinical settings and community yoga and emphasize modifications and adaptations including the use of props such as straps and blocks to minimize the risk of injury and make the poses accessible to people with health problems and limitations (Ruiz-Aranda et al., 2009). The instructor leads participants through a series of 23 yoga poses (32 total variations) at a slow-moderate pace. The manual developed to standardize the yoga intervention contains pictures and a description of how to perform each pose with typical instructor dialogue, which may be paraphrased and varied slightly, yet promotes more consistent replication and generalization of results. The intervention includes some poses that could aggravate back conditions if they are not modified for some people, so multiple modifications are suggested and many poses are only worked up to after weeks of practice and individual attention from the instructor. The more challenging poses are never included in the home practice. Participants receive a home practice manual containing some basic, safe postures that can be performed on days they are not attending the formal in-person sessions.

During the formal sessions, participants are instructed to take slow, deep breaths in conjunction with specific phases of poses. Participants are encouraged to emulate optimal alignment as demonstrated by the instructor and to focus on a goal or positive direction for their yoga practice. Yoga classes are constructed to allow optimal flow from one pose to another. Each session begins with a few minutes of deep breathing and mindfulness/meditation followed by about 15 minutes of basic postures (Poses 1-8) to warm up muscles by increasing circulation to provide increasing flexibility as the class progresses. Most poses are conducted once per side or with the opposite foot leading. After warm up, the instructor leads students through a series of standing poses (Poses 9-14) for about 15 minutes. After the standing poses, the class moves into floor poses (Poses 15-22) for about 20 minutes. Sessions end with 5-7 minutes of complete relaxation in the standard ending pose “savasana,” during which additional positive affirmations are provided.

Stretching/strengthening Control intervention. This intervention will be led by a physical therapy graduate student in their final year of study (TBN), upon recommendation from UConn faculty member Dr. Maryclaire Capetta. This intervention is designed to require a similar amount of physical exertion (stretching and strengthening exercises only, with no extreme movement). Classes involve conventional exercises appropriate for patients with CLBP, including a comprehensive set of exercises that stretch all the major muscle groups, with an emphasis on the trunk and legs. The intervention will include all 12

stretching exercises used in the exercise intervention of previous studies that have successfully used it in comparison to yoga (Sherman et al., 2005, 2011) (i.e., gastrocnemius, soleus, quadriceps, posterior and inferior shoulder, upper trapezius, hip flexor, back extension, back rotation, hamstrings, hip external rotators, back flexion), plus 3 additional stretches (hip internal rotators, hip adductors and hip flexion). Each stretch will be held for approximately 60 seconds and repeated once. In addition to a complete set of full-body stretches, the class will begin with a five minute warm-up period consisting of basic aerobics steps (i.e., 1 minute each of walking in place, marching, lateral shuffling, turning and reaching, and box step) and will also include four exercises that strengthen the back, abdomen and hips (i.e., squats, crunches, oblique crunches, back extensions) (Sherman et al., 2005, 2011). Over the 12 weeks, the repetitions of each strength exercise are increased from 8 to 30. Specific strength exercises are practiced in separate sets of 5 to 10 repetitions. Printed handouts will be provided to facilitate home practice. In addition, a video demonstrating all the exercises will be provided to assist participants in practicing safely. Classes will be led by a licensed physical therapist who has previous experience leading exercise classes (per Sherman, 2010).

> [If the study includes *measures, survey instruments and questionnaires (including the collection of demographic data)*, identify each and, if available, provide references for the measures. Describe what they intend to measure (relate to purpose/hypothesis) and their psychometric properties (e.g., reliability and validity). Identify any that were specifically created for the study and attach a copy for IRB review.]

Demographics A brief questionnaire will assess demographics (age, gender, race/ethnicity, education, and employment status) and medical/psychiatric history (comorbidities, medication usage, ongoing treatments). Alternate contact person and multiple modes of contact information will be requested. A list of demographic items that we intend to use for this study is attached to this protocol at the start of the "Appendix of Measures" attachment.

Emotion Regulation Our primary measure of ER ability is the Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004). The DERS is the gold standard self-report measure of individuals' abilities to respond to emotional experience in a goal-oriented manner. The 36 item DERS taps aspects of *difficulties with emotion regulation*, which we anticipate will *lessen* with yoga practice. Participants rate the extent to which each of 36 statements currently applies to them (e.g., "When I'm upset, I have difficulty getting work done." "When I'm upset, I believe that I will remain that way for a long time.") from "almost never" to "almost always." The measure yields a total score comprising summed subscales of Nonacceptance of emotional responses, Difficulties engaging in goal directed behavior, Impulse control difficulties, Lack of emotional awareness, Limited access to emotion regulation strategies, and Lack of emotional clarity. The DERS is sensitive to change over time in emotion regulation and internal consistency reliability is high (Gratz & Roemer, 2004).

We also include a behavioral laboratory-based assessment of ER as a secondary measure. Relative to self-reported ER, lab-based assessments are considered most useful in measuring individual differences in emotional attention, reactivity and appraisal, and although seldom used in the context of chronic pain, may provide understanding of individual differences in the ability to inhibit negative emotion and purposefully shift attention to more positive aspects of daily life. The Negative Affective Priming Task (Joormann & Gotlib, 2010) will be used to capture this aspect of adaptive ER abilities. Participants are exposed to neutral and affective words with a strong positive and negative valence in consecutive paired trials, one word serving as the "target" and the other as a "distractor." Participants are instructed to ignore the distractor and to attend to the target in both control and negative priming conditions, with "inhibition ability" operationalized as a difference score between response latencies in control and negative priming conditions. The stronger one's inhibition abilities, the longer the latency in the negative priming condition compared to the control condition (scored in milliseconds). Individuals with chronic depression and

greater tendency to engage in maladaptive rumination demonstrate reduced ability to inhibit negative, as opposed to neutral, words with no difference in ability to inhibit positive words (Joormann & Gotlib, 2010; Joormann et al., 2006).

Pain Sensitivity: Peripheral and central sensitivity. We will use a comprehensive QST battery of mechanical and thermal stimuli (Rolke et al., 2006): 1) cutaneous mechanical pain sensitivity, involving measures of tolerance, threshold, temporal summation, and after sensations; 2) heat and cold pain sensitivity, involving threshold, tolerance, ratings of supra-threshold stimuli; and 3) pressure pain thresholds. Equipment used to in the QST battery will match those used by the German Neuropathic Pain Network (Rolke et al., 2006). An advantage of QST is that it assesses inadequate function (hypoalgesia) as well as gain of function (hyperalgesia). Results are evaluated using age- and gender-matched reference data. Inter-rater reliability of the QST protocol has been reported in several clinical trials, with each individual test achieving a CI of .87-.94 (Frey et al., 2008; Siegenthaler et al., 2010).

The Medoc Pathway and Neurometer tools used for the QST battery are in Arjona 123, stored on a flat surface tabletop. The participant is asked to sit in a comfortable chair next to the table, close enough to comfortably apply the thermodes/electrodes to the skin surface of the arm and back. Electrodes are single-use and do not require cleaning.

Only trained research personnel will operate the QST devices. To ensure compliance, we will maintain a regularly-updated log in the study file that lists who was trained, the person conducting the training and the device(s) this person can operate.

The specifics of each test included in the QST battery are provided below. Please note that all applicable safety requirements described in the Medoc Pathway and Neurometer manuals will be adhered to during the experiment.

1. *Current Perception Threshold* - The CPT is measured using a Neurometer to assess the function of the peripheral sensory nerves. The Neurometer delivers electrical current at three frequencies to stimulate each of the three sensory fiber types independently (2000 Hz = Aβ, 250 Hz = Aδ, 5 Hz = C). This test will be conducted using single-use stimulus electrodes and ground electrodes placed on the skin. A series of stimuli with gradually increasing current are delivered at each frequency starting with 2000 Hz. Participants will press a button as soon as a sensation is felt. The amount of current (mA) being delivered at the time of the button press is recorded as the CPT.

   To ensure safety during the CPT, study staff will place electrodes on only one extremity and never on the torso or two separate extremities. Please note that electrode placement at the site of visible skin/mucosal lesions is contraindicated and these areas will be avoided. Further, use of a Neurometer is contraindicated for individuals with implanted electrical devices and thus these individuals will be excluded from testing.

2. *Thermal Detection and Pain Thresholds:* This test will be conducted using a thermode attached to a Medoc Pathway instrument, which will be applied to the skin. The thermal detection threshold test will consist of three cool and three warm stimuli being delivered. Participants will press a button to stop the stimulus as soon as they feel the temperature of the thermode change to become cool or warm. The temperature of the thermode when the button is pressed will be recorded as the cool and warm detection thresholds. The thermal pain threshold test will consist of three cold and three hot stimuli being delivered. For this test, participants will press a button to stop the stimulus when the temperature of the thermode becomes painfully cold or hot. The temperature of the thermode when the button is pressed will be recorded as the thermal pain thresholds.

To ensure safety, test subjects will be trained to use the panic button before beginning any test with the Pathway system. Test subjects will be instructed to hold the Pathway panic button throughout the entire duration of the test and the Pathway system will never be used when the panic button is disconnected.

To further reduce the risk of injury, we will attach the Thermode to the test subject only prior to running a test while the Medoc main station is in the test screen. We will remove the Thermode from subjects' skin before leaving the test screen. We will connect the Thermode to subjects' skin only during the test and not during system Self-Test, programming, or maintenance.

The computer that is used to operate the Pathway system will be connected to the Pathway power outlet or to a medical grade isolation transformer and will never be connected to a network while used for running tests. The device's construction prevents against electrical shock by grounding the appropriate metal parts; proper grounding will be verified on receptacles when using on human subjects. Further, the Medoc main station will be used on a circuit employing a Ground Fault Circuit Interrupter (GFCI) when used with human subjects. Because electrical storms can cause high voltage transients on electrical distributions lines, we will never connect electrical devices to human subjects during electrical storms.

3. *Thermal Sensory:* This test will be conducted using a thermode attached to a Medoc Pathway instrument, which will be applied to the skin. This test consists of a series of six alternating hot and cold stimuli. After each stimulus, participants will be asked whether the stimulus felt hot or cold and responses will be recorded.

4. *Mechanical Detection Threshold*: This test will be conducted using a series of graded thickness nylon monofilaments moving from the smallest to the largest. Each filament will be applied three times. During each filament application, participants will be asked whether they can feel the filament touching their skin. The bending force of the first filament in the series that they can feel during at least two of the three applications will be recorded as the mechanical detection threshold and the monofilament testing will be stopped.

5. *Sharp / Dull Detection* – This test will be performed by applying a random series of sharp and dull stimuli to the skin. After each stimulus, participants will be asked whether the stimulus was sharp or dull and their responses will be recorded.

6. *Vibration Detection Threshold* – This test will be performed by applying a vibrating calibrated tuning fork on the skin over a bony surface three times. The tuning fork has calibration bars with numbers that increase from 0 to 8 as the tuning fork vibration slows down over time. For each application of the tuning fork, participants will be asked to report when they can no longer feel the vibration and the number on the calibration bars at the time of the report will be recorded.

7. *Mechanical Temporal Summation* – This test will be performed by applying a blunt 256 mN weighted probe to the skin. First, the probe will be applied perpendicular to the skin for one second and participants will be asked to rate the pain on a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable; this pain rating will be recorded. This will be followed by a series of 10 repetitive applications of the probe (1/sec). At the completion of the 10 applications, participants will be asked to rate the overall pain of the 10 applications using the same 0-100 scale. This sequence will be repeated four more times for a total of 5 trials. The 0-100 pain rating will be recorded for each of the five trials.

8. *Pressure Pain Threshold* – This test will be performed by applying a Medoc Pressure Algometer with a 0.5 cm blunt rubber tip to the skin. Pressure will be applied with steadily increasing force at a rate of 30 kPa/sec. Participants will be asked to press a button to stop the testing as soon as the pressure becomes painful. The pressure reading at the time the button press is recorded.

   To ensure safety, the Algometer tip will be covered with a standard disposable biocompatible finger cot before it is placed on the skin. The computer that is used to operate the Algometer will be powered through a Medical Grade Isolation Transformer only and will not be connected to the network while used for running tests.

Biological markers of change in ER. In addition to the QST battery, we will isolate total RNA from whole blood for sequencing at each timepoint. We will examine how changes in expression of pain sensitivity genes, as well as the entire transcriptome, differ between the experimental and control group (those with complete data from yoga vs. stretching) x sex using statistical modeling and construct a database of gene expression profiles to generate a profile of change in ER, as well as identify novel therapeutic targets for better pain management. We will use a candidate approach to examine genes identified from our preliminary studies, and a hypothesis-generating approach to identify differentially expressed genes. Blood samples will be drawn for assessment of correlations among circulating gene expression patterns and ER over time using Paxgene blood RNA collection tubes. Isolation and purification of RNA will be conducted per the manufacturer's protocols in the CAMP Lab.

RNA sequencing to identify differentially expressed genes associated with change in ER. We will prepare libraries per Illumina standard protocols and sequence RNA on the Illumina HiSeq2500 System (Illumina Inc.) to obtain 150–base pair paired-end reads in the Institute for Genome Innovation (IGI) at UConn (see letter of support). Since each lane provides nearly 300M reads, we will barcode samples and multiplex them on a lane (n=4-6) to obtain 40-80M reads/sample, the gold standard for differential gene expression studies. We will map the reads to the most recent build of the Ensembl human genome with the short-read aligner TopHat. We will optimize parameters with respect to segment length in TopHat to generate contiguous as well as spliced alignments. The alignments will be merged to form complete alignments to the genome and will serve as the basis of further downstream analyses, including differential gene expression analysis and pathway analysis. Differential gene expression by RNA-seq will be performed using the count method. Briefly, the number of reads mapped on each gene will be counted with the HTSeq program against the gene annotation file for the Ensembl human genome build. Read counts will be used to measure gene expression. Data normalization and differential expression analysis will be performed with the methods implemented in the R package DESeq, which normalizes read counts for sequencing depth and distortion caused by highly differentially expressed genes. A negative binomial model is then used to test the significance of differential expression between two or more conditions. The criteria used to select significant genes will include a False Discovery Rate cutoff of less than 0.05 with a more than twofold change in gene expression between conditions and a normalized read count of 10 reads per gene in at least one condition. Selected differentially expressed genes and transcripts will be validated by quantitative polymerase chain reaction (qPCR) in the CAMP lab. Strict testing rigor will be maintained to ensure reproducibility.

Physical strength/flexibility. Study Co-Investigator Dr. Erik Groessl will train UCONN research staff in the following measures, which have been used extensively in his clinical yoga interventions trials: Grip Strength will be measured using two trials for each hand with a hydraulic dynamometer. The best performance is selected for each side, and the average of the left and right hand is used for analysis. Participants will be asked at the beginning of each testing session whether they are experiencing any pain in their hands or wrists. Painful or injured hands or wrists are not tested and the result of the good hand is used. Good reliability and predictive validity have been shown (Hogrel, 2015). Core Stabilization and Strength will be assessed using prone and supine bridge positions (Liemohn et al., 2005). Participants

begin on their elbows in the prone position with shoulders, hips, and ankles aligned. The supine position is tested next, with knees flexed 90 degrees and pelvis raised from the floor with shoulders, hips, and knees aligned. Assessors record length of time (120 seconds max) that each position is held in proper form. Hamstring and low back flexibility will be assessed using the sit-and-reach (SAR) test (Lemmink, Kemper, de Greef, & Stevens, 2003), which requires participants to sit on the floor with legs extended and lean forward, pushing an indicator forwards without bending their elbows. Flexibility is operationalized as the distance of the indicator, measured in centimeters.

Pain interference with daily function and pain severity will be measured with the Brief Pain Inventory (BPI) (Cleeland, 1991). The BPI has been validated with CLBP (Keller et al., 2004). The pain interference score is the mean of the 7 interference items. The pain severity score is the mean of 4 severity items. The BPI has good reliability (Keller et al., 2004).

Attendance/ Home practice. Attendance at yoga or stretching sessions will be assessed using sign-in logs verified by instructors. Self-reported practice of yoga or stretching at home will be assessed using a real-time report with time stamp by logging into a web portal to record each home practice session including amount of practice and estimated level of exertion.

Essential Properties of Yoga Questionnaire (EPYQ). The EPYQ (Park et al., 2018) will be used to rate both interventions (yoga and stretching/strengthening). This validated instrument assesses multiple dimensions of mind/body interventions. We have extensive experience using this measure via our team of trained objective raters. The EPYQ provides objective scores on the extent to which 14 different dimensions are emphasized in a mind-body intervention (e.g., physical challenge, breathwork, restorative postures, mindfulness).

Intervention credibility and expectations for intervention success will be measured with the Credibility Expectancy Questionnaire (CEQ; Devilly & Borkovec 2000), a 6-item self-report instrument assessing treatment credibility and patient expectancy for improvement. The CEQ demonstrates strong psychometrics (e.g., Cohen et al., 2015).

Use of medication and other treatment protocols. To monitor pain medication use trajectories and engagement in treatment over time, participants will complete brief assessments of their use of pain medication and use of other treatments at each timepoint. Multiple dimensions of medication and treatment use will be queried, including frequency of use (i.e., number of times) and length of use.

Substance Use. In order to assess participants' use of tobacco, alcohol, prescription medicines, cannabis, and other non-prescribed substances, the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST; World Health Organization, 2002) will be administered by study staff at each timepoint. The ASSIST demonstrates good psychometric properties and generally experienced as acceptable by patients recruited from drug abuse-specific and other healthcare settings (WHO, 2002).

Quality of Life. The 36-item Short Form Health Survey (SF-36; Ware & Sherborne, 1992) will be administered at each timepoint to gain a deeper understanding of the psychological, physical, and social limitations that participants experience as a result of pain. Subscales characterize participants' physical functioning, role functioning as impacted by physical and emotional health, energy/fatigue, emotional well-being, social functioning, pain, and general health. The SF-36 demonstrates excellent strong psychometric properties and predictive validity in a variety of diverse samples, including those experiencing chronic pain (Elliot, Reiner, & Palcher, 2003).

[If applicable, describe the use of audiotape and/or videotape, provide justification for use and indicate if this is a requirement of participation.]

Instructor fidelity to the yoga intervention or stretching intervention manuals will be evaluated using video-recordings of sessions, which we have successfully used in our previous intervention studies. All sessions will be recorded with a digital camcorder and tripod in the back of the room. Instructors and participants will be aware of and consent to the recordings.

[If the study involves use of *deception* or *incomplete disclosure*, explain the reason why this is necessary to answer the research question(s). Complete the alteration of consent section below]

N/A

[Describe opportunities provided to participants to ask questions in order for them to make an informed decision regarding participation.]

All potential participants who meet eligibility criteria will be given written and verbal information describing the project by a trained study staff member. All participants will have as much time as needed to decide whether or not to participate in the project. If participation is desired, informed consent procedures will be followed and written consent obtained.

Data Analysis: [For all studies, specify the analytic techniques the researcher will use to answer the study questions. Indicate the statistical procedures (e.g. specific descriptive or inferential tests) that will be used and why the procedures are appropriate. For qualitative data, specify the proposed analytic approaches.]

Planned data analyses are listed below by study aim:

Primary Aim: Test whether ER abilities improve as a result of the yoga intervention. Midway through and after a 12-week yoga intervention, ER will increase significantly compared to baseline and to the control (stretching/strengthening) group. Two-sided t-tests will be conducted to determine if raw mean differences in ER (DERS scores) change between groups at 6 and 12 wks, as well as differences from baseline within groups. A mixed effects model will be used to test between- and within-group differences, adjusted for covariates (e.g., physical strength/flexibility, cohort). Group (stretching/strengthening as reference), time (baseline as reference), and covariates will be added into a mixed effects model of ER, and magnitude of group and time effects will be assessed to determine adjusted mean differences.

To test whether effects of yoga on ER change will be maintained or strengthened over follow-up timepoints, identical two-sided t-tests will be conducted utilizing change in ER at 3- and 6-month follow-ups to assess raw mean differences. Identical mixed effects models will be created including 3- and 6-month follow-ups to assess mean differences, adjusted for covariates. Differences in the effect magnitudes of group and time on ER will be examined to test if any within- or between-group ER changes vary over time.

To test whether ER subcomponents will differentially change (e.g., higher increases specifically in acceptance of emotions), multivariate analysis will be conducted on multiple mixed effects models with individual ER subcomponents (DERS subscales) as the outcome for each model. Adjusted multiple comparisons via Tukey's HSD will test for differences in models dependent upon distinct ER subcomponents.

Secondary Aim 1: Test whether improvements in ER produce changes in pain severity/interference. We hypothesize that improvements in ER abilities at 6 wks will predict reductions in pain severity/interference at 12 wks., and improvements in ER at 12 wks (intervention end) will predict reductions in pain severity/interference at 3- and 6-month follow-ups. A mediation path analysis will be conducted, examining the indirect path of group and change in ER at 6 weeks (per Primary Aim; path a), and change in ER at 6 weeks and pain severity/interference (BPI scores) at 12 weeks (path b). The magnitude of indirect path b will be assessed, controlling for path a and the direct path between group and change in pain severity/interference at 12 weeks (path c'), to test if changes in ER predict subsequent changes in pain severity/interference. Identical models will be created with ER at 12 weeks, and pain severity/interference at 3- and 6-month follow-ups. If 95% confidence intervals of path estimates do not contain zero, they will be considered meaningful.

Secondary Aim 2: Test whether yoga's salutary effects on pain severity/interference operate via improvements in ER. To test whether yoga relative to stretching/strengthening produces reductions in pain severity/interference through greater improvement in ER, the magnitude of indirect path b (as described above for Secondary Aim 1) will be compared between groups to test if the path between ER and pain severity/interference is greater in the yoga group than the stretching/strengthening group. If 95% confidence intervals of differences do not contain zero, they will be considered meaningful.

Secondary Aim 3: Examine the role of pain sensitization in our mediational model. We hypothesize that pain sensitization will moderate effects of both interventions (higher baseline sensitivity = less effect on pain severity/interference). A series of moderated mediation path analyses will be conducted, examining measures of baseline pain sensitivity (QST scores and normalized gene expression values) as moderators of the hypothesized mediation model described in Secondary Aim 1. If there is a significant interaction between pain sensitivity and the path a or b predictor within either group, that path magnitude will be analyzed conditional on low (-1 SD), mean, and high (+1 SD) pain sensitivity, assessing the degree in which increased baseline pain sensitivity may reduce improvements in ER and subsequent pain severity/interference in that group.

We further hypothesize that pain sensitization will lessen more in the yoga than the control condition and will test whether mean pain sensitivity changes differ between groups at 6 weeks and following timepoints.

We also expect that pain sensitization will mediate effects of improved ER on pain severity/interference and will examine mediation by including pain sensitivity change at 12 weeks as a mediator between ER change at 6 weeks and pain severity/interference at 3-month follow-up. The magnitudes of indirect paths connecting changes in ER and pain sensitivity and changes in pain sensitivity and pain severity/interference will be compared to the direct path between changes in ER and pain severity/interference; the total indirect path including group will also be compared to the direct path also including group.

Finally, **sensitivity analyses** will examine 1) whether treatment responders/non-responders differ significantly in baseline ER and 2) whether baseline ER moderates the extent to which participants experience improvements in pain over time.

Inclusion/Exclusion Criteria: [List ALL inclusion and exclusion criteria. Any proposed exclusion criterion based on gender (women of childbearing potential), age, or race must include justification for the exclusion.]

Inclusion criteria include: a.) men and women age $\geq$18 years; b.) report of low back pain for $\geq$3 of the last 6 months; c.) willing to attend 12-weeks of yoga; d.) willing to complete 4 assessments; e.) English

literacy; f.) no changes in pain treatments over the past month; g.) no change in pain treatments during study unless medically necessary; h.) have not practiced yoga >2 x in the last 12 months.

Exclusion criteria include: a.) back surgery within the last 1 year; b.) back pain due to specific systematic problem (e.g. lupus); c.) weakness of the low extremities; d.) sciatica or (+) straight leg raise; e.) coexisting chronic pain problem (migraine headaches, fibromyalgia); f). serious or unstable psychiatric illness or current suicidal ideation; g.) major coexisting medical illness (cancer, COPD, morbid obesity); h.) positive Romberg test (with or without sensory neuropathy); i) pregnancy or plans to become pregnant over the course of the study.

This is a study of chronic low back pain, a condition primarily affecting adults. Although low back pain is not uncommon in children and adolescents, it is a much more common chronic and medically-treated condition in adults and mechanisms through which mind-body treatments may work differently for children than for adults. As such, we will exclude participants younger than 18 years of age.

[Describe the conditions under which participants may be removed from the study, i.e., noncompliance with study rules, study termination, etc.]

Participants may be prematurely removed from the study if the investigators determine that there is a risk to their safety. Otherwise, participants will be removed from the study following completion of their final 6-month follow-up assessment.

Potential Harms/Risks and Inconveniences: [Describe the potential risks to participants (and secondary participants, if applicable) and ***steps taken to minimize risks*** for each participant population. Assess the likelihood of the risk occurring and, if it were to occur, the seriousness to the participant. Types of risks to consider include, but are not limited to: physical, psychological, social, legal, employment, and financial.

[Describe any anticipated inconveniences the participants may experience (such as: their time, abstention from food, etc.).]

Loss of confidentiality and privacy are risks of participating in the study and adequate protections are in place to minimize these risks, as described in the Data Safety and Monitoring Plan below.

Risks associated with collection of blood specimens include bruising, bleeding, or fainting. We will only have experienced personnel draw blood to decrease the likelihood that these problems will occur. The only risk associated with the QST component of this protocol is the unlikely possibility of a superficial burn from the thermal stimulator. The thermal stimuli to be administered will not be of sufficient intensity or duration to produce a burn on the skin. Furthermore, the stimulator's controller is equipped with an emergency shut-down feature, which will be engaged if the stimulator's temperature were to exceed a safe level. The participant will always be free to move away from the stimulus or to stop testing at any time. The device and these types of stimuli have been widely used within our group and in groups around the world for many years with no adverse events. There is minimal risk associated with mechanical sensitivity measurement via von Frey monofilaments. These nylon filaments have a blunt tip that allows them to indent the skin without causing a puncture. Further, there is a finite amount of force that can be applied with any one filament. We will assess vibration detection via a Tuning Fork. This instrument has minimal to no chance for causing injury. The fork will be set to vibrate and the blunt base of the fork will be placed against the skin surface.

Risk of yoga and stretch interventions. Like other exercise activity, risks of injury from improperly performing yoga postures or physical exercise vary depending on how, where, and with whom they are practiced. However, the yoga for back pain intervention we will use has been successfully used in prior studies of veterans and older adults with CLBP with no adverse effects or injuries. Similarly, the stretching/strengthening condition has been used in multiple samples of adults with CLBP with no adverse effects noted.

The initial practice of yoga under the direction of experienced yoga instructors, or exercise taught by experienced fitness instructors, following a program with modifications for people with limitations, and the stringent screening process before starting a program, are all recommendations (Lewis et al., 2012) that we will follow. Yoga poses associated with increased risk of injury (e.g., head and shoulder stands) are not being used in the proposed study. Screening out patients at greater risk of injury (sciatica, +SLR), placing emphasis on slowly building a safe practice, and hands-on instruction from experienced instructors will be used to ensure that the yoga or exercise is practiced in the safest possible manner. Similarly, the exercise instruction will be conducted by experienced, licensed physical therapists trained specifically in the stretching/strengthening intervention. All participants will be instructed to report increasing pain or weakness immediately to the study staff who will assess the situation and refer participants to the emergency room when appropriate or to the participant's primary care provider (for non-urgent symptoms).

Benefits: [Describe anticipated benefits to the individual participants. If test results will be provided, describe and explain procedures to help participants understand the results. If individual participants may not benefit directly, state so here. Do not include compensation or earned course credits in this section.]

> [Describe anticipated benefits to society (i.e., added knowledge to the field of study) or a specific class of individuals (i.e., athletes or autistic children).]

While we anticipate that some participants may have an improvement in symptoms, there may be no direct benefits for participating in this research study. Subjects may experience satisfaction that future patients may benefit through our enhanced understanding of how yoga influences CLBP; however, it is possible that subjects will not perceive any benefit to study participation.

Risk/Benefit Analysis: [Describe the ratio of risks to benefits. Risks to research participants should be justified by the anticipated benefits to the participants or society. Provide your assessment of anticipated risks to participants and steps taken to minimize these risks, balanced against anticipated benefits to the individual or to society.]

Due to the physical, emotional and financial toll of CLBP pain and the minimal potential risks of the proposed study, the potential benefits to future patients far outweigh potential risks.

Economic Considerations: [Describe any costs to the participants or amount and method of compensation provided. Describe how you arrived at the amount and the plan for compensation; if it will be prorated, please provide the breakdown. Experimental or extra course credit should be considered an economic consideration and included in this section. Indicate when participants will receive compensation.]

There are no costs associated with study participation. Participants will receive a yoga/exercise mat and $50 following baseline, 6 and 12 week (post-intervention) and 3- and 6-month follow-up assessments, with an additional $50 for those who complete all 4 sessions.

Data Safety Monitoring: [This is a prospective plan set up by the study investigators to assure that adverse events occurring during studies are identified, evaluated, and communicated to the IRB in a timely manner. Although the investigators initially propose a Data Safety Monitoring Plan (DSMP), the IRB must approve the plan and may require revision of the plan. A DSMP is required for all human studies at the University of Connecticut except for studies reviewed under the Exempt Criteria. For studies that present more than minimal risk to participants, the IRB will review and determine on a case-by-case basis whether a data safety monitoring board is most appropriate. Please refer to the IRB's policy regarding data safety monitoring *before* completing this section - http://research.uconn.edu/policies-procedures.

Issues that should be addressed in the DSMP include the following:

1. Frequency of the monitoring.
2. Who will conduct the monitoring (Under UConn policy a student cannot be the sole person responsible for monitoring the data and safety of the protocol procedures?)
3. What data will be monitored (include compliance with approved IRB protocol?
4. How the data will be evaluated for problems?
5. What actions will be taken upon the occurrence of specific events or end points?
6. Who will communicate to the IRB and how will communication will occur?
7. Describe procedures to inform the sponsor.

Sample response to issues listed above for minimal risk/slight increase over minimal risk – "Survey results will be monitored by the PI in conjunction with the student investigator once every two weeks (items 1, 2 and 3). Survey responses will be reviewed to monitor for clarity (i.e., the same question is skipped by 5 or more participants). In that case, the question will be revised and an amendment will be submitted to the IRB (items 4, 5 and 6)."

We will have several mechanisms ongoing throughout the study as part of the Data Safety and Monitoring Plan and to monitor the potential occurrence of adverse events (AEs). **First**, the PIs and the study staff will oversee the day-to-day conduct of all study activities. All data will be stored in locked filing cabinets within locked office of PI Starkweather and password-protected study-designated computers. Electronic data will be encrypted for storage and de-identified for all study analyses. Data checks, for congruence and missing values, will occur weekly with double-checking (by two research study staff) to ensure accuracy. A log matching participant ID numbers and Protected Health Information (PHI) will be stored on a secure university computer, in a locked office on the UConn campus. The log will be password protected, and only principal investigators and primary study personnel will have access to this information. This log, as well as any other identifiable data, will be destroyed upon completing the study. Signed consent forms will be completed as hard-copies, signed in the presence of a study personnel member. A study personnel member is present for this process to not only explain the study procedures, but to also answer any additional questions about the study and consent after the participant has read the consent form. All consent forms will be signed and dated by both the participant and by the study personnel member obtaining consent. Signed consent forms will remain separate from the electronic REDCap questionnaires, and they will be stored in a locked file drawer in a secure, locked office on the UConn campus.

Second, participants will be provided with day and after hours contact information for the PIs and the study staff, and they will be instructed to report any and all concerns related to study participation to the PIs and/or the study staff. In addition, the PIs will have biweekly meetings with study staff to discuss study progress (recruitment, data collection and retention), any AEs that occur, and any issues that may arise during the study. Any adverse event that occurs will be directly reported by the PIs to the IRB and sponsoring agency within 48 hours of occurrence. Communication will occur through direct phone call and follow-up email.

Any participants that report suicidal ideation during study assessments will be screened thoroughly for risk (including severity of thoughts, presence of plan, presence of intent, past attempts) by study personnel, in consultation with the study PIs, to determine their current level of safety. Participants with current suicidal ideation will be encouraged to agree to a plan for safety, provided with appropriate referrals for low-cost mental health services, and counseled to cease participation in the study protocol. Participants who are determined to be at high acute risk for self-harm will be referred to the emergency room at UConn Health (or the nearest hospital) for further evaluation.

Third, we will assemble a Data Safety Monitoring Board. The DSMB will review the study protocol prior to activation and develop a DSMB plan. The DSMB will evaluate the data on an ongoing basis and assure participant safety and study integrity. The DSMB will be responsible for monitoring data and for making recommendations based on the data regarding appropriate protocol and any operational changes. The DSMB may also, as appropriate, consider the impact of newly published findings that bear on the safety profile of the study or recommend (in an advisory capacity) alteration of study methodology (e.g., inclusion/exclusion criteria, updating informed consent, suspension or termination of the study).

The review committee will meet every 6 months to review progress, preliminary data, and any adverse events. They will meet with the PI to make recommendations regarding the progress of the study and will be able to provide a written report to the Institutional Review Board of the University of Connecticut which summarizes oversight activities and recommendations, including any concerns regarding subject safety. These recommendations will be forwarded to the Principal Investigators, the IRB Chair at the University of Connecticut, and NIH.

Privacy/Confidentiality Part 1: [Explain how the privacy interests of participants will be maintained during the study (note that **privacy pertains to the individual not to the data**). Describe how data will be coded. Do not use the any potentially identifiable information such as initials of participants as part of the code. Explian how long data will be kept in an identifiable format and how long de-identified data will be retained. Explain how long the master key or audio or video recordings obtained, will be kept. Consider whether keeping de-identified data will be retained indefinitely and whether participants may be contacted for a follow-up study (explain procedures to retain identifiable contact data is kept.]

If identifiable, sensitive information (illegal drug use, criminal activity, etc.) will be collected, state whether a Certificate of Confidentiality will be obtained.

Be sure to state whether any limits to confidentiality exist (e.g. mandated reporting) and identify any external agencies (study sponsor, FDA, etc.) that will have access to the data.

If participants will be screened, describe the plans for storage or destruction of identifiable data for those that failed the screening.]

Screening data. Screening data for ineligible participants will be kept on file, separate from participant identifiers, until the completion of the study. The data will be used to compare demographics or other differences between those determined eligible and ineligible, for baseline equivalence testing and to get a sense of the generalizability of our resulting sample relative to those excluded.

Video and audio recordings. Video and audio recordings of classes will be recorded in digital format and stored on a securely-encrypted, password-protected computer. Given the importance of obtaining tapes as a record of instructor adherence to treatment, participants will be required to consent to recording in order to be

in the study. Tapes will be reviewed and scored by trained study personnel under the supervision of the study PIs.

Data storage and security. The researchers will keep all study records (including any codes to data) locked in a secure location. Research records will be labeled with a code. The code will be derived from a sequential 3 digit code that reflects how many people have enrolled in the study. A master key that links names and codes will be maintained in a separate and secure location. The master key and audio files will be destroyed after 7 years. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Only the members of the research staff will have access to the passwords. Data that will be shared with others will be coded as described above to help protect identity. At the conclusion of this study, the researchers may publish their findings. Information will be presented in summary format and participants will not be identified in any publications or presentations.

Self-report surveys collected on the web will utilize the online survey services of REDCap, for which the University has a paid subscription. All data stored on the servers at the Health Center are protected by multiple firewalls. Remote access from outside the Health Center is provided securely over an encrypted web connection.

REDCap is a secure, HIPAA-compliant online platform well-suited to longitudinal research such as clinical trials. REDCap system administrators and support personnel may access participant responses to provide support to study investigators. REDCap maintains a built-in audit trail that logs all user activity and all pages viewed by every user, including contextual information (e.g. the project or record being accessed). Whether the activity be entering data, exporting data, modifying a field, running a report, or add/modifying a user, among a plethora of other activities, REDCap logs all actions. The logging record can itself be viewed within a project by users that have been given privileges to view the Logging page. The Logging page allows such users to view or export the entire audit trail for that project, and also to filter the audit trail in various ways based upon the type of activity and/or user. The built-in audit trail in REDCap allows administrators to be able to determine all the activity and all the data viewed or modified by any given user.

To help protect and secure the data stored in REDCap's back end database, the software application employs various methods to protect against malicious users who may attempt to identify and exploit any security vulnerabilities in the system. In REDCap, all incoming data gets intentionally filtered, sanitized, and escaped. This includes all data submitted in an HTTP Post request and all query string data found in every URL while accessing REDCap, among other modes through which user-defined data gets submitted in the application. Server environment variables that are vulnerable to forgery by users are also checked and sanitized. All user-submitted data is properly filtered for any possibly harmful markup tags (e.g., <script>) and is then escaped before ever being displayed on a web page within the application. SQL queries sent to the database server from REDCap are all properly escaped before being sent. If any values used in an SQL query originated from user-defined values, they would have already been sanitized beforehand as well, as described above. User-defined data used within SQL queries also have their data type checked to prevent any mismatching of data types (e.g. making sure a number is really a number). These processes of sanitization, filtering, data type checking, and escaping all help to protect against methods of attack, such as Cross-Site Scripting (XSS) and SQL Injection. To specifically protect against Cross-Site Request Forgery (CSRF), which is another method of attack, REDCap utilizes a "nonce" (a secret, user-specific token) on every web form used in the application. The nonce is generated anew on each web page as the user navigates within REDCap during a session.

Certificate of Confidentiality. We will automatically obtain a certificate of confidentiality from the awarding organization, NIH, for this study.

Limits to Confidentiality. Study staff will be UConn employees, all of whom are mandated reporters. As such, if participants disclose intent to hurt someone helpless, such as a child or the elderly, we are required to report this by law. The investigators may be required to share the study data with NIH personnel (the study sponsor). The aforementioned limits to confidentiality will be noted in the informed consent form that participants sign at study start.

Privacy/Confidentiality Part 2: Complete the Data Security Assessment Form

: [**This form IS REQUIRED for ALL studies**. The form is available here - https://ovpr.uconn.edu/services/rics/irb/irb-forms-infoed/. This form will be used to assess procedures for protecting confidentiality of data collected during the study and stored after closure. It will also be used to assess plans for storage and security of electronic data in accordance with University Best Practices. Review the document proving tips to complete the form located at http://content.research.uconn.edu/pdf/storrs/rcs/irb/TipsDataSecurityAssessmentForm.docx.

Informed Consent

As PI, you are responsible for taking reasonable steps to assure that the participants in this study are fully informed about and understand the study. Even if you are not targeting participants from "Special Populations" as listed on page 4, such populations may be included in recruitment efforts. Please keep this in mind as you design the Consent Process and provide the information requested in this section.

Consent/permission Setting: [Describe the consent/permission process including *who* will obtain it, *where* and *when* will it be obtained, and *how* much time participants will have to make a decision. Describe how the privacy of the participants will be maintained throughout the consent process.

> State whether an assessment of consent/permission materials will be conducted to assure that participants understand the information (may be warranted in studies with complicated study procedures, those that require extensive time commitments or those that expose participants to greater than minimal risk).]

All potential participants who meet eligibility criteria will be given written and verbal information describing the project by a trained study staff member and will provide informed consent at the initial screening visit. Consent materials will be written at an 8th grade level and will be provided by a study staff member in a private research office. Participants will be encouraged to ask questions or call the study staff to discuss study-related concerns at any time. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Participants will be provided with ample time to ask questions of research staff to ensure that they understand the procedures of the study.

Capacity to Consent: [Describe how the capacity to consent will be assessed for participants with limited decision-making capacity, language barriers or hearing difficulty. If a participant is incapable of providing consent, you will need to obtain consent from the participant's legal guardian (please see the IRB website for additional information).]

N/A- No vulnerable populations will be used.

Parent/Guardian Permission and Assent: [If enrolling children, state how many parents/guardians will provide permission, when the child's assent will be obtained and if assent will be written or oral. Provide a copy of the script to be used if oral assent will be obtained. For longitudinal studies, assent may happen at several points during the study.]

N/A- This study only involves individuals aged 18 and older.

Documentation of Consent: [Specify the forms that will be used for each participant population, i.e., adult consent form, surrogate consent form, parental permission sheet. child assent form (written form or oral script) or an information sheet. Copies of all forms should be attached to this application in the same format that they will be given to participants (templates and instructions are available on the IRB website).]

Prior to the initial in-person screening, recruitment staff will obtain participants' signed informed consent using an adult consent form. Intervention instructors will also provide signed informed consent to be video-recorded for adherence monitoring. We will attach copies of these forms to the study protocol.

Waiver or Alteration of Consent: [The IRB may waive or alter the elements of consent in some minimal risks studies. If you plan to request either a **waiver of consent** (i.e., participants will not be asked to give consent), an **alteration of consent** (e.g., deception) or a **waiver of signed consent** (i.e., participants will give consent after reading an information sheet), please answer the following questions using specific information from the study:]

Waiver (i.e. participants will not be asked to give consent) or alteration of consent (e.g. use of deception/incomplete disclosure in research):

- Why is the study considered to be minimal risk?

  N/A

- How will the waiver affect the participants' rights and welfare? The IRB must find that participants' rights are not adversely affected. For example, participants may choose not to answer any questions they do not want to answer and they may stop their participation in the research at any time.

  N/A

- Explain why the research could not be practicably carried out without the waiver. For studies that involve deception, explain how the research could not be done if participants know the full purpose of the study.

  N/A

- Explain why the research could not be practicably carried out without using identifiable private information and/or identifiable biospecimens.

  N/A

- How will important information be returned to the participants, if appropriate? For studies that involve deception, indicate that participants will be debriefed and that the researchers will be available in case participants have questions.

  N/A

- Indicate if the waiver/alteration as noted above is applicable to the entire study or to a portion of the study.

  N/A

Waiver of ***signed*** consent (i.e. , no signature, participants give consent only after reading an information sheet). Tip: if the investigator will obtain information through oral or written communication with the prospective participant or if the investigator will obtain private identifiable information or identifiable biospecimens by accessing records, then a waiver of signed consent is NOT required.,:

- Why is the study considered to be minimal risk?

  N/A

- Does a breach of confidentiality constitute the principal risk to participants? Relate this to the risks associated with a breach of confidentiality and indicate how risks will be minimized because of the waiver of signed consent.

  N/A

- Would the signed consent form be the only record linking the participant to the research? Relate this to the procedures to protect privacy/confidentiality.

  N/A

- Does the research include any activities that would require signed consent in a non-research setting? For example, in non-research settings, normally there is no requirement for written consent for completion of questionnaires.

  N/A

- Describe if the participants or their legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk of harm to subjects and there is an appropriate alternative mechanism for documenting that informed consent was obtained. Not applicable to FDA Regulated Studies.

  N/A

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