Clinical Intervention Study Protocol

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APPENDICES

Optimization of Spinal Manipulative Therapy (SMT) Protocols

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Tool Revision History:

Version Number: 1.0
Version Date: September 26, 2016
Summary of Revisions Made: Original Version

Version Number 1.1
Version Date: November 9, 2016
Summary of Revisions Made: Section 10.3.1 – added clarification that 4 clinicians will be trained to provide study-related treatments at the University of Utah, 2 clinicians at the University of Alberta

Version Number 1.2
Version Date: January 3, 2017
Summary of Revisions Made: Section 5.3 – Refined definition of "adherence" for per-protocol analyses as requiring 80% attendance at scheduled sessions. Also clarified that attendance at <80% of scheduled sessions will be considered a protocol deviation.

Section 6.1 The Schedule of Evaluations Table was updated to specify the Oswestry and individual self-report questionnaires at appropriate time points.

Section 6.2.2.1 – changed allowed time between eligibility confirmation and enrollment from 72 hours to 1 week as specified in Section 6.2.1 and the IRB documents.

Section 6.2.3 - Spelling error was corrected. Clarification of language in this section to specify that a research staff member who becomes unblinded to a participant's randomization assignment is disallowed from future evaluations of that participant only, and not all future participants.

Section 6.2.2.3 was updated to reflect the randomization procedures that have been put in place using the REDCap system.

Appendix 2 updated to include the Study Visit Checklist

Version Number 1.3
Version Date: July 26, 2017
Summary of Revisions Made: Section 6.1 was updated to more precisely reflect the evaluations completed at the initial screening and baseline assessments.

Section 6.2.1 was updated to reflect a recently approved IRB amendment. Participants may complete the Oswestry Disability survey prior to their baseline visit to screen out those who are ineligible due to their Oswestry score, to reduce the burden on potential participants and researchers of having a baseline assessment only to find out they are ineligible.

Version Number 1.4
Version Date: January 3, 2018
Summary of Revisions Made: Section 5.2.1 was updated to correct a typographical error.

Section 6.1 was updated to clarify when the Oswestry and Global Rating of Change surveys, spinal stiffness and multifidus assessments and demographics are collected.

Version Number 1.5
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Summary of Revisions Made: Sample Size and Population (page 9), Section 3 and Section 9.2 were updated to reflect an increased sample size.

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PRÉCIS

Study Title

Optimization of Spinal Manipulative Therapy (SMT) Protocols

Objectives

Primary Aims

I. Identify SMT protocol components and interactions that independently predict SMT mechanistic outcomes (spinal stiffness and multifidus activation). We hypothesize that one or more combination of components will be identified that optimize improvement in SMT mechanisms.

II. Identify SMT protocol components and interactions that independently predict SMT patient-centered outcomes (function, pain). We hypothesize that one or more combination of components will be identified that optimize improvement in patient-centered outcomes.

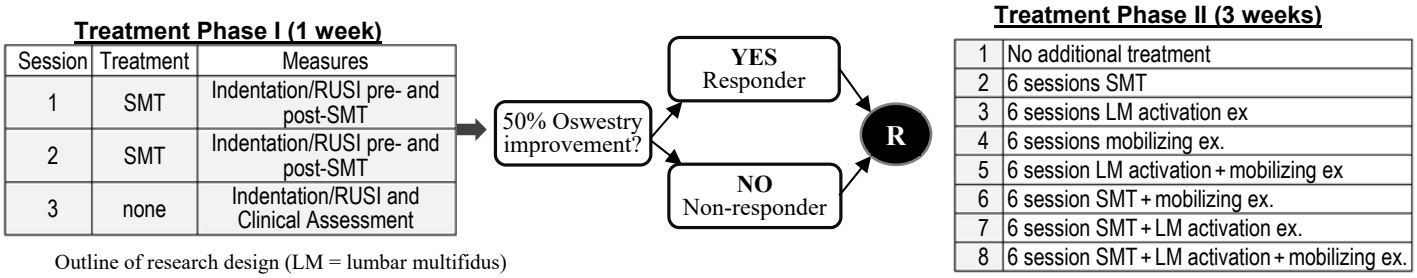
Secondary Aims

I. Explore the moderating effect of responder status after 2 SMT sessions. We hypothesize that responder status after 2 sessions will moderate mechanistic and patient-centered outcomes.

II. Define optimized SMT protocol(s) based on combined results of the primary and secondary aims. Optimized protocols will be considered as the combination of components that maximize improvement in patient-centered outcomes at 3 months while also improving SMT mechanisms to the greatest extent.

Design and Outcomes

This subject will recruit adults with non-specific low back pain (LBP). We will provide 2 sessions of SMT to all subjects. We will then assess responder status and randomize subjects stratified by responder status to a treatment group for an additional 3 weeks using a factorial design to evaluate different combinations of intervention components (muscle activation exercise, spinal mobilizing exercise, additional SMT) that influence pathways shown to modulate the effects of SMT. Outcomes will include spinal stiffness and muscle activation measures as well as patient-reported outcomes assessed at baseline, and after 1 week, 4 weeks and 3 months.



Outline of research design (LM = lumbar multifidus)

Interventions and Duration

All subjects will receive 2 sessions of SMT provided in the first week of participation. Subjects are then randomly assigned to receive an additional 3 weeks of treatment involving different combinations of exercise and/or additional SMT, or to receive no additional treatment. The final follow-up is conducted 3 months after enrollment. Therefore the total time for a subject to be “on study” is 3 months.

Sample Size and Population

We will recruit a total of 316 subjects age 18-60 with non-specific LBP and an Oswestry Disability score of at least 20%. Following Phase I treatment, subjects will be randomized in equal proportions to one of 8 possible treatment combinations in Phase II. Randomization will be stratified by responder status (yes/no) during Phase I.

1. STUDY OBJECTIVES

1.1 Primary Objectives

I. Identify SMT protocol components and interactions that independently predict SMT mechanistic outcomes (spinal stiffness and multifidus activation). We hypothesize that one or more combination of components will be identified that optimize improvement in SMT mechanisms.

II. Identify SMT protocol components and interactions that independently predict SMT patient-centered outcomes (function, pain). We hypothesize that one or more combination of components will be identified that optimize improvement in patient-centered outcomes.

1.2 Secondary Objectives

I. Explore the moderating effect of responder status after 2 SMT sessions. We hypothesize that responder status after 2 sessions will moderate mechanistic and patient-centered outcomes.

II. Define optimized SMT protocol(s) based on combined results of the primary and secondary aims. Optimized protocols will be considered as the combination of components that maximize improvement in patient-centered outcomes at 3 months while also improving SMT mechanisms to the greatest extent.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Low back pain (LBP) is a major public health problem. An estimated 60-80% of individuals will experience an episode during their lifetime, and prevalence rates have been increasing in the past decade. Considering the prevalence of LBP, it is not surprising that the condition imposes significant economic burden on individuals, the healthcare delivery system, and society. Total annual direct healthcare costs in the U.S. for LBP were estimated at $90 billion in 1998, with an inflation-adjusted rate of 65% over the next 7 years, a rate much higher than overall health care costs. LBP is the most common symptom for which complementary and alternative medicine (CAM) is sought. In 2007, 18% of adult CAM users in the U.S. were seeking care for LBP, more than double the next most common condition. The most common CAM intervention sought by those with LBP is spinal manipulative therapy (SMT). Several professions use SMT, although it is most often provided by chiropractors. Surveys in the U.S. suggest about half of those with chronic LBP have sought chiropractic care, and LBP the reason for at least 40% of chiropractic visits. The Institute of Medicine identifies LBP as a top 15 priority condition, calling for the development of innovative, evidence-based management strategies. In light of the prevalence of LBP and the frequency of SMT use for the condition, optimizing SMT protocols for LBP has important public health implications.

2.2 Study Rationale

Successful optimization of SMT treatment requires understanding the mechanisms underlying the effects of SMT among patients who are SMT-responders. Past research has identified numerous biologic phenomena that accompany SMT without relating these phenomena to the presence or absence of clinical benefit. In contrast, our research team has worked for more than 10 years to

develop and validate a model explaining the mechanisms that underlie the clinical effects of SMT. Specifically, our work supports the common clinical observation that SMT is not a broad-spectrum therapy, but one that preferentially benefits some individuals with LBP (SMT-responders) but not others (non-responders). This work has culminated in the development of a validated model that has identified specific biomechanical signals (changes in spinal stiffness and lumbar multifidus muscle activation) that relate to favorable clinical response (improved function). The clinically important signals we have identified (stiffness and muscle activation) are modifiable with interventions other than SMT; thus SMT protocols may be optimized through the use of co-interventions that modulate these signals. Our team has also developed safe, valid and reliable procedures to measure these signals, and have demonstrated successful application of both SMT treatment and signal measurement procedures in clinical populations.

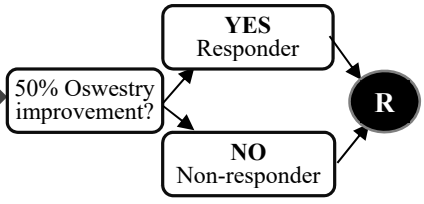
Our goal in this proposal is to optimize SMT treatment protocols for LBP. Our optimization strategy will evaluate SMT combined with other treatments known to modulate the same signals that underlie the clinical effects of SMT (spinal stiffness and muscle activation) using both mechanistic (stiffness, lumbar multifidus activation) and patient-centered (function and pain) outcomes. We have grounded our body of work in this area within the Multiphase Optimization Strategy (MOST) framework; which provides an efficient multi-step research strategy for optimizing multi-component interventions. In this project we will use innovative methodology to efficiently evaluate the effects of various individual treatment components towards an overall effect; identifying which components are contributing to the target outcomes and which, if any, may be discarded. Results of this project will provide optimized SMT protocols that will be ready for application in future randomized controlled trials examining the efficacy and effectiveness of SMT.

3. STUDY DESIGN

We will use a factorial design examining 3 intervention components (additional SMT, mobilizing and multifidus activating exercise) provided in 8 different combinations following provision of 2 SMT treatment sessions as in our prior work. We will recruit 316 subjects with non-specific LBP with the goal of enrolling 280 subjects after all eligibility screening are complete. All subjects will receive the 2-session SMT protocol used in our prior studies. At the third session subjects will be categorized as SMT responders or non-responders based on our previously-validated threshold of 50% improvement on the Oswestry (ODQ). Randomization to subsequent treatment will be stratified based on responder status. This will allow us to examine the moderating effects of early clinical response. In our prior studies 35%-45% of individuals with LBP are responders to SMT after 2 sessions. What is unknown is the persistence of the improvement observed in early responders and whether or not persistence can be augmented through additional SMT and/or co-interventions working on the same causal pathways as SMT. Likewise, it is unknown from our prior work if early non-responders can be converted to responders with additional SMT and/or co-interventions. Therefore, we will randomly assign subjects to receive 6 additional sessions (or no additional treatment) provided over 3 weeks with varied combinations of additional SMT and exercise co-interventions. We chose 6 additional sessions based on work related to SMT dose-response reporting only modest difference in clinical outcomes in subjects receiving 9-12 sessions relative to 3-6 SMT sessions without co-interventions. Outcomes including assessments of

Treatment Phase I (1 week)

Session	Treatment	Measures
1	SMT	Indentation/RUSI pre- and post-SMT
2	SMT	Indentation/RUSI pre- and post-SMT
3	none	Indentation/RUSI and Clinical Assessment



Treatment Phase II (3 weeks)

1	No additional treatment
2	6 sessions SMT
3	6 sessions LM activation ex
4	6 sessions mobilizing ex.
5	6 session LM activation + mobilizing ex
6	6 session SMT + mobilizing ex.
7	6 session SMT + LM activation ex.
8	6 session SMT + LM activation + mobilizing ex.

Outline of research design (LM = lumbar multifidus)

mechanisms and patient-centered outcomes will be examined at baseline and after 1 week (end of phase I), 4 weeks (primary outcome - end of phase II), and after 3 months (long-term outcome).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Subjects in this study must satisfy all of the following eligibility criteria:

I. Pain between the 12th rib and buttocks with or without symptoms into one or both legs, which, in the opinion of the examiner, originate from the lumbar region.

II. Age 18 - 60 years

III. Oswestry disability score $\geq$ 20%

4.2 Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be excluded from participation.

I. No prior surgery to the lumbosacral spine

II. Not currently pregnant

III. Not currently receiving mind-body or exercise treatment for LBP from a healthcare provider (e.g., chiropractic, physical therapy, massage therapy, etc.)

IV. No neurogenic signs including any of the following: positive ipsi- or contra-lateral straight leg raise test (symptoms reproduced <45^0); reflex, sensory, or strength deficit in a pattern consistent with lumbar nerve root compression

V. No “red flags” of a potentially serious condition including cauda equina syndrome, major or rapidly progressing neurological deficit, fracture, cancer, infection or systemic disease

4.3 Study Enrollment Procedures

Participants will be enrolled at two sites: the University of Utah and University of Alberta. At the University of Utah we will work within the University of Utah Health Care (UUHC) family practice and physiatry providers to encourage direct referral of interested individuals consulting for LBP into the study. We will also develop IRB-approved recruitment materials to be integrated into our EPIC electronic health record, allowing providers to print and provide the information to potentially-interested individuals. We will also work with the Center for Clinical and Translational Science (CCTS) Bioinformatics Core to use the UUHC electronic data warehouse (EDW) to identify patients with specific characteristics based on demographic information and ICD-10 codes. These individuals are informed of the study by mail with information on procedures to opt-in or out of the study by contacting research personnel. For this project we will identify patients with a family practice visit with an ICD-10 code related to non-specific LBP (M54.5, M54.9, M51.36) between the ages of 18-60 with no record of surgery in the EDW. We will also recruit individuals with LBP who are not seeking care with flyers and ads in the community.

At the University of Alberta we will recruit from clinics that have been used successfully in the past. These include general practice, physical therapy and chiropractic clinics within the main campus community. University of Alberta already has IRB-approved recruitment materials that have been used in these clinics previously and can be further distributed to potential participants through various approved electronic distribution services. We will also work with the various professional associations to identify patients with specific characteristics using established communication strategies (e.g. patient newsletters and social media postings). As is the case in Utah, potential participants informed by these means will contact research personnel directly to establish eligibility and will align with ICD-10 code related to non-specific LBP (M54.5, M54.9, M51.36) between the ages of 18-60 with no record of surgery.

Individuals interested in participation will meet the site study coordinator to insure eligibility. Reasons for non-enrollment will be tracked. Eligible subjects choosing to participate will sign an informed consent document approved by the University of Utah or Alberta IRB, after which baseline examination procedures and completion of all eligibility assessments will be performed by a Research Assistant who will remain blinded to the subject's treatment group assignment throughout the study. Following baseline examination, all subjects will begin phase I treatment. All assessment and treatment sessions will be conducted at the Patient Wellness Center at the University of Utah and in the Rehabilitation Robotics Sandbox at the University of Alberta. Treatment will be provided by clinicians licensed to provide SMT (DC or PT) and trained in study-related procedures.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

5.1.1 Spinal Manipulative Therapy

The same SMT procedure will be used in phases I and II. Our past work has found equivalent outcomes regardless of SMT technique, thus we will standardize our technique consistent with our past work. This SMT technique has been applied successfully at both performance sites. All SMT sessions will begin with a brief assessment followed by SMT. The subject is supine. The clinician stands opposite the side to be manipulated and side-bends the subject away from the clinician. The side to be manipulated is the side the subject identifies as more painful. If the subject cannot identify a more painful side the clinician selects a side. The subject interlocks their fingers behind the head. The clinician rotates the subject, and delivers a high-velocity, low-amplitude (HVLA) thrust to the anterior superior iliac spine in a posterior/inferior direction. The clinician notes if a cavitation (ie, a "pop") occurred. If it does, SMT treatment is complete. If no cavitation occurs, the subject is repositioned and SMT is performed again. If no cavitation occurs on the second attempt, the clinician will manipulate the opposite side. A maximum of 2 attempts per side is permitted. If no cavitation is noted by that time, SMT treatment is complete. The number of SMT attempts will be recorded by the clinician. Our previous research found no difference in outcome between this SMT procedure and a side-posture HVLA technique. We will permit substitution with side-posture HVLA if the preferred technique is not possible due to subject preference or comfort. In prior research we found the supine and side-posture HVLA techniques well-tolerated with no adverse events.

5.1.2 Multifidus Exercises

Subjects randomized to receive multifidus exercises will begin with isometric multifidus contractions in different positions with clinician feedback and exercises to isometrically co-contract the multifidus and deep abdominal muscles. These exercises have been shown to be effective for activating the multifidus. Subjects will also perform lumbar extensor strengthening exercises shown to produce 20%-50% of multifidus maximum voluntary contraction. This dose is adequate to enhance multifidus activation, without imposing high loads that may exacerbate LBP. Subjects will continue to perform isometric exercises throughout treatment. We have applied these exercises in prior research with no adverse events.

Activity	Description	Initial Dose	Goals for Progression
Preferential, isometric multifidus activation exercises	1. Isolated multifidus contraction while prone, seated, standing 2. Isolated co-contraction of multifidus and deep abdominals in sitting, standing	5 repetitions, 10 sec. hold with normal breathing (each exercise)	progress toward 10 repetitions, 10 sec. hold, perform 2-3x daily
General lumbar extensor and multifidus activation exercises	1. Quadruped single arm raises	10 lifts, 5 sec. hold each arm	progress towards 20 lifts, add arm+leg lift
	2. Side-support exercise	10 repetitions 5 sec. hold each side	progress towards 20 repetitions

Activity	Description	Initial Dose	Goals for Progression
(subjects prescribed no more than 2 exercises at a time)	3. Bridging while hook-lying	10 repetitions, 5 sec. hold	progress towards 20 repetitions
	4. Prone single leg lift	10 lifts, 5 sec. hold each leg	progress towards 20 lifts, add arm+leg lift
	5. Prone trunk lift	10 lifts, 5 sec. hold	progress towards 20 lifts

Table. Multifidus activation exercise protocol

5.1.3 Mobilizing Exercises

Subjects randomized to receive mobilizing exercises during phase II will be instructed in a program of repeated movements progressing into end-ranges of spinal flexion and/or extension based on principles described by McKenzie, and shown in past studies to reduce spinal stiffness. Subjects will be instructed in mid-range exercises and will be further assessed for a directional preference. A directional preference is present if movement in a particular direction decreases LBP intensity or causes symptoms to centralize towards the midline. Directional preference can be determined reliably and if present, matching the direction of mobilizing exercise to the directional preference improves outcomes. If a subject has a directional preference he or she will be prescribed exercises specifically in that direction along with mid-range exercise. Otherwise the subject will be assigned exercises moving into either flexion or extension based on the clinician's discretion. Subjects will perform their prescribed exercises following SMT at treatment sessions and will be instructed to perform the exercises daily on other days. We have applied these exercises in prior research with no adverse events.

Activity	Description	Initial Dose	Goals for Progression
Mid-range spinal mobility exercises	1. Supine pelvic tilts to promote lumbar flexion/extension 2. Quadruped rocking into lumbar flexion/extension 3. Supine to side lying rotational mobilizations 4. Sitting rotational mobilizations 5. Flexion/Extension	10-20 repetitions each direction performed daily (each exercise)	Full, pain-free ROM, progress to 40 repetitions throughout the day
Exercises specifically into spinal flexion	1. Supine pelvic tilt 2. Quadruped rocking into lumbar flexion 3. Double knee-to-chest while supine 4. Standing flexion 5. Seated flexion 6. Self mobilization into flexion	10-20 repetitions performed daily (prescribe 2 exercises)	Full, pain-free ROM, progress to 40 repetitions throughout the day
Exercises specifically into spinal extension	1. Supine pelvic tilt 2. Quadruped rocking into lumbar flexion 3. Supported on elbows while prone 30 sec 4. Prone press-ups to extended elbows 5. Prone press-ups to extended elbows with exhale 6. Extension while standing 7. Extension in standing with self over pressure	10-20 repetitions performed daily (prescribe 2 exercises)	Full, pain-free ROM, progress to 40 repetitions throughout the day

Table. Stiffness exercise protocol

5.2 Concomitant Interventions

5.2.1 Allowed Interventions

Interventions permitted during the study period include use of medication to control LBP symptoms (NSAIDs, muscle relaxants, etc.) The use of various medications will be recorded at the baseline examination. Visits to health care providers for LBP are allowed during the study period (e.g., physician visits) as long as no interventional procedures are received (e.g., spinal manipulation, massage, exercise therapy, etc.)

5.2.2 Prohibited Interventions

Prohibited interventions during the study period include any mind-body or other interventional procedures including spinal manipulation, massage, exercise therapy, acupuncture, spinal injections, surgical procedures, etc. If any prohibited events occur these will be recorded as off-protocol events. Subjects will continue to participate in study-related treatments and assessments unless the off-protocol intervention changes the risk-benefit profile for the subject.

5.3 Adherence Assessment

Treatment adherence will be assessed based on attendance at scheduled treatment sessions and compliance with treatment protocols during treatment sessions. Once enrolled, a participant will have forms in REDCap for each scheduled treatment session according to the participant's randomized group assignment. Treatment session forms will permit an evaluation of the number of scheduled sessions attended by each participant. For sessions that are attended, the treating clinician will information on the interventions provided and any reasons for non-adherence to protocols. The site study coordinator will monitor the forms at least monthly and discuss instances of non-adherence with the clinician. All off-protocol events will be recorded, such as the use of use of modalities (heat, cold, ultrasound, etc.), or application of manual therapy or exercise procedures not outlined in the protocol. For purposes of the data analysis per-protocol analyses we will define "adherence" as occurring when at least 80% of scheduled treatment sessions are attended. Attendance at <80% of scheduled sessions will be considered a protocol deviation.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening Assessment (Day -7 - 0)	Baseline Assessment, Visit 1 (Day 0)	TX Visits 1-2 (Days 0-7)	1 Week Follow-Up (Day 7-10)	TX Visits 3-8 (Days 8 – 35)	4 Week Follow-Up (Day 29-42)	3 Month Follow-Up (Day 83-97)
Informed Consent Form		X					
Eligibility Criteria	X	X					
Demographics		X					
Medical History		X					
Physical Examination		X		X		X	X
Enrollment		X					
Self-Report Questionnaires							
Oswestry Disability Index	X*	X*		X		X	X
Numeric Pain Rating		X		X		X	X
Psychological Covariates (FABQ, PSESF, PCSF)		X		X		X	X
Global Rating of Change						X	X
Spinal Stiffness Assessment			X	X		X	X
Multifidus Assessment			X	X		X	X
Adverse Events/Side Effects				X		X	
Randomization				X			
Treatment Session Form			X		X		

*Oswestry is to be administered once between screening and baseline, or twice if needed at clinician discretion or if > 7 days has passed since first Oswestry completed.

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Individuals who contact the site Study Coordinator will be provided information about the study. The Study Coordinator will confirm that the individual is between age 18-60 and is not receiving other interventional or mind-body procedures for their LBP. If the individual is interested in learning more about the project a baseline assessment will be scheduled to obtain informed consent, insure all eligibility criteria are met and schedule a full assessment to begin the study either at that time or within 7 days of the screening evaluation. Before the scheduled baseline assessment, the participant may complete the Oswestry Disability survey to determine if their score is ≥ 20%. If the Oswestry score is < 20%, the participant will be notified that they are ineligible for the study and the assessment cancelled.

6.2.1.1 Consenting Procedure

Interested individuals who are scheduled for a baseline assessment will begin the assessment by providing written informed consent using a form approved by the site institutional review board. The consenting process will be conducted by a research assistant who is trained by the Principal Investigator at the site and has completed Biomedical Research Training for Human Subjects research through the Collaborative Institutional Training Institute (CITI) which includes modules on human subjects research ethics and regulations related to informed consent. A copy of the signed informed consent document will be retained by the researchers. A single consent form will be used for the project. The research assistant consenting the participant will sign an Informed Consent Form (ICF) checklist which will be retained by the researchers.

6.2.1.2 Screening

Once informed consent is obtained the following screening procedures will be completed within 72 hours to insure eligibility:

- Confirm age on the date of consent is between 18 – 60 years old.
- Confirm that the participant is not aware that she is pregnant.
- Confirm that the participant is not currently receiving other interventions for their LBP.
- Confirm that the participant is experiencing LBP defined as pain between the 12^{th} ribs and buttock with or without symptoms that extend into the buttock(s) or leg(s). without “red flags” suggesting a possible non-musculoskeletal cause (recent trauma, unexplained weight loss, night pain, systemtic illness)
- Participant completes the Oswestry disability index to insure the score is ≥20%
- Research assistant conducts the physical examination to insure no signs of neurologic deficit are present (positive ipsi- or contra-lateral straight leg raise test (symptoms reproduced $<45^0$); reflex, sensory, or strength deficit in a pattern consistent with lumbar nerve root compression)

6.2.2 Enrollment, Baseline, and/or Randomization

6.2.2.1 Enrollment

This study uses a single informed consent document for both screening and treatment purposes. Thus the enrollment date is the date on which the consent document was signed and eligibility was confirmed. We anticipate that screening will be completed on the same day for the majority of participants because of the relatively simple and quick screening procedures required. At the latest screening will be completed within 7 days.

6.2.2.2 Baseline Assessments

Assessments involve collection of both mechanistic and self-report outcomes. Self-report

measures will be collected via REDCap (Research Electronic Data Capture), an NIH-supported, browser-based, software solution that allows researchers to create secure online forms for data capture, management and analysis. At each assessment participants will input data directly into REDCap. If a participant is unable to directly input data using a computer paper forms will be available with data uploaded at a later time.

The following assessments are collected at baseline:

- Demographic data will include age, sex, race/ethnicity, employment status and general medical and LBP history. Current medication use for LBP will be recorded. This information will be used for descriptive purposes and possible covariates in analyses.
- Physical examination will include spinal and hip range of motion and segmental mobility assessed with manually-applied posterior-anterior force.
- Oswestry Disability Index (OSW): a self-reported LBP-specific measure of function assessed on a 0-100 scale, with lower numbers indicating better function.
- Numeric Pain Rating Scale: a self-reported 0-10 rating of pain intensity ranging from '0' no pain, and '10' worst imaginable pain.
- Psychosocial Covariate Measures*:* will include Fear Avoidance Beliefs Questionnaire will be used to measure patients' beliefs about how physical activity and work may affect their LBP and perceived risk for re-injury. The Pain Catastrophizing and Pain Self-Efficacy short forms will be used to measure the extent to which people catastrophize in response to pain and their degree of confidence in the ability to function with pain respectively. These variables may serve as covariates in the analyses to control for psychosocial risk factors.
- Spinal Stiffness Measures: are obtained with a mechanically-assisted indentation device consisting of a motorized probe in an external frame. The probe contains a compressive-tension load cell. Displacement of the probe is measured by a linear variable differential transformer. Stiffness is assessed with the subject prone. The indentation probe is positioned over the L_3 spinous process. Indentation involves advancement of the probe from 5 N pre-load to 60 N final load maintained for 1 second. Three trials are performed with mean values used for analysis. Indentation data are used to calculate global stiffness (GS) (N) as the slope of the force displacement curve and terminal stiffness (TS) (N/mm) as the peak applied force and resultant displacement of underlying tissue.
- Lumbar Multifidus Activation Measures: are obtained with brightness-mode ultrasound images. The subject is prone with neck in neutral and arms overhead at about 120^0 of shoulder abduction. Ultrasound transducer is placed just lateral to the spinal midline and angled medially until a parasagittal view of the multifidus at the L_4-L_5 and L_5-S_1 levels is obtained. Images are acquired at each level with the multifidus at rest and during submaximal contraction elicited by lifting the contralateral arm 2 inches while holding a weight proportional to body weight. Three images in each state are acquired and averaged. Muscle activation is calculated as change in thickness at rest and submaximal contraction.

6.2.2.3 Randomization

Following baseline assessment all participants will receive 2 SMT treatment sessions in the next week. Randomization to additional treatment will be done at the 1-week assessment. A randomization schedule will be developed prior to enrollment by co-investigator Dr. Greene, Director of the Study Design and Biostatistics Center (SDBC) in the CCTS at the University of Utah. Blocked randomization with block sizes of 4 or 6 will be used. Randomization will be stratified based on site (Utah or Alberta) and responder status after 2 SMT sessions (based on re-assessment of the OSW) to balance these variables. At the 1-week assessment the study coordinator or research assistant will look up the participant in the study database and open the Responder & Randomization Status

form in REDCap. This form will display the Oswestry score from the baseline assessment and the calculation of score change. The percent change between baseline and 1-week scores determines responder status (>50% improvement = "responder"; <50% improvement= "non-responder"). Once the responder status is entered the study staff will select the randomize button on the screen to trigger study assignment based on the allocation table provided by the biostatistician, provided all of eligibility criteria are met and the participant has been assigned to one of the two study sites. If any of these criteria are not valid a warning message will be displayed indicating the criteria issue(s) and the randomization will not be completed.

6.2.3 Blinding

Participants cannot be blinded to study treatments. Randomization assignment will not be revealed until baseline examination, the first 2 SMT sessions, and the OSW assessment are complete to reduce potential bias by either the subject or research assistant. Follow-up assessments will be performed by a research assistant who will be blind to participants' treatment assignments. Participants will be reminded by the research assistant not to discuss aspects of their treatment during assessments. If a research assistant becomes unblinded during the course of a participant's study participation, he or she will not be allowed to conduct additional follow-up assessments for that participant. The research assistant may participate in assessments for other participants for whom blinding has not been compromised. Instances of unblinding during an assessment will be recorded as an unexpected event.

Clinicians providing treatment cannot be blinded. The use of standardized protocols for all treatments and clinician-compliance audits throughout the project will minimize potential bias related to differential treatment application.

6.2.4 Follow-up Visits

- Treatment Visits 1 and 2 (*completed within the 7 days following day 0)*:
  - Spine stiffness and multifidus activation assessments pre- and post-SMT treatment
  - Treatment Session Form
- 1-Week Assessment (*completed from Day 7 – Day 12*):
  - Physical examination
  - Self-report questionnaires
  - Spine stiffness measures
  - Multifidus activation measures
  - Side effects questionnaire
- Treatment Visits 3 - 8 (*completed from Day 8 – Day 35, no more than 2 sessions/week)*:
  - Treatment Session Form
- 4-Week Assessment (*completed from Day 29 – Day 42, 3 weeks after 1-Wk assessment*):
  - Physical examination
  - Self-report questionnaires
  - Spine stiffness measures
  - Multifidus activation measures
  - Side effects questionnaire

6.2.5 Completion/Final Evaluation

The final evaluation occurs 3 months after Baseline (*from Day 83 – Day 97*). The following assessments are performed at the final evaluation. If a participant wishes to terminate the study early, this is also the list of assessments we will attempt to complete at termination. Early termination will only be done at a participant's request or if a participant's risk-to-benefit ratio is substantially altered due to a change in status.

- Physical examination
- Self-report questionnaires
- Spine stiffness measures
- Multifidus activation measures

7. SAFETY ASSESSMENTS

Expected adverse events based on our prior experience and literature reports that may occur with the study interventions and assessments include the following:

- Increased back or spine pain intensity
- Muscle soreness
- Muscle spasms
- Psychological distress

7.1 Specification of Safety Parameters

Safety parameters intended to reduce risks for adverse events include having licensed clinicians specifically trained in the study procedures carry out all treatments. The spinal stiffness measurement procedure may be stopped at any time by the participant using a hand held switch. The potential risk of psychological distress from answering self-report questions about the impact of the individual's LBP on various aspects of his or her life will be minimized by telling participants that they are not required to answer any questions that are distressing.

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

The risk profile of the interventions in this study is minimal. Treatment procedures in the study are standard procedures used in everyday clinical practice and the measurement procedures have been applied by this research team in several preliminary studies.[1,2] The use of manipulation for patients with acute LBP is supported by clinical practice guidelines in the United States[3] and elsewhere, and is not associated with a high risk of serious side effects.[4] Ultrasound measurement procedures are similar to those used during pregnancy, using low intensity ultrasound waves spread over a large area which causes very minimal heating that is mostly undetectable to the subject. The spinal stiffness measurement procedure uses a 60 N force to assess spinal stiffness. We have tested several hundred subjects with this procedure with no adverse events.[2]

1. Fritz JM, Magel JS, McFadden M, et al. Early Physical Therapy vs Usual Care in Patients With Recent-Onset Low Back Pain: A Randomized Clinical Trial. JAMA. 2015;314(14):1459-67.
2. Wong AY, Parent EC, Dhillon SS, Prasad N, Kawchuk GN. Do participants with low back pain who respond to spinal manipulative therapy differ biomechanically from nonresponders, untreated controls or asymptomatic controls? Spine. 2015;40(17):1329-37.
3. Chou R, Huffman LH; American Pain Society; American College of Physicians. Non-pharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007;147(7):492-504.

4. Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med.2012:953139.

7.3 Adverse Events and Serious Adverse Events

Adverse events will solicited at each assessment (1 week, 4 weeks, 3 months). If an adverse event is identified unsolicited during a treatment session or other contact with research personnel, the event will be recorded and reported as outlined below.

Definitions

Adverse Event (AE)

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

Unanticipated Problems (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Event (SAE)

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

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

7.4 Reporting Procedures

The site PI at the University of Alberta must immediately report to the University of Utah PI any serious adverse event, whether or not considered study related, and must include an assessment of whether there is a reasonable possibility that the study caused the event within 72 hours of PI awareness of the event. The site PI for the University of Alberta must also report any unanticipated problems within the same timeframe. The Site PI must also report any other adverse events within 7 days of PI awareness. Participating centers must submit all reports to their local IRB other entities using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, DSM committee and NCCIH within 3 days of the investigator becoming aware of the event.

- Other unanticipated problem will be reported to the IRB, DSM committee, and NCCIH within 7 days of the investigator becoming aware of the problem.

Should an unanticipated problem need to be reported to the IRB it will be reported to the IRB of both the University of Utah and University of Alberta. A record of all reportable unanticipated problems will be maintained at the coordinating site and reported during annual DSM reports. In addition, researchers will record at each study visit the occurrence of any other adverse events (e.g., visiting the emergency room or medical provider for pain exacerbation, etc.) A report of all adverse events will be maintained by each site and reported annually on the DSM report.

Characteristics of an Adverse Event

Relationship to Study Intervention

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

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

Expectedness of SAEs

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

Severity of Event

The following scale will be used to grade adverse events:

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

7.5 Followup for Adverse Events

All adverse events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

The scope and the purpose of this study qualifies as a Phase III clinical trial, therefore a data and safety monitoring (DSM) board will be established based on the NIH guidelines and NCCIH input, and commensurate with the level of risk, size, and complexity of this study.

Composition of the DSM: The DSM Board will be composed of three individuals with expertise in disciplines relevant to the conduct of this study who are not involved in the study, and have no conflict of interest or economic interest in the results of the study.

Frequency and Character of DSM Meetings: Because this study involves procedures with minimal risk, we propose to conduct DSM meetings via conference call on an annual basis. Each DSM meeting will begin with an open session that will be attended by all trial Investigators, Study Coordinators and representatives from the NCCIH Program Office. Open session will review study procedures, plans for data and safety monitoring, recruitment and retention, gender and minority inclusion, protocol adherence, data management, the occurrence of any adverse events. The open session will be followed by a closed session that will be attended by only the DSMB members and NCCIH representatives. The closed session will be used to discuss data to which the other Investigators must remain blinded.

Content of DSMB Meeting Reports: DSM report from each meeting will review the topics discussed at the meeting with respect to study procedures, accrual and retention, data management, etc. The DSM report will include a recommendation concerning continuation of the study. Each DSM report will provide a tally of all adverse events in each of the categories listed above in all treatment groups. Blinding of adverse event results will be maintained and will be broken only if the DSMB indicates a need to un-blind groups for serious safety reasons. DSMB reports will be submitted to the Principal Investigator, the NCCIH Program Office, and the University of Utah ad University of Alberta Institutional Review Boards.

8. INTERVENTION DISCONTINUATION

The investigators will only discontinue a participant's intervention if the risk-benefit ratio for that participant changes substantially such that they would no longer meet the project's eligibility criteria. Examples include development of signs consistent with neurologic deficits or presentation of "red flag" symptoms. These circumstances will be identified by research personnel during study visits for treatment or assessments. If a participant is discontinued, we will continue to collect the self-report outcomes only.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This study uses a factorial design examining 3 intervention components (additional SMT, mobilizing and multifidus activating exercise) provided in 8 different combinations following provision of 2 SMT treatment sessions. All participants will receive 2 SMT sessions. At the third session participants will be categorized as responders or non-responders based on a threshold of 50% improvement on the OSW. Randomization to subsequent treatment is stratified by responder status. We will randomly assign participants to receive 6 additional sessions (or no additional treatment) over 3 weeks with varied combinations of additional SMT and exercise co-interventions. It is important to distinguish the factorial design from an 8-arm trial. The factorial approach evaluates the main effects of the 3 additional intervention components (additional SMT, mobilizing and multifidus activating exercise) and interactions among components. It does not compare 8 distinct treatment arms and thus is more efficient with a smaller sample size relative to an 8-arm randomized trial.

Our primary hypothesis is that one or more combination of treatment components will optimize improvement in SMT mechanistic effects (reduction in spinal stiffness and improvement in multifidus activation) as well as improvement in patient-centered outcomes (LBP-related disability and pain intensity). Our secondary hypothesis is that responder status after 2 sessions will moderate the mechanistic and patient-centered outcomes. Our work and the work of others has demonstrated that these mechanistic and patient-reported outcomes are valid and can be collected reliably.

9.2 Sample Size and Randomization

Based on our past trials, we project 95% retention at 4-weeks. We estimated standard deviations of each outcome based on patients in a similar project with analogous eligibility criteria, and conservatively estimated pre-post correlations to be 4%-7% smaller than the values in this study. Assuming a sample size of 316, of which 280 meet all eligibility criteria and 92% of enrolled participants are retained to 4 weeks, the table below displays minimum detectable effect sizes for a) main effects of each protocol component, b) pairwise interactions between components, c) comparison of mean outcome between two levels of one component at a fixed level of another component, d) main effects of the 3 components in subgroup analyses involving half the participants, and e) pairwise interactions between 2 components in subgroup analyses with half the participants. This sample size provides at least 80% power to detect the MCID or hypothesized effect sizes for the main effects of each component for all outcomes, and for analyses of main effects in subgroups and conditional comparisons for each outcome except global stiffness. Power is more limited for secondary aims, such as pairwise interactions within subgroups.

	Assumptions for Outcome Measures in Project			
	Global Stiffness (N)	Multifidus Activation (mm)	Oswestry	Numeric Pain Rating
Assumption				
Mean (SD)	5.55 (1.60)	2.60 (0.124)	24.3 (14.9)	5.06 (2.12)
Pre-post score correlation	0.80	0.70	0.70	0.45
MCID or hypothesized effect size from past work	0.40	0.074	6.0	2.0
Type of effect	**Detectable Effect Size**			
Main effect	0.37	0.034	4.12	0.76
Pairwise interaction	0.74	0.064	8.24	1.53
Conditional comparison	0.53	0.045	5.83	1.08
Main effect in 50% of subjects	0.53	0.045	5.83	1.08
Interaction in 50% of subjects	1.05	0.091	11.65	2.16

Table. Assumptions and detectable effect sizes informing sample size for the project.

Because the analyses of the longitudinal models will be based on restricted maximum likelihood estimation, statistical inferences will remain valid so long as missing data follow a missing at random structure, and based on our past work we expect little missing data at the 4 week assessment. Thus we do not believe missing data will lead to substantial bias in our primary evaluation of protocol components. However, we will compare subject characteristics between subgroups with missing and nonmissing data at 4 weeks and if substantial deviations are detected, or the rate of missing data is greater than expected, multiple imputation will be applied using comprehensive imputation models which include auxiliary variables to account for additional predictors of missingness and/or the values of the outcome variables.

9.2.1 Treatment Assignment Procedures

A randomization schedule will be developed prior to enrollment by Dr. Greene, Director of the Study Design and Biostatistics Center at the University of Utah. Blocked randomization with block sizes of 4 or 6 will be used. Randomization will be stratified based on site (Utah or Alberta) and responder status after 2 SMT sessions to balance these variables. Sequentially-numbered, sealed envelopes will be prepared containing treatment group assignments. The randomization envelope will be opened by the site Study Coordinator after completion of all baseline procedures and the 2 SMT sessions.

Subjects cannot be blinded to study treatments. Because our purpose is to optimize protocols, not to evaluate the SMT efficacy, we will not use placebos or attempt to balance clinician time. Randomization assignment will not be revealed until baseline examination, the first 2 SMT

sessions, and the OSW assessment are complete to reduce potential bias by either the subject or research assistant. Follow-up assessments will be performed by a Research Assistant who will be blind to subjects' treatment assignments. Clinicians providing treatment cannot be blinded. The use of standardized protocols for all treatments and clinician-compliance audits throughout the project will minimize potential bias related to differential treatment application. The PI at each site will be able to break the blinding if necessary for participant safety considerations.

9.3 Definition of Populations

Intention-to-treat principles will be used with all participants analyzed in their randomized group regardless of compliance. We will compare compliance between groups and "per-protocol" secondary analyses may be considered if non-compliance is high or disproportionate between groups. A compliant treatment episode will be defined as receiving at least 80% of study sessions based on randomized group.

9.4 Interim Analyses and Stopping Rules

Because of the minimal risk of the procedures in this study we have not proposed any stopping rules. We have not defined any procedures for interim analyses to avoid the risk of inflating Type I error. We will monitor the occurrence of adverse events throughout the study. If the number of serious adverse events warrants, we will suspend enrollment and review the safety of the study procedures under the direction of the DSM board and NCCIH representatives.

9.5 Outcomes

Outcome measure for the primary and secondary hypotheses of the study are outlined below. These outcomes will not require any adjudication.

9.5.1 Primary and Secondary Outcomes

The outcomes used to address the primary and secondary hypotheses of this project are each collected at baseline, 1-week, 4-week and 3-month assessments.

Oswestry Disability Questionnaire (OSW): The OSW is a LBP-specific measure of function for patients with LBP assessed on a 0-100 scale, with lower numbers indicating better function. Our past research has found the ODQ to have high test-retest reliability (ICC = 0.90), good construct validity, and responsiveness to change for patients with LBP, with a minimum clinically important difference (MCID) of 6 points.

Numeric Pain Rating Scale (NPRS): A 0-10 NPRS ('0' no pain, and '10' worst imaginable pain) will be used to assess LBP intensity. The NPRS has excellent test-retest reliability. Our previous research has found the NPRS to be responsive to change with an MCID of 2 points for acute LBP.

Spinal Stiffness: Spine stiffness will be assessed with a mechanically-assisted indentation device developed by Dr. Kawchuk and used in our previous research. The device consists of a motorized indentation probe supported by an external frame. The probe contains a compressive-tension load cell (Entran, Fairfield, NJ) connected in-series with the probe. Displacement of the probe is measured by a linear variable differential transformer (Honeywell International Inc., Morristown, NJ) attached between the probe and its external housing. Signals from the load cell and transformer are collected by customized LABview software (National Instruments, Austin, TX) at a collection rate of 200 Hz.

Spinal stiffness is assessed with the subject prone on a table with arms at the side and a neutral neck position. The examiner manually identifies and marks the L_3 spinous process, and positions the indentation probe over it. The subject is instructed to inhale and exhale comfortably, and hold their breath at the end of exhalation during indentation, which lasts about 5 seconds. Indentation involves advancement of the probe from a 5 N pre-load to 60 N final load maintained for 1 second, then the probe raises automatically. Three indentation trials are performed with mean values used

for analysis. Indentation data (force and displacement) are used to calculate stiffness variables. Global stiffness (GS) (N) is calculated as the slope of the force displacement curve between 5-60 N, representing stiffness of underlying tissues during indentation. Terminal stiffness (TS) (N/mm) represents peak applied force and resultant displacement of underlying tissues. We have found excellent within- and between-day reliability of stiffness measures made with this device (ICC = 0.98-0.99). A safety switch is provided to the subject and assessor that raises the indentation probe immediately if pressed, providing additional safety features.

Lumbar Multifidus Muscle Activation: Multifidus activation will be measured with brightness-mode ultrasound images using a 60mm, 2-5 MHz curvilinear array. We have previously reported excellent intra- and inter-rater reliability for these measurs. The subject is prone with neck in neutral and arms overhead at about 120^0 of shoulder abduction. The ultrasound transducer is placed just lateral to the spinal midline and angled medially until a parasagittal view of the multifidus at the L_4-L_5 and L_5-S_1 levels is obtained. Images are acquired at each level with the multifidus at rest and during submaximal contraction elicited by the subject lifting the contralateral arm about 2 inches while holding a weight proportional to body weight. Images are acquired at the end of exhalation to minimize effects of respiration. Three images in each state are acquired and averaged. Images are stored and measured offline by a blinded rater using NIH (Bethesda, MD) Image J software (V1.38t). Offline multifidus thickness measures are obtained from determining the distance between the posterior-most aspect of the facet joint inferiorly and the plane between the multifidus and thoracolumbar fascia superior. Activation is calculated as the change in thickness from rest to submaximal contraction ($Thickness_{contract}$–$Thickness_{rest}$) / $Thickness_{rest}$). Research has shown these measures of multifidus activation have good concurrent validity compared to EMG activity of the muscle.

9.6 Data Analyses

Primary Aim 1: Spine stiffness and multifidus activation will be co-primary outcomes for evaluating effects of SMT protocol components on SMT mechanisms. The effect of intervention components (A additional SMT; B multifidus activation; C mobilizing exercises) on each outcome will be evaluated using linear mixed models to relate mean levels of each outcome at 1-, 4-weeks and 3-months to indicator variables to represent the main effects of each interventions (A, B, C) as well as each pairwise interaction between the interventions (AxB, AxC, BxC) and the 3-way interaction (AxBxC). 1-week assessment, which occurs just before randomization, will serve as the baseline for these analyses and the model will be assumed equal between the randomized groups. This model, sometimes referred to as a constrained longitudinal model, leads to adjustment for baseline levels as in analysis of covariance (ANCOVA), which has been shown to remove conditional bias in treatment group comparisons due to chance imbalances and improve statistical power over unadjusted comparisons. An unstructured covariance matrix will be used to account for correlation of serially measured outcome scores in the same subject. By using an unstructured covariance matrix, the model will constitute a special case of a general linear mixed model which avoids imposing specific assumptions concerning distribution of random effects. This modelling approach is recommended in randomized trials when the number of follow-up outcome assessments is small. Restricted maximum likelihood estimation will be used for estimation of parameters and their associated standard errors.

Linear mixed effects analysis will provide estimates and CIs for the following quantities for each outcome at both 4-week and 3-month assessments: a) Main effects evaluating effects of each of the 3 interventions while averaging over the levels of the other 2 interventions. b) Three pairwise interactions evaluating if the effect of an intervention differs between levels of another

interventions, while averaging over levels of the 3rd intervention. Pairwise interactions will inform whether the effects of each intervention pair are additive, synergistic or antagonistic. c) 3-way interaction evaluating if each pairwise interaction differs depending on the 3rd intervention.

Adjusted means with CIs will be provided for each treatment combination. Interaction plots will be used to depict significant interactions and linear contrasts constructed to evaluate the effect of each intervention conditional on the presence or absence of the other intervention. To account for 2 primary outcomes, each of the hypothesis tests noted above will be performed with 2-sided α=0.025 and confidence intervals will be constructed using a confidence coefficient of 0.975. The indicated comparisons at 4-weeks will be given primary emphasis in evaluating the effects of each intervention. Comparisons at 3-months will evaluate persistence of effects following intervention.

Primary Aim #2: The OSW and NPRS will be co-primary outcomes for evaluating the effects of the 3 SMT protocol components on patient centered outcomes. The same analytic approach described above will be used. To account for 2 outcomes, we will again apply a 2-sided α=0.05 and 97.5% CIs for statistical inference.

Secondary Aim #1: It is unknown how early SMT response may affect response to additional intervention. We will examine this question by evaluating responder status after 1 week as a possible effect moderator by adding a main effect for responder status and interaction terms between responder status and the indicator variables for treatments (and treatment combinations) which are retrained in the final simplified models for the different outcomes developed using the BIC criteria for each of the co-primary outcomes for the primary aims 1 and 2. Statistically significant interactions between responder status and main effect and/or interaction terms between treatment intervention components will be interpreted as suggesting effect moderation. Recognizing that tests for interactions have limited statistical power, we will also fit the simplified models developed in Aims 1 and 2 separately under the presence and absence of each factor (dichotomizing using a median split for continuous factors), and graphically display the estimated treatment effects at both levels of responder status. Recognizing the potential for lower statistical power, the results of Secondary Aim #1 will be interpreted as exploratory.

Secondary Aim #2: In order to assess which intervention component combinations provide optimal outcomes, we will first simplify the fully saturated factorial analysis of variance model by comparing the Bayes Information Criterion (BIC) among all possible models including different combinations of main effects, pairwise interactions and the 3-way interaction which satisfy the hierarchical consistency constraint that the main effects corresponding to each term in a pairwise interaction are retained in models with pairwise interactions, and all component main effects and pairwise interactions are retained when considering the 3-way interaction. This will result in a more parsimonious model to increase statistical power. Then, using the simplified model, for each outcome we will use a simulation approach to derive simultaneous 97.5% CIs for all comparisons of estimated mean outcome under each possible treatment combinations (No further treatment, A, B, C, AxB, AxC, BxC, AxBxC). After ordering the treatment combinations in accordance with the observed mean outcome, the simultaneous CIs will be used to identify which combinations are statistically indistinguishable from the optimum treatment, thus identifying a set of candidate options for the best combination of treatments. This process will be applied for both mechanistic and patient-centered outcomes. We anticipate that more than one combination will be considered optimal for different outcomes, and that the combinations that are optimal will differ for different outcome measures. Our interpretation of optimized protocols will give preference to longer term outcomes (ie, 3-month scores) and patient-centered outcomes. We will also consider an application of the robust modelling approach to derive a model for the optimum combination of components as a multivariate function which jointly incorporates each the potential effect modification of week 1 responder status in the same model. This approach will estimate the combination of components providing the optimum expected outcome for each participant based on their responder status after 1 week.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Participant-reported measures will be collected via REDCap (Research Electronic Data Capture), an NIH-supported, browser-based, software solution that allows researchers to create secure online forms for data capture, management and analysis. At each assessment participants will input data directly into REDCap. If a participant is unable to directly input data, paper forms will be available with data uploaded at a later time. Self-report data will be downloaded from REDCap and integrated with mechanistic and physical examination data by the SDBC at the University of Utah. A research assistant blinded to the participant's randomly-assigned treatment group will conduct the assessments to avoid bias. Confidentiality of participant's records will be protected by storing all electronic information on encrypted, password-protected computers.

The database for this study will be kept on a server supplied by the University of Utah Health Sciences Center (UUHSC). The UUHSC utilizes technology from Hitachi Data Systems called the Universal Storage Platform for providing a virtualized storage area network. This network is maintained on a server by the University of Utah Health Sciences Information Technology Support. All programming for the analyses will also be stored on the same server and coordinated through the University of Utah SDBC.

Source documents not stored electronically will be maintained in locked cabinets within the personal offices of the PI and study coordinator at each site.

10.2 Data Management

Each subject enrolled in the study will receive a site-specific unique Patient Identifier that will be generated prior to beginning the study. Once a subject provides informed consent to participate in the study, the Study Coordinator will create a new Patient Profile in REDCap. The Patient Profile will be identified by the unique Patient Identifier, and will not contain the patient's name, Social Security number, or any other type of Personal Health Information data that could be used to identify the individual patient. The link between the Patient Identifier and the subject's Personal Health Information will be maintained by the Investigators, and will be available only to the Study Coordinators and Investigators. After the Patient Profile is created, the subject will be able to input all self-report data directly into REDCap using a computer or laptop using a web-based interface. All data entered by the subject into REDCap is identified only by the unique Patient Identifier. For participants who are unable to complete online data forms, paper forms will be provided.

All self-report subject data will be collected using the REDCap data collection platform. Additional subject information (e.g., informed consent documents, demographic and physical examination forms completed by the Research Assistant) will be entered into REDCap by the Study Coordinator or Research Assistant as appropriate. The University of Utah Study Design and Biostatistics Center (SDBC) at the University of Utah Center for Clinical and Translational Science (CCTS) will download study data monthly once enrollment begins. This information will not include any patient identifying information.

10.3 Quality Assurance

10.3.1 Training

Project investigators will conduct training sessions for all research assistants and clinicians who will provide interventions. The University of Utah will train 4 clinicians in the provision of study-related treatments. The University of Alberta will train 2 clinicians. Training will consist of written instructions for the performance of study-related techniques and hands-on practice. Both investigators are experienced in training clinicians to successfully perform treatment procedures, and researcher personnel in collection of human subjects data. All personnel will be trained for their role in the project before enrollment begins. During the first 3 months of the study, prior to

beginning data collection, a detailed Study Protocol will be compiled under the supervision of the Dr. Fritz with input from all investigators. The Protocol will be approved by the DSM prior to recruitment. All study personnel will review and familiarize themselves with the Study Protocol in detail prior to participation.

The Principal Investigators will conduct training sessions based on the Study Protocol for clinicians and research personnel during the first 3 months of the study. All research staff and clinicians will receive instruction in administrative aspects of the study (informed consent, subject recruitment, data and safety monitoring and subject confidentiality issues, etc.). Clinicians will receive additional training in all study-related treatment procedures previously described. Training goals will be accomplished by providing theoretical and practical information related to this project and the procedures employed. Management strategies based on group assignment will be highlighted with case examples. All clinicians and research personnel must complete training before participating in any study-related procedures. A training log will record successful completion of training activities.

10.3.2 Monitoring

All protocol deviations and adverse events will be recorded at both sites as previously outlined. Deviations or adverse events will be reported in a timely manner to the PI and to the IRBs of the participating institutions as required. Annually, a report will be compiled for review by the DSM and NCCIH representatives. The DSM may request more frequent reviews if necessary.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents from each study site (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., person with power of attorney), this individual must sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's study record.

11.3 Participant Confidentiality

Participant confidentiality will be protected in the data collection process. All personnel involved with the research at both sites responsible for collecting and handling the data will have completed the Collaborative Institutional Training Institute (CITI) modules for Human Subjects Research and Responsible Conduct of Research. Approval has been obtained by the respective Institutional Review Boards. Consent forms that identify the patient by name will be stored in a locked cabinet by the site Investigator. All data are assigned a unique identifier (not containing PHI) to identify each participant. Participants will be instructed not to identify themselves by name on any instrument. The data file linking names and code numbers will be accessible only to the site PI or Coordinator, and data will be entered into study databases by this unique identifier. If data are used in scholarly presentations or journal articles, the investigators will protect the anonymity of

individual participants and will report only aggregate data where appropriate. No audio or video taping will be conducted as part of this study. Information will not be released without written permission of the participant, except as necessary for monitoring by IRBs, NCCIH, and the OHRP.

11.4 Study Discontinuation

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

APPENDIX I

Informed Consent Documents