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A randomized control trial to determine the effectiveness and physiological effects of spinal manipulation and spinal mobilization compared to each other and a sham condition in patients with chronic low back pain: Study protocol for The RELIEF Study

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Abstract

BACKGROUND—Low back pain (LBP) is one of the most common reasons for seeking medical care. Manipulative therapies are a common treatment for LBP. Few studies have compared the effectiveness of different types of manipulative therapies. Moreover, the physiologic mechanisms underlying these treatments are not fully understood. Herein, we present the study protocol for

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Authors' contributions

BCC, DWR, MN, CRF, SW, DC and JST contributed to the design of the study and assisted in the development of the protocol. BCC and JST gained ethical approval through the Ohio University's Institutional Review Board (IRB). DC will only see de-identified data and, as per the Ohio University IRB guidelines, is not responsible for obtaining ethics approval from Northwestern University. TDL served as the Medical Director, and DWR, SW, JO, SH and BS served as treatment providers. MA, NM, and SL assisted with data collection. All authors read and approved the final manuscript.

The Researching the Effectiveness of Lumbar Interventions for Enhancing Function Study (The RELIEF Study).

METHODS AND STUDY DESIGN—The RELIEF Study is a Phase II RCT with a nested mechanistic design. It is a single-blinded, sham-controlled study to test the mechanisms and effectiveness of two manual therapy techniques applied to individuals (n=162; 18–45 years of age) with chronic LBP. The clinical outcome data from the mechanistic component will be pooled across experiments to permit an exploratory Phase II RCT investigating the effectiveness. Participants will be randomized into one of three separate experiments that constitute the mechanistic component to determine the muscular, spinal, and cortical effects of manual therapies. Within each of these experimental groups study participants will be randomly assigned to one of the three treatment arms: 1) spinal manipulation, 2) spinal mobilization, or 3) sham laser therapy. Treatments will be delivered twice per week for 3-weeks.

DISCUSSION—This data from this will shed light on the mechanisms underlying popular treatments for LBP. Additionally, the coupling of this basic science work in the context of a clinical trial will also permit examination of the clinical efficacy of two different types of manipulative therapies.

Keywords

low back pain; spinal manipulation; manual therapies; mobilization; muscle energy

INTRODUCTION

Low back pain (LBP) is one of the most common reasons for seeking medical care and accounts for over 3.7 million physician visits/year in the U.S. alone. Ninety percent of adults will experience low back pain in their lifetime, 50% will experience recurrent LBP, and 10% will develop chronic pain and related disability.[1–4] Manipulative therapies are a common conservative treatment approach for LBP. According to a national survey, more than 18 million Americans over the age of 18 years received manipulative therapies in 2007 at a total annual out of pocket cost of \$3.9 billion.[5]

Spinal manipulative treatments can be broadly classified as manipulation-based or mobilization-based techniques. Manipulation-based techniques (e.g., translatory thrust) apply a high-velocity, low-amplitude force to the spine and are often accompanied by an audible sound from one or more joints. In contrast, mobilization-based techniques (e.g., muscle energy) use a low-velocity, low-force approach that generally does not produce audible joint sounds. Few studies have compared the clinical effectiveness of these two different types of manipulative therapies, [6–10] and the existing studies yield discrepant results, with some studies suggesting manipulation-based techniques are more effective [6, 8] while other suggest no differences [7, 9, 10].

Over the past two decades there has been growing scientific evidence supporting the clinical effectiveness of manual therapy treatments for low back pain.[11–24] However, the physiologic effects and mechanisms underlying these treatments are not fully understood. The lack of empirical data hinders acceptance by the wider scientific and health-care

communities, and it also limits the development of rational strategies for using manipulative therapies. Many scientists and clinicians have long postulated that spinal manipulation exerts its biologic effects on segmental components of the central nervous system.[25–40] It has been proposed that manual therapies act through a cascade of neurophysiologic responses [33, 41] to reduce muscle spasm and subsequent pain. Two general models of low back pain that have received the most attention (i.e., pain adaptation and pain-spasm-pain models) have been used to support these propositions.

The pain adaptation model posits a decrease in trunk agonist muscle activity and an increase in antagonist muscle activity during movement that serves a protective function.[42] This model also predicts no difference in resting activity of the trunk muscles. In contrast, the pain-spasm-pain model of LBP (Figure 1) suggests that pain leads to muscular hyperactivity (spasm), which in turn causes pain.[43] While two distinct neural pathways have been proposed to support this model, the common theme is that increased excitatory input to the alpha-motorneuron pool leads to sustained and intense muscle activity in LBP patients (for reviews see Van Dieën et al., 2003, and Clark et al., 2012) [44, 45]. Spinal manipulation has been proposed to act *via* the pain-spasm-pain model [45], yet this has not been clearly demonstrated.

We have previously reported that a single session of spinal manual therapy—involving a combination of manipulation and mobilization techniques—reduces activation of trunk muscles, as determined by muscle functional magnetic resonance imaging [25]. Consistent with these findings, a few studies [46–49] and anecdotal reports [33, 50] have noted reduced paraspinal muscle activity, as determined by surface electromyography, following spinal manipulation on individuals with low back pain. Further, our preliminary data also indicate that spinal manipulation treatments reduce the amplitude of short-latency stretch reflexes, but only if an audible joint sound is produced [51]. While manipulative treatments could act *via* the pain-spasm-pain model by reducing the underlying nociceptive stimulus (e.g., a hypomobile segment),[48, 50, 52–56] there are three primary limitations to these studies that make such conclusions tenuous. Specifically, these studies have:

- Not taken a comprehensive approach to determine the effects of manipulation on the various segmental components of the central nervous system (cortical and spinal) that could explain the reported reductions in muscle activity. Thus, the neurophysiologic mechanisms underlying spinal manipulative treatments remain largely unknown.
- Primarily focused on manipulation-based treatments and disregarded mobilization-based treatments. Thus, the physiologic effects of manipulation-based versus mobilization-based treatments are unknown.
- Not examined both the immediate physiologic effects, those following a course of treatment, as well the sustained effects (i.e., changes lasting after treatment has concluded).

The RELIEF Study (Researching the Effectiveness of Lumbar Interventions for Enhancing Function Study), which is a Phase II randomized controlled trial with a nested mechanistic design, will address these shortcomings. There are two major goals of this study. One is to

determine the biological mechanisms of two manual therapy interventions commonly used in the treatment of chronic low back pain (hence forward referred to as the ‘Mechanistic Component’). The second is to conduct a randomized clinical trial (RCT) to determine the effectiveness of these two manual therapies at reducing pain and disability in patients with chronic low back pain compared to each other as well as a sham control group (henceforth referred to as the ‘RCT Component’). In this article we will describe the study design and protocol (NCT01854892).

METHODS

Design and Outcomes

This is a single-blinded (investigator-blinded), sham-controlled study. The purpose is to test the mechanisms and effectiveness of two manual therapy techniques applied to individuals (18–45 years of age) with chronic LBP. Specifically, the clinical outcome data from the mechanistic component will be pooled across experiments to permit an exploratory Phase II RCT investigating the effectiveness of manual therapies in treating chronic LBP.

Participants with chronic LBP will be recruited and enrolled into one of three separate experiments that constitute the mechanistic component to determine the muscular, spinal, and cortical effects of manual therapies. For this objective we seek to determine the acute effects of manual therapies as well as the effects following a course of treatment. Within each of these experiments study participants will be randomly assigned to one of the three treatment arms: 1) spinal manipulation, 2) spinal mobilization, or 3) sham laser therapy. Treatments will be delivered twice per week for 3-weeks. The primary outcome variables for both components are illustrated in Table 1.

Sample Size and Population

Target population—Forty-two patients with chronic LBP will be enrolled into experiment 1 (Muscular Effects) and randomly assigned to the following 3 treatment arms (14 patients per arm): 1) spinal manipulation, 2) spinal mobilization, or 3) sham laser. Sixty patients with chronic LBP will be enrolled into experiment 2 (Spinal Effects) and randomly assigned to the same 3 treatment arms (20 patients per arm). Sixty patients with chronic LBP will be enrolled into experiment 3 (Cortical Effects) and randomly assigned to the 3 treatment arms. The clinical outcome data from the individuals will be pooled across the three physiological experiments for the RCT component. This pooling will result in a total of 54 patients being assigned to each of the three treatment arms (total n=162 patients). Table 2 lists the inclusion and exclusion criteria for the study.

Study Location

This is a single site study conducted in laboratory-based facilities specifically designed for musculoskeletal and neurological clinical research at Ohio University.

Study Timeline

The study duration for an individual participant is approximately 8 weeks. The typical amount of time between enrollment ascertainment and randomization will be 3–5 days

(maximum 7), and randomization will occur when study participants begin a study intervention (visit 2). The study intervention will occur over a 3-week period followed by an approximately 4-week follow-up. Specifically, in the first visit we will obtain informed consent and conduct a screening exam to determine if candidates meet the inclusion/exclusion criteria for a given experiment. If subjects meet the inclusion/exclusion criteria for an experiment they will be enrolled into the study and allocated to one of three experimental measurement groups (i.e., Muscular, Spinal, or Cortical). At the second visit, participants will then be randomized to an intervention arm (i.e., mobilization, manipulation, or sham laser), baseline assessments of both clinical and physiological outcome measures will be obtained, a treatment intervention will be performed, and clinical and physiological outcome measures will be repeated (i.e., follow-up assessment). Participants will then undergo an additional five treatments over the next three weeks (visits 3–7; total treatments: 6; treatment frequency: 2×/week). It should be noted that just prior to treatment 2 we will assess expectancy and credibility expectations for the respective treatment intervention. Three days $\pm$ 1-day after the final treatment, subjects will report back to the laboratory for a follow-up assessment of the clinical and physiological outcome measures (visit 8). Lastly, to determine the long-term effects of the interventions, subjects will report back to the laboratory approximately 4 weeks (28-days $\pm$ 4-days) after their last treatment for the final follow-up assessment of the clinical and physiological outcome measures (visit 9).

The primary endpoint for the RCT Component will be following the 3-week course of treatment (visit 8). A detailed study diagram is provided in Figure 2 along with a schedule of evaluations in Table 3.

Randomization, Stratification, and Blinding

Randomization & Stratification: The study statistician will use the R statistical language to block-randomize treatments stratified by sex for each of the three separate experiments. Specifically, within each experiment there will be two strata within which we will create blocks of 3 patients, where treatments are permuted. Based on the randomization table the study coordinator will assign subjects to the treatment arms. In instances where multiple experiments are actively enrolling study participants and a participant meets eligibility requirements for more than one experiment, we will then use an adaptive randomization method to allocate them to one of the experiments. This method ensures that an experiment with fewer participants enrolled will have a higher allocation ratio. Specifically, with two potential experiments, the allocation ratio for Experiment_{*i*} (p_i) will be $p_i = 1 - (n_i/N)$, where n_i is the sample size for Experiment_{*i*} and N is the total sample size thus far enrolled. With three active experiments, the allocation ratio will be $p_i = (1 - n_i/N)/2$. Note that this allocation to an experimental measurement group occurs prior to the randomization to a treatment arm.

Masking or Blinding: In the RELIEF Study the principal investigators, the statistician, and members of the data collection team will remain blinded to intervention assignment throughout the duration of the study. They will be given the identifying codes only at the end of the study when it is necessary to interpret the results of the study. The un-blinded study coordinator, who is responsible for scheduling testing and treatment sessions, will serve to receive the study patients and escort them to the various testing and treatments sites to

minimize the interaction between patients; however, the study coordinator will not participate in the assessments.

Study Interventions

Manipulation Treatment—All patients will receive the same technique. The participant will be placed in a side-lying position facing the clinician with the more painful side facing upward. If the participant cannot specify a side, the clinician will select the side to be manipulated. The clinician will passively flex the participant's hips and knees to induce lumbar spine flexion. The degree of flexion will be dependent on the level of the identified hypomobile segment. For example, if the clinician identifies hypomobility at the third lumbar vertebra, they will flex the knees until they feel the spinous process of the fourth lumbar vertebrae begin to move. Next, the clinician will passively rotate the participant's torso opposite to the side they are lying on until they feel rotation in the vertebra above the suspected lesion. Now the participant is positioned for the high velocity low amplitude thrust procedure. The clinician will then deliver a rapid thrust to the shoulder (anterior to posterior force) and pelvis (posterior to anterior force) resulting in a rotation force couple on the hypomobile segment. If a cavitation (that is, a "pop") occurs, the treatment will be considered complete. If no cavitation was produced, the participant will be repositioned and the manipulation will be attempted again. A maximum of 2 attempts per side will be permitted. If no cavitation is produced after the fourth attempt, the treatment will be considered complete.

Mobilization Treatment—The participant will be placed in a side-lying position facing the clinician with the more painful side facing upward. If the participant cannot specify a side, the clinician will select the side to be mobilized. The clinician will passively flex the participant's hips and knees to induce lumbar spine flexion. The degree of flexion will be dependent on the level of identified hypomobile segment. For example, if the clinician identifies hypomobility at the third lumbar vertebra they will flex the knees until they feel the spinous process of the fourth lumbar vertebrae begin to move. Next, the clinician will passively rotate the participant's torso opposite to the side they are lying on until they feel rotation in the vertebra above the suspected lesion. Now the participant is positioned for the mobilization procedure. The clinician will then place one hand on the anterior shoulder and one hand on the posterior pelvis. The participant will then be asked to try to gently push the shoulder and pelvis into the clinician's hands. Thus they will be performing an isometric rotation of the torso resulting in a rotation force couple on the hypomobile segment. The clinician will have the participant hold the contraction for a minimum of 7 seconds and up to a minute if the patient can comfortably tolerate the stretch. The clinician will reposition the patient as needed and repeat the treatment for up to 10 minutes.

Sham Laser Treatment—Sham laser (MedX 1100;) will be delivered while the study participant is placed in a side lying position with the hips and knees flexed as described for the manual therapy treatments. The clinician and the participant will don protective eye goggles (standard operating procedure in laser therapy), and then the clinician will apply the laser head over the primary area of pain and proceed to perform the technique with no power to the Laser head (i.e., sham laser). It should be noted that the clinician will be unaware that

the laser treatment was actually a sham intervention. Specifically, the laser manufacturer (MedX Health Corp, Ontario, Canada) custom developed their MedX 1100 system for us such that it looks as if it is fully functional, but does not actually deliver any significant amount of light energy or heat. Here, the laser accessory LCT200 has only guide light-emitting diodes and “active” light-emitting diodes coming on while laser diodes are disabled and emitting no energy. Additionally, the superluminescent diode light cluster accessories only have red visible diodes (9 diodes 633nm) coming ON, but all infrared diodes (52 diodes 870nm) are in-active and not delivering any energy.

Controlling Treatment Time—The treatment duration time will be held constant across all treatment groups. Specifically, each treatment group will receive between 10–15 minutes of contact time with the clinicians. Following the first treatment intervention, we will quantify subject expectations of treatment success using the credibility/expectancy questionnaire developed by Devilly and Borkovec [57].

Treatment Provider Team—Members of the treatment provider team will deliver the respective treatments. Members of the treatment provider team must: 1) hold either a D.C., D.O., or P.T. degree and be licensed in the state of Ohio, 2) have received formal training in manual therapies, 3) have at least 3 years of clinical experience using manual therapies on a regular basis, and 4) complete a workshop organized by the principal investigators and study Medical Director.

Adherence—Successful adherence will be defined as study participant who achieves at least an 83% adherence rate (i.e., receive at least 5 out of the 6 treatments).

Safety Assessments—At all visits, study participants will be asked if they have had any change in general health since the last visit. All negative changes in health status will be recorded as adverse events, attribution to treatment determined (definite, probable, possible, or unknown), and grading (severity) for each adverse event determined based on the National Cancer Institutes Common Terminology Criteria for adverse Event.

Physiological Outcomes of the Mechanistic Component

The following physiological outcomes will be obtained based on the experimental group to which they are randomly assigned to (i.e., muscular, spinal, cortical):

Group 1 (Muscular Effects)—Skeletal muscle proton transverse relaxation time (T2) will be calculated from the lumbar muscles as we have previously described [25]. In brief, standard spin-echo magnetic resonance images (MRI) of the lumbar spine will be obtained by a 0.25-Tesla Musculoskeletal MRI system (Esaote G-Scan Brio, Genoa, Italy). Transaxial images (2,800 milliseconds repetition time; 22 milliseconds and 57 milliseconds echo times; 9-mm thick images with a 9.5-mm slice-to-slice interval) will be obtained from the lumbar region while study participants lie supine position with the legs slightly bent. After scanning, the images will be transferred to a computer for calculation of muscle T2 using custom written MatLab software. Muscle T2 will be calculated on a pixel-by-pixel basis and averaged over five slices. The T2 values will be calculated from regions of interest within

the following muscles: psoas, quadratus lumborum, multifidus, and the iliocostalis lumborum/longissimus thoracis (these two muscles are grouped due to the difficulty in defining distinct fascial borders in some subjects). The dependent variables calculated from the MRI data will be T2 and T2 asymmetry. T2 will be calculated by averaging the left and right side values for each individual muscle, whereas T2 asymmetry is the percent difference in T2 between the sides. Prior to the MRI scan subjects will lie supine for 30-minutes to minimize the effects of fluid shifts on the calculated outcomes.

Group 2 (Spinal Effects)—Short-latency stretch reflex excitability will be measured from the lumbar muscle as we have previously described [51]. In brief, electrical signals will be recorded bilaterally from the erector spinae (ES) muscles using bipolar surface electrodes located longitudinally over the muscle at the vertebral level of L2 and L4 on shaved and cleaned skin with a reference electrode located on the anterior superior iliac spine. The electromyogram (EMG) signals will be amplified (1000×), bandpass filtered (10–500 Hz), and sampled at 5,000 Hz. ES muscle stretch reflexes will be elicited by mechanically tapping the belly of the left and right ES muscles at the L3 vertebral level between the EMG electrodes. To elicit the stretch reflex, an electromechanical prod will be placed against the skin and the pressure applied to the low back tissue will be gradually increased to a pre-load of 30-N at which time the device will deliver a mechanical tap to the muscle with a net force of 90-N. A total of 10 short-latency stretch reflexes will be elicited from each muscle by tapping the muscle with at least 10 s separating each reflex response. The corresponding EMG responses will be recorded, and the peak-to-peak amplitude of the reflex responses will be averaged to assess stretch reflex excitability. During these measures, subjects will lie prone with their upper body on a scale and they will be instructed to contract their trunk extensor muscles to lift 5% of their upper body mass (while real time visual feedback is provided).

Trunk muscle onset latencies in response to postural perturbations will be measured. Here, the subject will be seated with the lumbar spine in a neutral position. The subject's pelvis will be securely fastened using seatbelts that cross the mid-thigh and across the anterior superior iliac spine. A chest harness will be snugly attached to the subject at the level of the 3rd thoracic vertebrae. Kevlar cables (3/16" diameter) will be attached to the 4 corners of harness by gimbals and run to the Parker™ actuators controlled with a custom LabView Program. Specifically, the participant will sit in the perturbation reference frame with their arms held across their chest. To generate the perturbing force, the actuators will be engaged in pairs (e.g. front, back, left side, right side) to induce a perturbation in one of the following directions: flexion, extension, side-bend left, side-bend right, rotation left, or rotation right. The actuators will pull back precisely 2 inches in a 100-ms duration to provide the perturbation force. The magnitude of the force applied by the actuators will be scaled to the anthropometrics of the participant to ensure a 2 inch displacement in 100 ms. All 4 actuator motors will immediately release tensions on the Kevlar cable at the end of the 100 ms perturbation force. The forces will be delivered at random time intervals between 2–30 seconds. The onset of the force will result in a small trunk angular displacement (5–10 degrees) and a long latency postural reflex response of the trunk muscles. Prior to these perturbations, surface EMG electrodes will be placed bilaterally over the muscle belly of the

following trunk muscles using double sided tape collars: 1) ES at the L2 level aligned parallel to the line between the posterior superior iliac spine and the lateral border of the muscle at the 12th rib, 2) Rectus Abdominis 1 cm above the umbilicus and 2 cm lateral to the midline, 3) External Oblique just below the rib cage along a line connecting the most inferior portion of the costal margin and the contralateral pubic tubercle, and 4) Internal Oblique 1 cm medial to the anterior superior iliac spine and just beneath a line joining both anterior superior iliac spine. EMG signals will be collected using a 16 channel wireless Delsys Trigno system (bandwidth of 10- 500 Hz). The raw EMG data will be amplified ($\times 1,000$), sampled at 2000 Hz, filtered with a 60 Hz notch filter, and then rectified. The rectified EMG data will first be filtered using a 4th zero-lag Butterworth filter with a cut-off frequency of 100 Hz. Next, perturbation onset (t_0) will be defined as the point where peak velocity of the thorax segment exceeds a fixed threshold (2.5% of peak velocity), and movement offset (t_1) will be defined as the point where thorax segment drops below a fixed threshold (less than 2.5% of peak velocity). Movement time will be calculated as $t_1 - t_0$. The onset of muscle activity will be determined automatically using custom algorithms developed in Matlab. Each muscle onset determined by the algorithm will be visually inspected to ensure that appropriate onsets and not spurious events (e.g. EMG artifacts) are chosen. To determine onset of EMG activity, the baseline and standard deviation will first be calculated from 100 data points beginning 200 ms prior to t_0 . The algorithm will initially determine onset by searching the smoothed EMG signal from the point 100 ms prior to t_0 until the point at which the EMG signal is greater than or equal to threshold criteria ($\text{baseline} + 4 \times \text{SD}$). Once onset is determined for each muscle, the latencies from the onset trunk displacement to trunk muscle onset will be determined.

Lumbar motion during volitional movement tasks will be measured as we have previously described [58–61]. In brief, participants (while standing) will perform reaching tasks in which they are instructed to touch their index finger to targets located in the mid-sagittal plane. The target locations will be normalized to the subject's hip-to-shoulder length, arm length (humerus + forearm), and hip height. The "high" target will be placed in a position calculated so that the subject (with the elbow extended and the shoulder flexed 90 degrees) could, in theory, reach the target by flexing the pelvis 15 degrees without any flexion of the ankle, knee, and lumbar spine. The "low" target location will be determined such that the subject could, in theory, reach the targets by flexing the hip 60°. Normalization of target location allows for comparison of movement patterns across individuals and is sensitive to changes in low back pain populations.[60, 62–65] The participant will pause at the target for 2 seconds and then return to an upright posture. The participant will be allowed to rest between each trial. After completing the reaches at a comfortable pace, the participant will then be asked to reach for the targets as fast as possible. Again, three fast movement trials at each target location for each hand condition will be collected. Movement of light-reflective markers attached to the forearm, humerus, trunk, pelvis, thigh, and shank will be measured and recorded using a Vicon MX-13. The system is an optoelectric-based kinematic system that can track, with a spatial resolution of 0.1 mm, the three-dimensional coordinates of light reflective markers attached to the subject. The time series joint angle data are calculated from the 3-D segment coordinate data using an Euler angle sequence of: 1) flexion-extension, 2) lateral bending, and 3) axial rotation using Motion Monitor software.

Kinematic data will be sampled at 100 Hz. Joint excursions are defined as the change in joint angle, and are defined as the difference between the joint angles at the beginning of the trial before the go signal and those extracted 100 ms after target contact.

Group 3 (Cortical Effects)—Motor evoked potential amplitude, intracortical facilitation, and short-interval intracortical inhibition will be measured as we have previously described [51]. In brief, electrical signals will be recorded bilaterally from the ES muscles using bipolar surface electrodes located longitudinally over the muscle at the vertebral level of L2 and L4 on shaved and cleaned skin with a reference electrode located on the anterior superior iliac spine. The EMG signals will be amplified (1000×), bandpass filtered (10–500 Hz), and sampled at 5,000 Hz. For the transcranial magnetic stimulation (TMS) measures, the center of a 110-mm double cone TMS coil will be positioned over the vertex. Single- and paired-pulse magnetic stimuli will be delivered using a Magstim 200² magnetic stimulator with the direction of current flowing from an anterior-to-posterior direction. During TMS, subjects will lie prone with their upper body on a scale and the subject will be instructed to contract their trunk extensor muscles to lift 5% of their upper body mass (real time visual feedback being provided). The TMS protocol will begin by delivering an initial single pulse at 30% of the maximum stimulator output to determine if this stimulus intensity is above or below motor threshold. Based on this finding the motor threshold will be determined by increasing or decreasing the stimulus intensity in 5% increments to determine the stimulation intensity where motor evoked potentials are consistently observed. Once the motor threshold is determined single pulses at intensity equal to 140% of motor threshold will be delivered to quantify motor evoked potential peak-to-peak amplitude. Next, intracortical facilitation will be quantified by delivering two pulses (conditioning and test pulse) with an interstimulus interval of 15-ms. The conditioning pulse intensity will be set to 70% of motor threshold and the test pulse intensity will be set to 140% of motor threshold. Short-interval intracortical inhibition will be assessed by delivering these pulses at the same intensity except with an interstimulus interval of 3-ms. A maximum of 6 trials for each outcome will be assessed in a blocked (a single pulse followed by the paired-pulse trials), with ~15-seconds separating each pulse sequence and ~60-seconds separating each block.

Statistical Considerations

This study was primarily designed to investigate the mechanisms underlying the biology of manual therapies. As such, our statistical power considerations are primarily based on the Mechanistic Component of The RELIEF Study. Below we detail the statistical considerations for the Mechanistic Component first, followed by a discussion of statistical considerations for the exploratory Phase II RCT Component. Importantly, this exploratory Phase II RCT with a nested mechanistic design allows us to maximize the data to be generated to address critical clinical and mechanistic questions necessary to improve our understanding of manual therapy treatments from chronic LBP.

Mechanistic Component—Below we list our primary and secondary hypotheses for the Mechanistic Component. Note that all sample size calculations are based on the primary alternative hypotheses. For more specific information, see *Data Analysis* below.

Group 1 (Muscular Effects) Primary Hypothesis: We hypothesize that there is a significant effect of treatment on skeletal muscle proton transverse relaxation time (T2) asymmetry of the lumbar muscles either immediately following the first treatment intervention (outcome assessment 2), post-treatment measure (outcome assessment 3), and/or follow-up measure (outcome assessment 4), after controlling for the baseline outcome value.

Group 2 (Spinal Effects) Primary Hypothesis: For short-latency stretch reflex excitability, we hypothesize that there is a significant effect of treatment on this outcome at outcome assessment 2, outcome assessment 3, and/or outcome assessment 4, after controlling for the baseline outcome value. Secondary Hypotheses include: i) for trunk muscle onset latencies in response to postural perturbations, we hypothesize that there is a significant effect of treatment on the principal component score (i.e., the linear combination of onset latencies of eight muscles) at outcome assessment 2, outcome assessment 3, and/or outcome assessment 4, after controlling for the baseline outcome value; and ii) for lumbar motion during volitional movement tasks, we hypothesize that there is a significant effect of treatment on the principal component score at outcome assessment 2, outcome assessment 3, and/or outcome assessment 4, after controlling for the baseline outcome value.

Group 3 (Cortical Effects) Primary Hypothesis: We hypothesize that there is a significant effect of treatment on measures indicative of increased intracortical excitability (i.e., increased motor evoked potential amplitude, increased intracortical facilitation, and/or decreased short-interval intracortical inhibition) at outcome assessment 2, outcome assessment 3, and/or outcome assessment 4, after controlling for the baseline outcome values.

RCT Component—To test the following RCT hypotheses, we will collapse the clinical outcome data across the three physiological outcome groups. Our Co-Primary Outcomes are NPR and RMDQ scores. The NPR and RMDQ are classic measures for the assessment of pain and disability in low back pain. Our secondary outcomes are change in PROMIS measures of Pain Behavior, Pain Interference, Pain Intensity, and Physical Function. Our primary endpoint is outcome assessment 3 (visit 8, 3-days $\pm$ 1-day after completion of course of treatment intervention).

Our primary hypotheses are that i) the manipulation and the mobilization groups will display a significantly lower NPR level than the sham control at the post-treatment measure (outcome assessment 3, our primary endpoint) after controlling for the baseline value; and ii) the manipulation and the mobilization groups will display a significantly lower RMDQ level than the sham control at outcome assessment 3 after controlling for the baseline value. Because we have directional hypotheses, we will use a one-tailed test. A 2-point reduction in NPR score [66] and a 3-point reduction in RMDQ score [67] will be considered a clinically-meaningful important differences. Our secondary hypotheses are that the manipulation and the mobilization groups will display significantly lower levels in PROMIS Pain Behavior, Interference, Intensity, and/or Physical Function than the sham control at outcome assessment 3 after controlling for the baseline value.

Sample Size Calculation for Mechanistic Component—For each primary hypothesis, sample size to achieve the power of 0.80 was computed using Monte Carlo simulation studies. For all simulation studies, the following were assumed: 1) The Type I error rate (the α level) was set at 0.05 and the Type II error rate (the β level = 1 - power) at 0.20; and 2) A first-order autoregressive temporal structure was assumed with ρ of - 0.50 to make the simulated data more closely resemble real data; 3) Holm's method was used to adjust the alpha level, depending on the size of observed p-values; and 4) To produce a plausible attrition rate, 10% of the participants dropped out at either 2-days or 4-week post treatment measure completely at random and contributed no scores at subsequent measures. To make the sample-size calculation slightly conservative, missing observations remained missing. 5) Linear mixed effects regression with individual ID as a random intercept will be used to analyze the data. 6) To ensure the acceptable precision, each simulation study was repeated 10,000 times. 7) The baseline measure was included in the model as a covariate to improve power and precision of the test.

The primary dependent variable (DV) for group 1 (muscular effects) is asymmetry in skeletal muscle proton transverse relaxation time (T2) of the lumbar muscles. Our pilot study (n=9) indicated that the primary difference in this outcome was 22.7% asymmetry observed at baseline.[25] Following a manual therapy treatment that included a combination of manipulation and mobilization techniques we observed a reduction in T2 asymmetry to 6.0% immediately following treatment and T2 asymmetry remained reduced (9.4% asymmetry) 2-days post-treatment with a residual standard deviation of 12.8. For this analysis, these values were used as population means. While the mean T2 asymmetry level for 4-weeks post-treatment is unknown, for our power analysis we assume an asymmetry value of 15.0%. For the mobilization treatment arm we assumed T2 asymmetry levels of 22.7%, 7.7%, 10.7%, and 16.7% at baseline, immediately following treatment #1, 2-days following a course of treatment, and 4-weeks post course of treatment, respectively. The rationale for these predicted group differences are based on our recent work suggesting that the cavitation (i.e., audible 'pop') associated with manipulation results in larger physiological changes (i.e., changes in stretch reflex excitability). Given that cavitation is less likely to occur with joint mobilization, we assume smaller physiological effects from this treatment. For the sham control group, we set the baseline mean at the same 22.7% and a placebo effect of ~5%; that is, the population mean T2 asymmetry level for this groups at subsequent measures were set at 21.7%. Our simulation studies indicated that 14 participants in each of the 3 Groups would be sufficient to achieve power of 0.80 to detect a significant Group effect either immediately following treatment #1, 2-days following a course of treatment, or 4-weeks post course of treatment (assuming an attrition rate of 10% and appropriate alpha adjustments).

The primary dependent variable (DV) for group 2 (spinal effects) is the short-latency stretch reflex amplitude. Our preliminary work indicated that spinal manipulation reduced stretch reflex amplitude in individuals with chronic LBP who exhibited an audible joint sound by 30% from 0.56 to 0.39.[68] In study participants with no audible joint sound, there was a non-significant 10% increase from 0.62 to 0.68. The baseline standard deviation was 0.25 for both groups. We assumed manipulation would result in a 25% reduction 2-days

following a course of treatment and a 20% reduction 4-weeks post course of treatment. Given our pilot data indicating the importance of cavitation, we assumed smaller reductions in stretch reflex amplitudes at each time point for the joint mobilization treatment arm. (i.e., 28, 23, and 18% reductions at the three endpoints). Finally, we assumed that sham control would have the same mean (0.68) at each testing point. Our simulation studies indicate that 20 participants in each of the 3 Groups would be sufficient to achieve power of 0.80 to detect a significant Group effect either immediately following treatment #1, 2-days following a course of treatment, or 4-weeks post course of treatment (assuming an attrition rate of 10% and appropriate alpha adjustments).

For group 3 (cortical effects), changes in cortical excitability following manual therapy treatments are assumed to follow our observed changes in spinal reflex excitability. Accordingly, we assumed the same magnitudes of changes for these DV's as detailed above. Specifically, we assumed a 30%, 25%, and 20% reduction in measures of intracortical excitability in the manipulation treatment arm immediately following treatment #1, 2-days following a course of treatment, and 4-weeks post course of treatment, respectively. Likewise, we assumed 28%, 23%, and 18% reduction for the mobilization treatment arm, and no change for the sham control group. The residual variance was set at 50% of the initial value, similar to the Group 2 variables. Our simulation studies indicate that 20 participants in each of the 3 Groups would be sufficient to achieve power of 0.80 to detect a significant Group effect either immediately following treatment #1, 2-days following a course of treatment, or 4-weeks post course of treatment (assuming an attrition rate of 10% and appropriate alpha adjustments).

Sample Size for RCT Component—Our co-primary outcomes are NPR and RMDQ at the primary endpoint (i.e., 3-days +/-1-day following a course of treatment). As stated previously, we will collapse the clinical outcome data across the three physiological outcome groups for a total sample size of 54/treatment arm. A recent review of a large number of RCTs on the effects of spinal manipulation for the treatment of chronic LBP indicates that small treatment effect sizes are observed.[69] However, the effect sizes reported for studies that used a clinical prediction rule to identify individuals most likely to respond to manipulation treatment report large effect sizes. (e.g., effect size $d > 1.3$ for clinically meaningful reductions in disability).[70] The RELIEF Study will use a modified-clinical prediction rule to define a target population of patients with chronic low back pain who are most likely to respond to manual therapy treatment. However, because our population is chronic rather than acute (a factor in the original clinical prediction rule) we took a more conservative approach and based our power calculations on the assumption of a moderate effect of treatment (i.e., effect size $d=0.5$) on disability reduction.

Our calculations were based on an assumed moderate effect size (effect size $d=0.5$; based on data from Maughan and Lewis' work indicating standard deviations for NPR being 2.5 and RMDQ being 6 for patients with chronic low back pain).[71] Our simulation studies indicated that 54 subjects/treatment arm would be sufficient to achieve power of 0.80 to detect a significant treatment effect at our primary endpoint (i.e., 2-days following the course of treatment) assuming an attrition rate of 10% and appropriate α adjustments. With this sample size we will have sufficient power to detect changes in $NPR > 2$ and $RMDQ > 3$,

which are the classically defined levels of clinically-meaningful important differences in these outcomes.

Interim Analyses and Stopping Rules—No interim analyses are planned as they relate to either the primary or secondary outcome data. An individual subject would be discontinued from the study intervention if a medical condition develops that precludes the continuation of the treatment intervention. Additionally, the study will be stopped if the Independent Monitoring Committee, in consultation with NIH's National Center for Complimentary and Integrative Health, decides that the risks associated with the treatment interventions (i.e., excessive serious adverse events) outweigh the potential benefits of the knowledge gained from continuing the study.

Data Analyses

Here we describe three stages at which both the Mechanistic and RCT data will be analyzed in the same fashion: preliminary analysis, checking assumptions, and detailed analytic approach.

Preliminary Analysis—At the first preliminary-analysis stage, we will examine whether the randomization is successful by using χ^2 tests for categorical variables and one-way analysis of variances for continuous variables. If significant differences in the demographic variables or health characteristics emerge, they will be treated as covariates in a model at the second stage. The effect of random factors (i.e., the blocks and treatment providers) will also be examined. If the variances of these factors were not significant at a liberal α level of 0.20, they will be excluded from further analysis. However, if a significant block and/or treatment-provider effect is detected, this will be included as a random effect in the model at the second stage. Likewise, we will perform an analysis of variance (ANOVA) to evaluate whether the means for the three mechanistic experiments differ in the clinical outcome variables. If the experiment factor is significant, this factor will be included as a fixed effect in further analysis. Otherwise, clinical outcome data will be pooled across the experiments.

We will use means and standard deviations as the primary descriptive statistics for continuous variables and proportions for categorical variables. If variables are skewed, medians and interquartile ranges will be used. We will also compute pairwise correlation between a pair of endpoints as well as autocorrelations through all endpoints for each outcome measure. We will compute confidence intervals around the means as well as effect-size indices (e.g., Cohen's d for two-group comparisons and f for multiple-group comparisons) and confidence intervals around the effect sizes.

Checking Assumptions—We will check for the following key assumptions: 1) independence of cases (the study design will satisfy this); 2) normal distribution of random intercepts and slopes as well as residuals; and 3) homogeneity of residual variances across the three treatment groups. To ensure that these assumptions are met, we will visually examine random intercepts, slopes, and residual, using boxplots, and q-q plots, and normalized residuals. If the normality or homogeneity assumptions are violated, we will transform the data or use Generalized Mixed Linear Models to incorporate the non-normal

distribution of the data (e.g., the log-normal family for a skewed outcome). Outliers will be detected using Cook's distance and DFFIT. If one or more outliers are detected, we will check whether there has been a type or data mis-entry.

The pattern of missingness will be examined as follows. Missing data due to subject-reported or investigator-observed factors related to treatment effectiveness will be deemed missing not-at random and will be described in detail in all future manuscripts or presentations of the data. Missing data that is missing solely due to equipment failure will be assumed potentially missing completely at random. In addition to these classifications, we will examine patterns of missingness to establish whether missing data are reasonably assumed to be Missing at Random. Specifically, missing observations will be set as a dichotomous variable and its correlation with other factors will be examined. If the missing factor is not significantly related with any other factors, the missingness is tentatively deemed Missing Completely At Random. If the missing factor is significantly related with other factors, the missingness is deemed Missing At Random, and maximum likelihood estimation will be used to estimate missing observations for the ITT analysis. Next, to test whether the missingness is potentially Missing Not At Random, sensitivity analysis will be performed by imputing missing observations using a multivariate multiple imputation method under different scenarios. If the influence of missingness is extensive, multiple-imputed data will be used for the ITT analysis.

Detailed Analytic Approach—Linear mixed-effects regression analyses will serve as the main analytic framework, because it offers distinct advantages in statistical power and estimation of population parameters over ANOVA or multivariate ANOVA (MANOVA). First, LMER incorporates miscellaneous factors (e.g., blocks and treatment providers) as random effects so that the variances due to those factors can be partitioned. As a result, linear mixed-effects regression models typically offer less biased parameter estimation and potentially higher statistical power. Finally, linear mixed-effects regression's maximum-likelihood estimation allows patients with missing observations to be included in a model if the observations are missing completely at random or missing at random. This advantage is important because some degree of attrition is unavoidable given the longitudinal nature of our project.

All of our LMER models will incorporate random intercept terms to accommodate the within-subject variance associated with longitudinal experimental designs, and fixed-factor parameters for the main effects of group (sham-laser control as reference), main effect for time (baseline as reference), and the simple interaction terms of Group by Time (relative to control and baseline). Because we will stratify our samples by sex, sex will also be included in each of the models we will describe below. We will include the significant main effect parameter for sex as well as its interaction with the Group and Treatment factors.

Additional a-priori contrasts comparing changes from baseline (i.e. simple interaction contrasts) between the two intervention groups will also be performed, using Holm's alpha adjustments to preserve the family wise error rates to 0.05.

Intention to Treat Analysis (ITT): We will include all randomized study participants who have at least baseline endpoint assessments in our ITT analysis. The ITT analysis is our primary method for assessing outcomes, and how it is performed will be determined based on the pattern of missingness. If the pattern of data missingness is deemed missing at random, missing observations will remain missing, and maximum-likelihood estimation, the default estimation algorithm of linear mixed-effects regression, will be used to estimate these observations. If the missingness is found to be potentially MNAR, multiple-imputed data will be used to construct linear mixed-effects regression models.

Per-Protocol Analysis (PPA): For the PPA we will exclude study participants who: 1) fail to attend 4 out of 6 treatment sessions; and 2) receive prohibited concomitant interventions, or 3) develop an exclusionary medical condition while on study protocol. Finally, we will assess how comparable estimated parameters vary between ITT and PPA analyses.

DISCUSSION

LBP is widely accepted as a significant health problem. There is a tremendous lack of high quality mechanistic studies on one of the most prevalent treatments for this disorder (i.e., manipulation treatment). Accordingly, this work is significant and of high scientific impact because it will provide critical information on the neurophysiologic consequences and effects of the most common manipulation treatments for chronic LBP.

Although it has long-been suggested that manual therapies exert their beneficial effects by affecting the nervous system,³⁰ few studies have comprehensively examined these claims in individuals with LBP. As such, this study is highly innovative for several reasons. First, this work represents the first set of experiments to systematically examine the neurophysiological mechanisms underlying the two most common spinal manipulative treatments (i.e., manipulation and mobilization) in a population of individuals with chronic LBP. Whereas the physiologic effects of manipulation have been studied, previous work has limited primarily to animal studies or healthy asymptomatic populations. Second, this work utilizes mfMRI to measure muscle activity of both superficial and deep trunk extensor muscles following manipulation treatments. To date, we have the only publication that uses this technique to quantify and localize muscle activation abnormalities in patients with sub-acute LBP, as well as assessing the physiologic effects of spinal manipulation on these abnormalities [72]. Third, we are proposing the first study to examine the amplitude (or excitability) of the short-latency stretch reflex of the trunk extensor muscles in response to spinal manipulation and mobilization. Few studies have examined this reflex in the low back muscles [73–75], and to our knowledge none have examined these reflexes in a patient population or in response to manual therapies. Fourth, we will use a novel technique to assess the effects of spinal manipulation on postural response to multi-directional trunk perturbations. No published studies have examined the effects of manipulation on postural reflex responses, even though there is convincing evidence of impairments in these responses in individuals with LBP [76, 77]. Fifth, we have pioneered the use of paired-pulse TMS of the trunk extensor muscles [51] and in this study we will use this technique to assess the cortical effects of spinal manipulation. To our knowledge, we have the only published article describing the application of this technique to the trunk extensor muscles [78].

Finally, there are no reports that compare the immediate and long-term physiologic response to the two most common spinal manipulation treatment approaches (manipulation and mobilization).

In summary, the data from the present study will shed light on the mechanisms underlying popular treatments for one of the most common musculoskeletal problems in the world [79]. Lastly, the coupling of this basic science work in the context of a clinical trial will also permit examination of the clinical efficacy of two different types of manipulative therapies.

Trial status

Data collection on this study (NCT01854892) has been completed. To ensure blinding and masking this manuscript was not made publically available until data collection was completed.

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Abbreviations

LBP	Low back pain
RELIEF Study	Research the Effectiveness of Lumbar Interventions for Enhancing Function Study
RCT	Randomized controlled trial
DC	Doctor of Chiropractic
DO	Doctor of Osteopathic Medicine
PT	Physical Therapist
MRI	Magnetic resonance imaging
T2	Skeletal muscle proton relaxation time
EMG	Electromyography
TMS	Transcranial magnetic stimulation
OA	Outcomes assessment
NPR	Numerical Pain Rating
RMDQ	Roland Morris Disability Questionnaire
ANOVA	Analysis of variance

ITT	Intent-to treat
MANOVA	Multivariate analysis of variance
PPA	Per protocol analysis

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Figure 1.

Two neural pathways suggested to form the basis of a pain-spasm-pain cycle. Left side: Nociceptive afferents (N) transmit feedback via excitatory interneurons (E) to the alpha motor neurons (α) that cause increased muscle activation (spasm). Right side: Nociceptive afferents (N) provide excitatory input on the gamma motor neurons (γ) that increase the sensitivity of the muscle spindles (s), which activate alpha motoneurons via excitatory interneurons (E) further increasing muscle activation and pain.

From Van Dien et al., J Electromyography Kinesiol, 2003.

Figure 2.
Detailed overview of study protocol.

Table 1

Primary outcomes for the Mechanistic and RCT Components of The RELIEF Study.

	Primary Outcome(s)	Secondary Outcome(s)
Mechanistic Component		
Experiment 1: Muscular Effects	Skeletal muscle proton transverse relaxation time (T2) of the lumbar muscles	
Experiment 2: Spinal Effects	Short-latency stretch reflex excitability	
	Trunk muscle onset latencies in response to postural perturbations	
	Lumbar motion during volitional movement tasks	
	Dynamic trunk stiffness	
Experiment 3: Cortical Effects	Motor evoked potential amplitude	
	Intracortical facilitation	
	Short-interval intracortical inhibition	
RCT Component	Change in Numerical Pain Rating (NPR) score for average over the last 7-days	Change in PROMIS Pain Behavior
	Change in Roland Morris Disability Questionnaire (RMDQ)	Change in PROMIS Pain Interference
		Change in PROMIS Pain Intensity
		Change in PROMIS Physical Function
		Change in NPR scores for current pain, and worst and best pain in the last 7-days

Table 2

Inclusion and exclusion criteria along with Allowed and Prohibited Concomitant Interventions for Study Participation.

Inclusion Criteria	
Participants must meet all of the following inclusion criteria to participate in this study:	
<ul style="list-style-type: none"> • Between 18 to 45 years of age. 	
<ul style="list-style-type: none"> • Answer yes to the following questions <ul style="list-style-type: none"> ◦ Have you had low back pain constantly or on most days for the last three months? ◦ Has your back pain caused you to seek care or consultation from a health care provider? 	
<ul style="list-style-type: none"> • Average pain intensity, assessed using the Numerical Pain Rating (NPR) scale over the past week 2 on a 0–10 numerical pain scale 	
<ul style="list-style-type: none"> • Roland Morris Disability Questionnaire score 4 	
<ul style="list-style-type: none"> • Exhibit 3 of 4 of the following findings reported in the clinical prediction rules for spinal manipulation <ul style="list-style-type: none"> ◦ No symptoms distal to the knee ◦ Fear Avoidance Beliefs Questionnaire (FABQ) work subscale score <19 ◦ At least 1 hypo-mobile lumbar spinal segment ◦ At least 1 hip > 35 degrees internal rotation range of motion 	
Exclusion Criteria	
To be eligible for the study participants <u>must not</u> :	
<ul style="list-style-type: none"> • Have a personal history of the following neurological disorders: Alzheimer's, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson's, Stroke 	
<ul style="list-style-type: none"> • Have a personal history of the following cardiorespiratory disorders: Congestive heart failure, Heart attack in past 24 months 	
<ul style="list-style-type: none"> • Have a personal history of the following musculoskeletal disorders: Rheumatoid Arthritis, pathologic fractures of the spine, avascular necrosis or osteonecrosis, severe osteoarthritis. Including a history of spine surgery or a hip arthroplasty 	
<ul style="list-style-type: none"> • Have active cancer 	
<ul style="list-style-type: none"> • Be Blind 	
<ul style="list-style-type: none"> • Have used narcotics or muscle relaxants within 30 days prior to study enrollment. 	
<ul style="list-style-type: none"> • Report being pregnant, lactating, or that they anticipate becoming pregnant in the next 3-months 	
<ul style="list-style-type: none"> • Have a body mass index greater than 35 kg/m² 	
<ul style="list-style-type: none"> • Have clinical depression (i.e., subjects who score 24 or higher on the Center for Epidemiology Depression Scale). 	
<ul style="list-style-type: none"> • Report unexplained weight loss over the past month (>10 lbs). 	
<ul style="list-style-type: none"> • Report they have pending litigation related to an episode of LBP or are receiving any type of disability services related to low back pain. 	
<ul style="list-style-type: none"> • Report having received any manual therapy intervention applied to the spine 30 days prior to first study intervention. 	
<ul style="list-style-type: none"> • Current drug or alcohol use or dependence that, in the opinion of the PIs, would interfere with adherence to study requirements. 	
<ul style="list-style-type: none"> • Applies to Experiment 3 (Cortical Effects) only: Have a personal or family history of epilepsy or seizures, Migraine Headaches within 6 months (186 days) of V2 physiologic testing, or taking medications in the benzodiazepine class. 	
<ul style="list-style-type: none"> • Applies to Experiments 1 and 3 (Muscular Effects and Cortical Effects) only: Have contraindications for exposure to a magnetic field. 	
<ul style="list-style-type: none"> • Applies to Experiment 1 (Muscular Effects) only: Have a positive result from pregnancy test administered the day of each MRI. 	
Concomitant Interventions	
<u>Allowed Interventions:</u>	
<ul style="list-style-type: none"> • Over the counter pain relief medications (e.g., Non-Steroidal Anti-Inflammatory Drugs, Acetaminophen, Aspirin). 	
<ul style="list-style-type: none"> • Heat or Ice. 	

<u>Prohibited Interventions:</u>
• Narcotics
• Muscle relaxants
• Any treatment specific for low back pain delivered by a health practitioner (e.g., physician, physical therapist, chiropractor, massage therapist, or acupuncturist).

Schedule of evaluations.

Table 3

ASSESSMENT	Screening Visit	OA1	T1	OA2	T2	T3	T4	T5	T6	OA3	OA4
Visit Number	1	2	2	2	3	4	5	6	7	8	9
Week Number	-1	1	1	1	1	2	2	3	3	4	8
Informed Consent	X										
Demographics	X										
Low Back Pain Rating - NPR	X	X		X	X	X	X	X	X	X	X
RMDQ	X	X								X	X
CES-D	X										
FABQ	X										
TSK	X										
Medical History	X										
Medication History	X										
Inclusion/Exclusion Criteria	X										
Physical Exam	X										
Enrollment/Randomization	X										
Prior & Concomitant Medications		X			X	X	X	X	X	X	X
Change in Medication Use		X			X	X	X	X	X	X	X
PROMIS		X								X	X
Physiological Outcomes		X		X						X	X
Intervention			X		X	X	X	X	X		
Expectancy/Credibility					X						
Intervention Administration Form			X		X	X	X	X	X		

OA: Outcomes assessment; T: Treatment session.