Clinical Intervention Study Protocol

SMART LBP: Optimized Multidisciplinary Treatment Programs for Nonspecific Chronic Low Back Pain

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Tool Revision History:

Version Number: 1.0
Version Date: November 1, 2018
Summary of Revisions Made: Original Version

Version Number: 2.0
Version Date: February 28, 2019
Summary of Revisions Made:

i. Study Roster – updated site personnel to reflect new personnel hired for the project

ii. Section 4.2 – Clarified Exclusion Criteria: Exclusion for PT in past 90 days is specific to treatment for LBP. Exclusion for CBT and mindfulness in past 90 days is for any condition. Added exclusion for current substance use disorder treatment (other than AA/NA programs)

iii. Sections 5.1.1 and 5.1.2 – the timeline for initiating study interventions following randomization was adjusted from 7 days to 30 days based on feedback from clinicians and health system stakeholders

iv. Section 5.4 – Adherence assessment was modified to define an adherent episode of care as occurring when ≥75% of study sessions are complete instead of 80%. Because there are 8 sessions in each protocol a threshold of 75% corresponds to attendance at 6 of 8 sessions.

v. Section 6.1 – Schedule of events – The window to complete the 10-week assessment was adjusted from 60-80 days post-enrollment to 70-90 post-enrollment to reflect the increased time frame allowed from enrollment to beginning study intervention.

vi. Section 6.1 – Schedule of events – The mode of collection of secondary PROMIS domain outcomes was changed from computer-adapted tests (CAT) to short forms from the PROMIS-29. Using short forms will allow individuals without internet access to provide data on these domains by not requiring a connection to web-based algorithms necessary for CAT administration. Section 6.1 – Schedule of events – The timing of assessment of health care utilization outcomes was modified from separate monthly inquiries to inquiries at scheduled follow-up assessments to reduce participant burden.

vii. Section 6.1.1.1 – Consenting Procedure - Informed consent process was modified to reflect the IRB-approved processes. The IRB at each site has approved the use of consent cover letter instead of requiring written informed consent documents to be signed.

viii. Section 6.2.2.2 – Baseline Assessments – modified to reflect collection of secondary outcomes measures reflecting PROMIS domains using short forms instead of CAT procedures and modification of utilization outcomes process.

ix. Section 6.2.4 – Follow-up Visits – Timeframe for completing 10-week assessment was modified from 60-80 days to 70-90 days post-enrollment

x. Section 9.5.1 – Primary and Secondary Outcomes – changes made to reflect change from CAT to short form application of PROMIS secondary outcome measures.

xi. Section 11.2 – Informed Consent – Changes made to reflect consenting process that does not require written informed consent.

Version Number: 2.1
Version Date: February 9, 2021
Summary of Revisions Made:

i. Section 4.1 – added inclusion criterion for ability to participate in telehealth sessions if necessary.

ii. Section 5.1 – Intervention Administration – clarified the methods used to determine if a study intervention will be delivered in-person or using remote telehealth delivery.

Version Number: 3.0
Version Date: April 11, 2022
Summary of Revisions Made:

i. Study Roster – updated site personnel

ii. PRÉCIS and Section 1.1 – Aim 1i – specified the main secondary outcome is long-term opioid use. Specified other secondary outcomes are considered exploratory

iii. PRÉCIS and Section 1.1 – Aim 2 – specified that the co-primary aim compares the effectiveness of Phase II treatments (mindfulness v. switching) among all Phase I non-responders. Aims 2A and 2B that compare Phase II treatments in the sub-group of non-responders in one of the Phase I treatment arms (PT or CBT) are designated as exploratory.

iv. PRÉCIS and Section 1.1 – Aim 2Ai and 2Bi – These sub-aims which proposed to examine Aims 2A and 2B for secondary outcome measures were deleted because power will not be sufficient for these analyses.

v. PRÉCIS and Section 1.2 – Aims 3A and 3B – changed the designation of these Aims from "Main Secondary" to "Secondary".

vi. PRÉCIS and Section 1.2 – Aims 3Ai and 3Bi – clarified that these Aims will be examined using the PROMIS secondary outcome measures.

vii. PRÉCIS and Section 1.2 – Aims 3Aii and 3Bii – These sub-aims which proposed to examine Aims 3A and 3B within patient sub-groups were deleted because power will not be sufficient for these analyses.

viii. PRÉCIS – Sample Size and Population – clarified that the sample size is now 748 instead of 945.

ix. Section 9.1 – removed the word "main" in reference to the secondary objective.

x. Section 9.2 – deleted the statement "Hence our design achieves power ≥ 0.999 for all hypotheses involving pain with α=0.01, allowing allocation of a larger α to the ODI"

xi. Section 9.2 – deleted the statements: "However, co-primary aims 2A and B address related questions as both compare Mindfulness to a Phase I intervention. Thus, hypothesis tests for aims 2A/B use 2-sided α=0.02 for ODI and 0.005 for pain to maintain an overall Type 1 error ≤ 0.05. For aims 1 and 3A/B, the sample size (945) is larger than required to detect MCIDs for the ODI and pain."

This was replaced with the following text to reflect changes to Aim 2.: "If the response rate is 30%, the design provides 80% power with 2-sided α=0.05 to detect mean differences in the ODI and pain of 3.76 and 0.77 points, respectively, at 1 year among phase 1 non-responders between patients assigned to Mindfulness vs switching to the alternative Phase I intervention in phase II. If the response rate is 45%, the design provides 80% power with 2-sided α=0.05 to detect mean differences in the ODI and pain of 4.25 and 0.87 points, respectively, at 1 year among phase 1 non-responders between patients assigned to Mindfulness vs switching to the alternative Phase I intervention in phase II. "

xii. Section 9.2 – The following text was deleted because it no longer applies due to the reduced sample size: "We selected this sample size to obtain sufficient power to address aims 2A/B where power is limited because analyses are restricted to subsets of non-responders to one Phase I treatment. A sample size of 945 is also necessary to provide well-powered subgroup analyses for aims 1 and 3A/B for subgroups as small as 1/3 of the cohort. We provide additional details for the power calculations for aims 1-4 below. Importantly, power for all designated analyses exceeds 83%, and continues to exceed 80% even if the attrition rate is 20% instead of 15%."

xiii. Section 9.2, Table of Power and Detectable Effect Sizes – This table was updated to reflect modifications to sample size and specific Aims

xiv. Section 9.6 – updated description of data analysis for Aim 1i to specify long-term opioid use as the secondary outcome with other outcomes (PROMIS scores) designated as exploratory analyses.

xv. Section 9.6 – updated the description of the Aim 2 analysis to specify that the analyses will examine all Phase I non-responders. Aims 2A/B have been updated to specify that the analyses will be exploratory.

xvi. Section 9.6 – removed the section explaining the data analysis for Aims 2Ai/Bi has been removed because these sub-aims have been removed.

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PRÉCIS

Study Title: SMART LBP: Optimized Multidisciplinary Treatment Programs for Nonspecific Chronic Low Back Pain

Objectives

Our objective is to improve health care for patients with chronic LBP and increase the likelihood that patients obtain outcomes that matter most to them. We will accomplish our goal using a sequential multiple randomization (SMART) design comparing the effectiveness of Phase 1 (PT v. CBT) treatments for patients with chronic LBP; and among patient non-responsive to Phase I treatment, compare the effectiveness of Phase II treatments (switching to PT or CBT v. mindfulness). Effectiveness will be based on patient-centered outcomes. Sub-aims will compare main effects of Phase 1 and 2 treatment options and the sequencing effects of different treatment combinations.

Our primary aims compare the effectiveness of the Phase I treatments (Aim 1) and of Phase II treatments among non-responders (Aims 2A, 2B). Our main secondary aims compare the effectiveness of Phase I treatments when followed by Mindfulness or switching to the alternative Phase I treatment among non-responders (Aims 3A, 3B):

Aim 1 (Primary): Compare the effectiveness of the Phase I treatments (PT vs. CBT) on co-primary outcomes of function and pain at 10 weeks. Aim 1 comparisons will be supported by the following secondary aims:

- ***Aim 1i* (Secondary):** Compare the effectiveness of the Phase I treatments on the main secondary outcome of long-term opioid use and explore differences in other secondary outcomes including PROMIS scales and health care utilization measures.
- ***Aim 1ii* (Secondary):** Compare the effectiveness of the Phase I treatments on function and pain at 10 weeks in pre-specified sub-groups defined by age, gender, opioid use and psychosocial risk.

Aim 2 (Co-Primary): Among all non-responders to Phase I treatment, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching) on co-primary outcomes of function and pain at 1 year. Aim 2 will be supported by the following exploratory aims:

Aim 2A (Exploratory): Among non-responders to Phase I treatment with PT, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching to CBT) on co-primary outcomes of function and pain at 1 year.

Aim 2B (Exploratory): Among non-responders to Phase I treatment with CBT, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching to PT) on co-primary outcomes of function and pain at 1 year.

Aim 3A (Secondary): Compare the effectiveness of Phase I treatments (PT vs. CBT) with Mindfulness as Phase II treatment on co-primary outcomes of function and pain at 1 year.

Aim 3B (Secondary): Compare the effectiveness of Phase I treatments (PT vs. CBT) with Switching to the alternative Phase I treatment as Phase II treatment on co-primary outcomes of pain and function at 1 year. (This aim addresses if the temproal ordering of PT and CBT leads to different outcomes.)

Aims 3A and 3B comparisons will be supported by the following secondary aims:

- ***3Ai* (Secondary)** Compare the effectiveness of the Phase I treatments with Mindfulness as Phase II treatment on PROMIS outcomes at 1 year.
- ***3Bi* (Secondary)** Compare the effectiveness of the Phase I treatments with Switching as Phase II treatment on PROMIS outcomes at 1 year.

we will implement two additional exploratory Aims:

Aim 4 (Exploratory) Determine which 2-stage treatment strategy provides optimal average outcomes for the patient population with chronic LBP on the co-primary outcomes of pain and function.

Aim 5 (Exploratory) Determine the optimal individualized 2-stage treatment strategy considering sub-groups of patients defined by key baseline characteristics (age, gender, opioid use and psychosocial risk) using the co-primary outcomes.

Design and Outcomes

The study uses a sequential multiple randomization (SMART) design (fig. 1). We will compare the effectiveness of common first-line treatments for chronic LBP: PT or CBT. Initial treatment will be 8 weeks duration with re-evaluation at 10-weeks after enrollment to allow time to complete treatment. At the 10-week assessment we will examine if the patient has responded to initial treatment using a patient-centered, validated definition of successful response. Patients who are responders to initial treatment will receive up to 2 additional sessions of the same treatment to assist transition to self-management. Non-responders will be re-randomized to a second treatment strategy of either *switching* to the other initial treatment (i.e., patients receiving PT switch to CBT or vice versa), or mindfulness. The second treatment phase is also 8 weeks in duration.

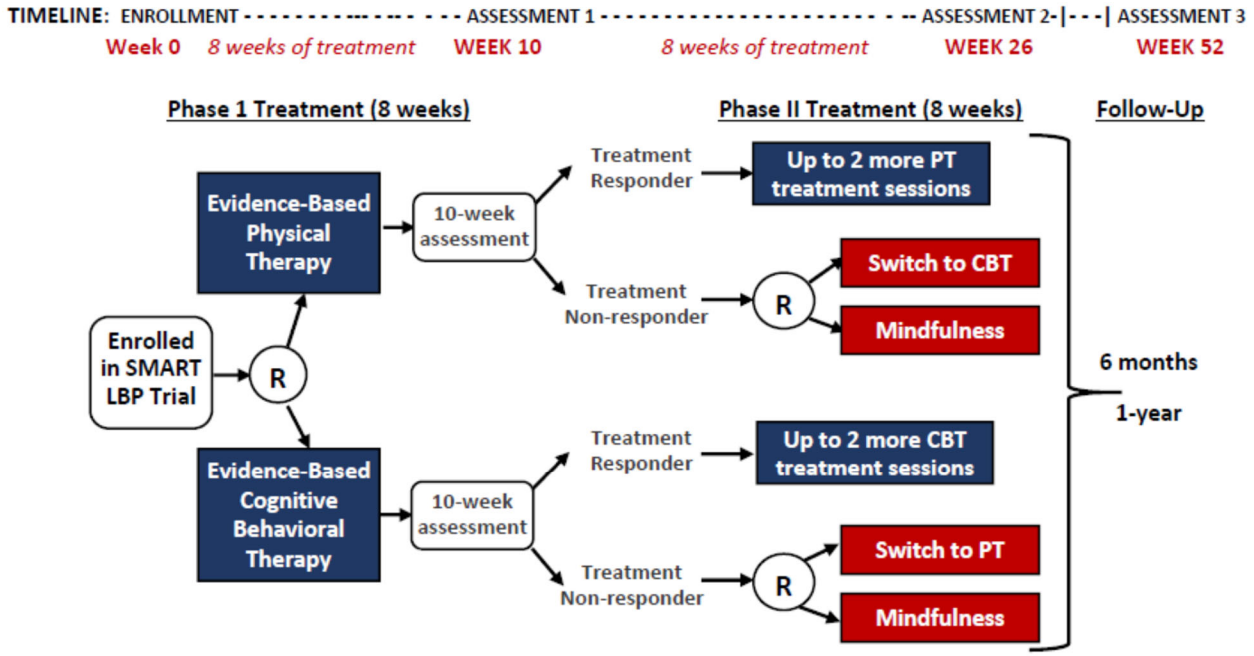

Fig 1. Overview of SMART Trial Design

The study has two co-primary outcomes; function and pain. We will use the Oswestry Disability Index (ODI), a well-validated, reliable and responsive patient-reported measure of LBP-related function[67] recommended by the NIH Back Pain Task Force.[26] We will assess pain intensity with 0-10 ratings ('0' indicating no pain and '10' worst imaginable pain).[68] Separate ratings are made for current, worst and best pain over the past 24 hours with an average computed to represent pain intensity.[69] Secondary outcomes will assess dimensions of quality of life, work and healthcare utilization.

Interventions and Duration

All participants will receive 8 weeks of Phase I treatment of either CBT or PT based on random allocation. Ten weeks after enrollment participants will be evaluated and determined to be a treatment responder or non-responder based on self-reported change from baseline on the primary outcome measure (ODI). Responders will continue with Phase I treatment receiving up to 2 additional

treatment sessions during Phase II. Non-responders will be re-randomized to a Phase II treatment of either mindfulness or switching to the alternative Phase I treatment. Phase II treatment lasts for 8 weeks. Additional follow-ups are conducted 6 and 12 months after enrollment. Therefore the total time for a participant to be "on study" is 12 months.

Sample Size and Population
We will recruit a total of 748 participants age 18-64 with non-specific, chronic LBP based on the definition of chronic LBP from the NIH Back Pain Task Force.[26] Participants are required to have at least moderate degrees of pain and disability. Participants meeting all eligibility criteria will be randomized to a Phase I treatment (PT or CBT). Initial randomization will be stratified by site. Participants determined to be non-responders to Phase I treatment will be re-randomized to a Phase II treatment (Switching or Mindfulness) with randomization stratified by site and Phase I treatment. Phase I responders will receive up to 2 additional sessions of the same treatment during phase II.

1. STUDY OBJECTIVES

1.1 Primary Objectives

Our primary aims compare the effectiveness of the Phase I treatments and the Phase II treatments among non-responders.

Aim 1 (Primary): Compare the effectiveness of the Phase I treatments (PT vs. CBT) on co-primary outcomes of function and pain at 10 weeks. Aim 1 comparisons will be supported by the following secondary aims:

Aim 1i **(Secondary):** Compare the effectiveness of the Phase I treatments on the main secondary outcome of long-term opioid use and explore differences in other secondary outcomes including PROMIS scales and health care utilization measures..

Aim 1ii **(Secondary):** Compare the effectiveness of the Phase I treatments on function and pain at 10 weeks in pre-specified sub-groups defined by age, gender, opioid use and psychosocial risk.

Aim 2 (Co-Primary): Among all non-responders to Phase I treatment, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching) on co-primary outcomes of function and pain at 1 year. Aim 2 will be supported by the following exploratory aims:

Aim 2A (Exploratory): Among non-responders to Phase I treatment with PT, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching to CBT) on co-primary outcomes of function and pain at 1 year.

Aim 2B (Exploratory): Among non-responders to Phase I treatment with CBT, compare the effectiveness of the Phase II treatments (Mindfulness vs. Switching to PT) on co-primary outcomes of function and pain at 1 year.

Aims 2A and 2B comparisons will be supported by the following secondary aims:

1.2 Secondary Objectives

Our main secondary aims compare the effectiveness of Phase I treatments when followed by Mindfulness or switching to the alternative Phase I treatment among non-responders (Aims 3A, 3B). In addition we will implement two exploratory Aims (4 and 5):

Aim 3A (Secondary): Compare the effectiveness of Phase I treatments (PT vs. CBT) with Mindfulness as Phase II treatment on co-primary outcomes of function and pain at 1 year.

Aim 3B (Secondary): Compare the effectiveness of Phase I treatments (PT vs. CBT) with Switching to the alternative Phase I treatment as Phase II treatment on co-primary outcomes of pain and function at 1 year. (This aim addresses if the temproal ordering of PT and CBT leads to different outcomes.)

Aims 3A and 3B comparisons will be supported by the following secondary aims:

***3Ai* (Secondary)** Compare the effectiveness of the Phase I treatments with Mindfulness as Phase II treatment on PROMIS outcomes at 1 year.

***3Bi* (Secondary)** Compare the effectiveness of the Phase I treatments with Switching as Phase II treatment on PROMIS outcomes at 1 year.

Aim 4 (Exploratory) Determine which 2-stage treatment strategy provides optimal average outcomes for the patient population with chronic LBP on the co-primary outcomes of pain and function.

Aim 5 (Exploratory) Determine the optimal individualized 2-stage treatment strategy considering sub-groups of patients defined by key baseline characteristics (age, gender, opioid use and psychosocial risk) using the co-primary outcomes.

2. BACKGROUND AND RATIONALE

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

Low back pain (LBP) is a nearly universal human experience. About 80% of adults have at least one episode in their life-time and 25% of adults in the U.S. report LBP lasting at least one day in the past 3 months.[1,2] LBP is common and can be very burdensome for impacted individuals. The tremendous burden imposed by LBP on health and well-being was recently highlighted in the Global Burden of Disease initiative of the World Health Organization.[3,4] Of 291 conditions studied, LBP ranked first in terms of associated disability and overall burden in detracting from perfect health.[5] LBP results in more disability and overall burden for affected individuals than conditions such as depression, Alzheimer's disease, substance abuse disorders, or arthritis. The high ranking of LBP reflects the number of people who experience the condition and the amount of pain, functional loss, and overall decrease in quality of life that individuals with LBP experience.

Considering its prevalence and impact, it is not surprising that LBP imposes a substantial societal burden. Back pain is among the most common conditions encountered in healthcare, accounting for about 5% of all physician visits in the U.S.[6-9] Back pain is the 3rd costliest medical condition in the U.S, behind only diabetes and heart disease; and costs have been increasing at the 2nd fastest rate over the past 10 years.[10] Despite intensive and expensive treatment efforts, the number of individuals with chronic LBP continues to increase. From 2000 - 2007 the prevalence of chronic LBP increased from 4% to 6% of the U.S. adult population.[11] Ineffective LBP management by healthcare systems is also contributing to the crisis of opioid over-prescribing. Chronic LBP is the most common non-cancer pain condition for which opioids are prescribed despite a lack of evidence for beneficial effects.[12,13]

Acute LBP episodes tend to improve quickly, but many experience lingering or recurrent symptoms.[14] Once LBP persists beyond 6 weeks improvement is more difficult to achieve. For those with chronic LBP only a third report resolution of pain and disability after 1 year.[15] A large number of treatments provide some benefit for chronic LBP. A report from the Agency for Healthcare Research and Quality (AHRQ)[16] lists 20 distinct non-pharmacologic, non-invasive, chronic LBP treatments with some level of supporting evidence, but effect sizes for these treatments are generally small. Our conversations with patients support the challenge of sorting through options to find the treatment that may work for them.

2.2 Study Rationale

This project, the *SMART LBP Trial*, addresses the dilemma faced by patients with chronic LBP searching for a treatment that will work for them. The presence of a large number of marginally beneficial interventions strongly suggests treatment effects are heterogeneous; with some patients benefiting greatly from a treatment while others are nonresponsive. Unfortunately, there is little evidence on

how an individual patient can select a treatment, or how to effectively combine individual options into more effective multi-disciplinary care. Our project addresses these important questions. In addition, even with better targeting of initial treatment, some patients will not benefit. For these patients there is presently no information on strategies to sequence treatments in a manner to optimize outcomes.[16]

3. STUDY DESIGN

We will use a sequential multiple randomization (SMART) design (fig. 1). We will compare the effectiveness of Phase I treatments for chronic LBP: PT or CBT. Phase I treatment will be 8 weeks of weekly treatment sessions with re-evaluation at 10-weeks post-enrollment to allow time to initiate and complete treatment. At the 10-week re-assessment we will examine if the patient has responded to initial treatment using a patient-centered definition of successful response based on a 50% change in the ODI. Patients who are responders to Phase I treatment will receive up to 2 additional sessions of the same treatment to assist transition to self-management. Non-responders will be re-randomized to a second, Phase II strategy of either *Switching* to the alternative Phase I treatment, or beginning a *Mindfulness* program. Treatment Phase II is 8 weeks in duration. Patient-centered outcomes will be collected 6 months (post-Phase II treatment) and 12 months after enrollment using a web-based platform to collect outcome variables.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

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

1. Age 18 – 64 years at the time of enrollment.
2. Meets NIH Task Force[26] definition of chronic LBP based on two questions: 1) *How long has LBP has been an ongoing problem for you*? and 2) *How often has LBP been an ongoing problem for you over the past 6 months*? A response of greater than 3 months to question 1, and "at least half the days in the past 6 months" to question 2 is required to satisfy the NIH definition of chronic LBP.
3. Healthcare visit for LBP in the past 90 days.
4. At least moderate levels of pain and disability requiring ODI score $\geq$24 and pain intensity rating $\geq$ 4.
5. Has access to two-way video technology, such as smartphone, iPad/tablet, or laptop with webcam for telehealth visits.

4.2 Exclusion Criteria

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

1. Evidence of serious pathology as a cause of LBP including neoplasm, inflammatory disease (e.g., ankylosing spondylitis), vertebral osteomyelitis, etc.
2. Evidence of a specific spinal pathology as the cause of LBP including spine fracture, spinal stenosis, radiculopathy, etc.
3. Knowingly pregnant
4. Has received physical therapy for LBP in prior 90 days
5. Has received mindfulness or CBT in prior 90 days for any condition.
6. Any lumbar spine surgery in the past year.
7. Currently receiving treatment or counseling for substance use (does not include attending AA or NA meetings only)

4.3 Study Enrollment Procedures

We will use two strategies to systematically offer participation to potentially eligible patients. ***First,*** we will identify potential participants in real-time at the point-of-care. Recruitment at the point-of-care will make use of electronic alerts to providers of the potential eligibility of a patient while he or she is in a provider office. Alerts may be triggered using Best Practice Alerts from the EHR or from clinical information input by the patient using tablets in clinic. In addition, study fliers or other advertising materials may be posted in provider offices based on preferences of study sites. When a patient is identified at the point-of-care and wishes to be contacted by a researcher the patient's contact information will be contacted by study personnel to further explain the study. Any patient is not interested in the study will not be contacted by study personnel. The patient's care will not be impacted by declining interest in the study.

Our ***second*** recruitment strategy leverages the EHRs of participating sites to identify and contact patients with chronic LBP not offered participation at the point-of-care. We will create regular EHR reports of potentially eligible patients based on study eligibility criteria represented in the Common Data Model and included in the EHRs of the participating sites. We will cross-reference EHR reports with lists of patients offered participation at the point-of-care to avoid multiple inquiries. We will coordinate with site Institutional Review Board (IRB) and Human Research Protection Program (HRPP) requirements to identify approved strategies to contact potentially-eligible patients and offer the opportunity to speak with study personnel.

Regardless of the recruitment method, we will track the status of all individuals with whom participation is discussed with a research team member in a screening log for each study site. For each individual who discusses participation but does not enroll in the study we will record the reason for ineligibility or declining participation. The screening logs will be maintained in REDcap.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Study interventions are provided across two treatment phases. Phase I treatment will begin after enrollment and completion of all baseline assessment procedures. Participants will be randomly assigned to receive a phase I treatment of either Physical Therapy (PT) or Cognitive Behavioral Therapy (CBT). Phase I treatment will last 8 weeks with weekly treatment sessions. Re-assessment will occur 10-weeks after enrollment at which time participants will be judged to be treatment responders or non-responders based on the percent change in the ODI from baseline. Participants determined to be Phase I treatment responders will be allowed up to 2 additional sessions of their assigned Phase I treatment during Phase II to facilitate transition to self-management. Participants determined to be non-responders will be re-randomized to a Phase II treatment of either Mindfulness or a Switching to the alternative Phase I treatment. Phase II treatment will also last 8 weeks with weekly treatment sessions.

This study is designed to be pragmatic. Therefore we are permitting flexibility for providers in determining details of the administration of all interventions. Parameters are provided for the weekly treatment sessions within which pragmatic decisions can be made by providers based on an individual participant's needs. These parameters are described for each treatment in the following sections. Detailed provider instruction manuals describing each intervention are provided in Appendix I.

Due to changes to in-person delivery of health care in response to the COVID-19 pandemic, the mode of intervention delivery (in-person or telehealth visits) will be determined based on the predominant mode of delivery for the intervention in the health care system from which a participant is enrolled. The predominant mode of delivery is defined as the mode of delivery that is being used for 50% or more of provider visits at the time of the participant's enrollment. Once the participant begins

treatment in either Phase I or Phase II using either in-person or telehealth delivery, the same mode of delivery will be used for the entire 8-week episode of care.

5.1.1 Physical Therapy

Participants randomized to Physical Therapy (PT) will be referred to a physical therapist trained in study-related procedures by the investigators. Every effort will be made to conduct the initial PT treatment session within 30 days of randomization (to either Phase I or Phase II treatment). The PT treatment is designed to be provided in weekly sessions over an 8-week period. In order to accommodate participant's schedules, we will allow up to 2 sessions to be held in the same week, but no more than 8 sessions total to be received in the 8-week treatment period. As part of study-related training, physical therapists will be trained to provide evidence-based physical therapy for chronic LBP consisting of patient education, exercise instruction and spinal manipulative therapy (SMT).[16,55] Education will focus on reassurance, positive recovery expectations, addressing maladaptive pain perceptions and the importance of physical activity.[56] Education may be tailored to individual patients' needs based on the 9-item STarT Back screening tool (SBST), an evidence-based tool for identifying patients with high levels of psychosocial risk for poor recovery.[27] Exercises will address general conditioning and physical activity as well as deficits in strength, flexibility and postural control tailored to the clinical presentation and needs of individual patients. SMT may include a variety of hands-on manual therapy techniques tailored to spinal mobility deficits identified in individual patients. Participants randomized to receive PT as a Phase II intervention will receive the same 8-week protocol provided in the manner outlined for Phase I. The PT intervention activities for each session is outlined below. More detailed intervention instructions for training PT providers are provided in Appendix I.

PT Treatment Group Activities		
Each session includes reassessment and review of prior session and patient's exercise and SMT program.		
WK	**Topics**	**Content and Patient Activities**
1	Assessment, Establish Exercise Plan	Assess strength, flexibility, endurance deficits, develop exercise plan, minimum 20 minutes daily home exercise, patient education and reassurance provided
2	SMT Assessment, Progress Exercise	Identify spine mobility deficits, develop SMT plan and provide SMT, review exercise plan and progress. Minimum 20 minutes daily home exercise.
3	SMT, Progress Exercise	Provide SMT, exercise plan reviewed and progressed. Increase daily home exercise to minimum 30 minutes.
4	SMT, Progress Exercise, Review Education	Provide SMT, review and progress exercise plan. Review patient education, elicit patient questions and concerns. Minimum 30 minutes daily home exercise.
5	SMT, Progress Exercise, Self-Management	Provide SMT, exercise plan reviewed and progressed. Discuss self-management plan. Minimum 30 minutes daily home exercise.
6	SMT, Progress Exercise	Provide SMT, exercise plan reviewed and progressed. Increase daily home exercise to minimum 30 minutes.
7	SMT, Progress Exercise, Self-Management	Provide SMT, exercise plan reviewed and progressed. Review self-management plan. Minimum 30 minutes daily home exercise.
8	Review and Self-Management	Finalize self-management and ongoing exercise program. Minimum 30 minutes home exercise 4-5 times per week. Patient questions and concerns elicited and addressed.

5.1.2 Cognitive Behavioral Therapy (CBT)

Participants randomized to Cognitive Behavioral Therapy (CBT) will be referred to a licensed behavioral health provider trained in study-related procedures by the investigators. Behavioral health providers may be psychologists, advanced practice nurses, social workers or other licensed providers with behavioral health training. Every effort will be made to conduct the initial CBT session within 30 days of randomization (to either Phase I or Phase II treatment). The CBT protocol is adopted from studies demonstrating effectiveness in patients with chronic LBP by Cherkin[20] and Lamb[117] as well as the work of Thorn.[63] Patients will receive 8 sessions focused on key components of effective CBT; 1) identifying and monitoring maladaptive cognitions, 2) developing coping strategies (e.g., distraction, relaxation, etc.), 3) setting and working towards behavioral goals, especially focused on physical activity, and 4) focusing on self-management skills and home instruction.[118,119] Each CBT session will begin with a person-centered assessment of function using cognitive interview and identification of psychological risk factors (pain catastrophizing and fear of movement). Education focuses on increasing knowledge about pain and the association between activity-related behavior, motives for these behaviors and setting of goals to increase activity and function. Patients will be instructed in activities to perform on their own between sessions and for ongoing self-management. Participants randomized to receive CBT as a Phase II intervention will receive the same 8-week protocol provided in the manner outlined for Phase I. The CBT intervention activities for each session is outlined below. More detailed intervention instructions for training CBT providers are provided in Appendix I.

CBT Treatment Group Activities*		
Each session includes reassessment of patient's beliefs and attitudes towards pain and review previous session.		
WK	**Topics**	**Content and Patient Activities**
1	Assessment, Stress and Coping Model of Pain	Assess attitude and beliefs toward chronic pain, skills for coping with pain, provide rationale and practice relaxation as coping. Take home Daily Learning Activity worksheet
2	Behavioral Activation	Identify preferred physical activates, Learn and practice activity pacing, behavioral goal setting. Take home Daily Learning Activity worksheet
3	Automatic Thoughts and Creating New Ones	Naming automatic thoughts (negative and positive), challenging automatic thoughts, create realistic thoughts regarding pain. Take home Daily Learning Activity worksheet
4	Core Beliefs	Understand core beliefs, identify sense of control (external/internal). Review behavioral goals. Take home Daily Learning Activity worksheet
5	Coping Skills	Create and use positive coping statements. Practice relaxation as coping skill. Take home Daily Learning Activity worksheet
6	Effective Communication	Learn and practice self-expression, learn about and practice assertive communication. Take home Daily Learning Activity worksheet
7	Managing Setbacks	Expectation of pain flare-ups, practice coping with flare-ups. Review behavioral goals. Take home Daily Learning Activity worksheet
8	Relapse Prevention	Thoughts tool Box (review of prior sessions as tools to prevent relapse), Personal plan to maintain coping skills and behavioral goals. Certificate of Completion

5.1.3 Mindfulness

Participants randomized to receive mindfulness as a Phase II intervention will discontinue their Phase I treatment. The mindfulness program used in this study is Mindfulness-Oriented Recovery Enhancement (MORE). MORE was designed specifically to address symptoms and underlying mechanisms of chronic pain. MORE is provided in 8 individual sessions with a behavioral health provider trained by the study

investigators. Behavioral health providers may be psychologists, advanced practice nurses, social workers or other licensed providers with behavioral health training. Throughout the 8 MORE sessions, the following three core areas are emphasized:

- *Mindfulness*. Participants will be guided in each within-session mindfulness practice to: a) become aware of when their attention is being engaged by pain, uncomfortable physical sensations, and aversive thoughts and feelings; b) acknowledge and accept that this attentional engagement has occurred ("It's okay to have these thoughts and feelings, because I don't have to react to them!"); and c) disengage attention from pain and aversive experience, and then shift and engage attention to neutral or health-promoting stimuli via the practice of mindful breathing.
- *Cognitive reappraisal*. After cognitive restructuring is introduced in Session 3, week, patients will be queried about their use of mindfulness to become aware of and decenter from automatic thoughts, challenge automatic thoughts, and become open to new, more adaptive appraisals.
- *Savoring of positive experiences*. After savoring of pleasant experiences is introduced in Session 4, patients will be queried about their use of mindfulness to become aware of, focus their attention on, and savor day-to-day positive experiences (e.g., the taste of an enjoyable meal, a beautiful sunset, nice weather, etc.).

The Mindfulness intervention activities for each session are outlined below. More detailed intervention instructions for training mindfulness providers are provided in Appendix I.

	Mindfulness Treatment Group Activities	
Each session includes meditation practice, review of prior sessions, instructions for practice between sessions.		
WK	**Topics**	**Content and Patient Activities**
1	Automatic Reactivity to Pain	Introduction to mindfulness and the relationship between nociception, pain and emotional suffering; mindful breathing and body scan
2	Cognitive Control through Mindfulness	Automatic pain coping habits; awareness of automatic coping; instruction in mindfulness of automatic pilot; mindful breathing
3	Mindful Awareness of Pain and Stress-Related Cues	Mindful reappraisal as means of coping with negative emotions, stigma; mindful breathing
4	Shifting Attention from Pain or Stress-Related Cues	Savoring natural rewards; positive emotion regulation; mindful savoring practice
5	Re-Orientation of Attention through Mindful Breathing	Mindfulness of negative pain coping (e.g., bed rest, reliance on medication) and contemplation of negative consequences; mindful breathing practice
6	Reappraisal of Maladaptive Thoughts	The relationship of the stress response to pain and negative coping; imaginal stress exposure; mindful breathing; body scan
7	Moving between Mindful Disengagement and Adaptive Reappraisal	The concepts of thought suppression, aversion, and attachment; exercise in the futility of thought suppression; mindful breathing and acceptance
8	Review	Review; discussion of maintaining mindfulness practice; finding meaning and purpose of life; development of mindful recovery plan; imaginal rehearsal of skill learning; mindful breathing

5.2 Handling of Study Interventions

Consistent with a pragmatic clinical trial, neither participants nor providers will be blinded to the interventions received. We will evaluate provider fidelity to study interventions. Direct observation as a fidelity assessment is impractical for a pragmatic study. Provider self-reported fidelity provides a

pragmatic, acceptable alternative, particularly when focused on interventions' core components with checklist formats.[127] We will use provider-reported fidelity checklists to identify if core components of each study intervention are provided to participants. Fidelity checklists will be completed through the EHR or REDcap for each provider session.

5.3 Concomitant Interventions

Consistent with a pragmatic study, we will record all concomitant interventions. We will advise participants on the purpose of the study and the concomitant interventions considered allowed and prohibited based on the study's goals. We will not remove any participant from the study for receiving a prohibited intervention. We will record the occurrence of any prohibited intervention during the study intervention period as a protocol deviation.

5.3.1 Allowed Interventions

Concomitant interventions allowed during the study intervention period include use of medication to control LBP symptoms (NSAIDs, muscle relaxants, opioids, etc.) The use of various medications will be recorded at the baseline examination and across the study period through monthly utilization assessments. Visits to health care providers for LBP are allowed during the study period (e.g., physician visits) as long as no interventional procedures (e.g., spinal injections, surgery, etc.) or mind-body interventions inconsistent with the participant's assigned intervention group (e.g., chiropractic, acupuncture, etc.) are received.

5.3.2 Prohibited Interventions

Prohibited concomitant interventions during the study intervention period include any interventional procedures or mind-body interventions not consistent with the participant's assigned intervention group including chiropractic care, massage therapy, acupuncture, spinal injections, surgical procedures, etc. If any prohibited events occur these will be recorded as protocol deviations. Consistent with a pragmatic study and intention-to-treat principles, participants will continue in the study and receive study-related treatments and assessments unless off-protocol intervention changes the participant's risk-benefit profile.

5.4 Adherence Assessment

Treatment adherence will be assessed based on attendance at treatment sessions and compliance with protocols during sessions from provider self-report checklists. Site EHRs will be used to determine the number of weekly treatment sessions attended by each participant in Phase I and II. For attended sessions, the provider will complete an intervention core component checklist and identify any off-protocol interventions provided. The site study coordinator will monitor checklist forms and review at least 25% for each study provider. Once a provider reaches 90% fidelity to core components the coordinator will continue to monitor at least 10% of the provider's intervention session checklists. Feedback will be provided to providers whose fidelity falls below 90%. All off-protocol events will be recorded, such as the use of techniques or 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 <75% of scheduled sessions will be considered a protocol deviation.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

OUTCOME	Pre-Screening Assessment (Pre-baseline)	Baseline Assessment (day 0)	10 week Assessment (day 70– 90)	6 month Assessment (day 161 – 203)	1 year Assessment (day 341–386)
Eligibility Questions	X	X			
Informed Consent Form		X			
Baseline Patient Form		X			
Baseline Researcher Form		X			
Randomization		X	X **π**		
Follow-Up Researcher Form			X		
Oswestry Disability Index (ODI)	X *	X *	X	X	X
Numeric Pain Rating Scale (NPRS)	X *	X *	X	X	X
StartBack Screening Tool (SBST)		X	X	X	X
PROMIS Pain Interference		X	X	X	X
PROMIS Social Role Participation		X	X	X	X
PROMIS Sleep Disturbance		X	X	X	X
PROMIS Depression		X	X	X	X
PROMIS Anxiety		X	X	X	X
Treatment Forms			X	X	
Side Effects Questionnaire			X	X	
Healthcare and Opioid Utilization for LBP		X	X	X	X

* To be administered at pre-screening assessment and only repeated at baseline assessment if > 14 days has passed since 1st pre-screening
π ONLY if deemed "Non-Responder" to Phase I intervention

6.2 Description of Evaluations

6.2.1 Pre-Screening Assessment

Individuals who discuss or meet with a site Research Assistant will be provided information about the study. The Researcher will confirm the individual meets the eligibility criteria for participation including questions asked to the patient (e.g., age, NIH definition criteria, etc.) and the ODI and pain rating scales required for inclusion. If the individual meets the pre-screened eligibility criteria and is interested in participation, he or she will meet with a Researcher and undergo the consenting process outlined below. The individual may begin the consenting process either on the date of pre-screening or within 14 days of preliminary eligibility confirmation. If the consenting process is initiated beyond 14 days eligibility will need to be re-confirmed.

6.2.1.1 Consenting Procedure

Individuals potentially eligible and interested in participation will be provided with a written informed consent document using a form approved by the site IRB. The consenting process will be conducted by a Researcher trained by the Investigators who has completed Biomedical Research Training for Human Subjects and Good Clinical Practice training through the Collaborative Institutional Training Institute (CITI) or the National Institutes of Health. This training will include modules on human subjects research ethics and regulations related to informed consent. The Researcher will be available throughout the consenting process to explain the study and answer questions. The voluntary nature of the participation will be stressed, and individuals will be reminded that they may withdraw from the study at any time and will be assured that a decision not to participate will have no impact on their ability to access health care.

The low-risk nature of this project does not require written informed consent. Participants will consent electronically through consent cover letters approved by respective Institutional Review Boards with records retained in REDCap. A single consent will be used for the study.

6.2.1.2 Screening to Confirm Eligibility

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

- Confirm the participant is experiencing LBP defined as pain between the 12th ribs and buttock with or without symptoms in the buttock(s) or leg(s) without "red flags" suggesting a possible non-musculoskeletal cause (unexplained weight loss, night pain, systemic illness) or diagnosis of a specific cause (radiculopathy, spinal stenosis, fracture, etc.)

Individuals meeting all eligibility criteria will proceed with study participation. Individuals who are ineligible after all screening procedures will be advised to return to their healthcare provider for continued pain management as necessary.

6.2.2 Enrollment, Baseline, and/or Randomization

6.2.2.1 Enrollment

This study will use an informed consent document approved by the appropriate recruitment site for enrollment into the SMART LBP Trial. Thus the enrollment date for a participant is the date on which eligibility was confirmed and the informed consent document was signed. We anticipate that screening will be completed on the same day for many participants because of the relatively simple and quick screening procedures required. At the latest screening will be completed within 14 days of providing informed consent. Some study sites may require consent to complete the ODI and pain intensity forms required for eligibility if these questionnaires are not part of standard clinical care. In these instances a consent cover letter or other manner of obtaining consent may be required. Providing consent to complete questionnaires for screening purposes will not be considered enrollment into the trial.

6.2.2.2 Baseline Assessments

Assessments involve collection of participant- and researcher-reported data. Patient-reported outcome (PRO) measures will be collected via REDCap (Research Electronic Data Capture), a NIH-supported, browser-based, software solution that uses secure online forms for data capture, management and analysis. Participants and researchers can input data directly into REDCap and participants can also be sent surveys electronically for completion. 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/Medical History: will include age, sex, race/ethnicity, employment status, tobacco use and general medical and LBP history. Current medication use including opioids for LBP will be recorded. This information will be used for descriptive purposes, identifying pre-specified sub-groups and possible covariates in analyses.
- Oswestry Disability Index (ODI): Pain and function are co-primary outcomes in our study. Function will be assessed using the ODI, a reliable, valid and responsive PRO for LBP-related function recommended by national and international experts.[26,73] The ODI asks patients to rate their function on 6-point scales (scored 0 - 5), for 10 domains (lifting, sitting, traveling, etc.). Items are summed and expressed on 0 – 100 scale with higher scores reflecting greater disability.
- Numeric Pain Intensity Rating: Pain intensity will be assessed with numeric ratings. Scores range from 0 ("no pain") to 10 ("worst imaginable pain"). Separate ratings are made for current, best and worst pain intensity in the past 24 hours with the mean used as a measure of pain intensity. Numeric pain scales have excellent test-retest reliability.[68] and are valid and responsive among patients with LBP.[69]

- StartBack Screening Tool (SBST): The SBST is a 9-item tool that categorizes patients with LBP based on risk for poor outcome based on psychosocial and physical risk factors.[27] Patients are categorized as high, medium or low risk.
- PROMIS Pain Interference (PI): The PROMIS-PI 4-item short form measures the self-reported consequences of pain on relevant aspects of life including impact on social, emotional, cognitive, physical and recreational activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater pain interference.
- PROMIS Physical Function (PF): The PROMIS-PF 4-item short-form measures patients' capability related to physical activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater physical function.
- PROMIS Sleep Disturbance (SD): The PROMIS-SD 4-item short form measures qualitative aspects of sleep and wake function. The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater sleep disturbance.
- PROMIS Depression (DEP) : The PROMIS 4-item short form measures affective and cognitive manifestations of depression. The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater levels of depression.
- PROMIS Anxiety (ANX): The PROMIS 4-item short form measures fear (e.g., worry, feeling of panic), anxious misery (e.g., dread), hyperarousal (e.g., tension, nervousness, restlessness) and somatic symptoms related to arousal (e.g., cardiovascular symptoms, dizziness). The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater levels of anxiety.
- Treatment Side Effects: We will collect information about side effects participants may experience with the study interventions. We will ask participants about possible physical (e.g., increased pain or stiffness, etc.) and psychological (e.g., increased stress or anxiety, etc.) side effects that they believe resulted from study interventions and extent to which they were impacted by the side effect (ranging from "not at all" to "extremely"). The questionnaire was developed from existing side effect questionnaires used in studies of physical and psychological interventions for individuals with chronic pain.[128,129]
- Long-Term Opioid Use: EHR data only identifies prescription of opioids, not use, and only from providers in one system. We will therefore ask patients to self-report opioid use for LBP. This information will be collected using REDcap. We will first ask patients if they have used opioids for their LBP since the last assessment as a "yes/no" question. No further questions will be asked for patients responding "no". For those responding "yes", we will inquire if the patient has used opioids for their LBP "daily or near daily in the past 3 months" as a yes/no question. For patients responding "yes" to this question we will ask for the approximate number of days of regular opioid use. Daily or near daily use of opioids over at least 120 days across the 1-year follow-up period is used to define long-term opioid use by AHRQ and other organizations.[80] We will evaluate days of regular opioid use for LBP and long-term opioid use for LBP as outcome measures collected at each assessment.

- Healthcare Utilization: We will use self-reported utilization to identify use of specific tests / procedures for LBP across the follow-up period assessments delivered through REDcap. We will record the occurrence of utilization for LBP in the following categories:
  - Emergency Room visit
  - Spinal Imaging (Radiographs, MRI, CT)
  - Provider visits (complimentary providers, surgeon consults, etc.)
  - Spinal Epidural Injections with or without Imaging Guidance, Radiofrequency Ablation
  - Lumbar Spinal Surgery (Discectomy, Laminectomy, Fusion)

6.2.2.3 Randomization

Following baseline assessment all participants will be randomized to a Phase I treatment group (PT or CBT). A randomization schedule will be developed prior to enrollment and integrated into REDcap by co-investigator Dr. Greene, Director of the Study Design and Biostatistics Center (SDBC) at the University of Utah. Blocked randomization with block sizes of 4 or 6 will be used. Randomization will be stratified based on site (University of Utah, Johns Hopkins or Intermountain).

At the 10-week assessment all participants will complete the ODI. The 10-week and baseline scores will be compared to determine if the participant is a "responder" or "non-responder" to Phase I treatment. A threshold of at least 50% improvement on the ODI from baseline will define a responder. A 50% threshold defining "responder" has been validated as more stringent than a 30% improvement threshold often used to define "minimal important difference".[40,41] Participants with <50% ODI improvement will be defined as treatment non-responders. Treatment Non-responders will be randomized a second time following completion of all 10-week assessments. Randomization of non-responders to a Phase II treatment will be done through REDcap. The second randomization scheme will be developed prior to enrollment using the same procedures. The second randomization will be stratified by site and Phase I treatment group.

6.2.3 Blinding

As is often the case in pragmatic trials, participants and providers cannot be blinded to study treatment. Randomization assignment will not be revealed until the baseline assessment is complete to reduce potential for bias by either the participant or researcher. The use of clinician-compliance checklists during the study will allow for assessment of the impact of any differential treatment application.

Follow-up assessments will be performed by a research assistant who will be blind to participants' treatment group assignment(s). Participants will be reminded by the research assistant not to discuss aspects of 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. Instances of unblinding during an assessment will be recorded as an unexpected event.

6.2.4 Follow-up Visits

- Initial Phase 1 Treatment Visit (*completed within the 7 days following day 0)*:
  - Treatment Session Checklist
- Phase 1 follow-up Treatment Visits (*completed between days 2-65, 8 total treatment visits are the goal with no more than 2 visits per week during Phase I)*:
  - Treatment Session Checklist
- 10-Week Assessment (*completed from Day 70 – Day 90, after completion of Phase I treatment visits*):

- Patient-reported outcomes
- Patient-reported opioid use and healthcare utilization
- Side effects questionnaire

- Phase II Treatment Visits - Responders (*completed from Day 70 – Day 160, no more than 2 additional visits of Phase I treatment)*:
  - Treatment Session Checklist
- Phase II Treatment Visits – Non-Responders (*completed from Day 70 – Day 160, no more than 2 visits per week of Phase II intervention)*:
  - Treatment Session Checklist
- 6-Month Assessment (*completed from Day 161 – Day 203; online assessment*):
  - Patient-reported outcomes
  - Patient-reported opioid use and healthcare utilization
  - Side effects questionnaire
- 12-Month Assessment (*completed from Day 341 – Day 386; online assessment*):
  - Patient-reported outcomes
  - Patient-reported opioid use and healthcare utilization

6.2.5 Completion/Final Evaluation

The final evaluation occurs 12 months after Baseline Assessment (*Day 341 – Day 386*). 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.

- Patient-reported outcomes
- Patient-reported opioid use and healthcare utilization

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Safety of participants and integrity of data collected in this study will be protected throughout the study according to the Data Safety Monitoring Plan (DSMP). The DSMP specifies the oversight and monitoring procedures that will be used throughout the study. Elements of the DSMP are outlined in further detail below and include the following:

- Description of methods and timing for assessment of safety parameters
- Description of adverse event definitions and reporting procedures
- Establishment of a Data Safety Monitoring Board (DSMB)

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

The risk profile of interventions in this study is minimal. The physical therapy, cognitive behavioral, motivational interviewing and mindfulness treatment procedures used in this study are standard procedures used in everyday clinical practice. Risks from these procedures may include increased pain or muscle soreness from exercises performed by a participant or psychological distress related to education, counseling or mindfulness activities. We have attempted to minimize these risks by requiring licensed providers to perform all study treatments. Additional risks arise from privacy protections for participants' data. We will protect participant privacy by adhering to policies of the

National Institutes of Health and other regulatory agencies on education of key personnel on the protection of human subjects participants in the conduct of research. All key personnel will complete online tutorials approved by the NIH on Protecting Human Research Participants (Notice Number NOT-OD-08-054) and Good Clinical Practice (Notice Number NOT-OD-16-148).

Participant safety and confidentiality will be monitored throughout the study. Adverse events will be solicited at each assessment. If an adverse event occurs the event will be recorded and reported based on the definitions and guidelines outlined below. The safety and protection of participants and their data will be overseen by a DSMB established for the study. The DSMB will convene at least annually during the study and will review study data to ensure the safety of participants and data integrity. Specific details and responsibilities of the DSMB are detailed below in section 7.6. The Charter guiding DSMB activities is provided in *Appendix V*.

7.3 Adverse Events and Serious Adverse Events

Definitions

Adverse Event (AE)

An adverse event (AE) is any experience or abnormal finding that has taken place during the course of a research project and was harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio; Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign, symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to research participation.

Unanticipated Problems (UP)

An unanticipated problems (UP) are defined as any incident, experience or outcome that occurs during the course of a study 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

Or is another condition which investigators judge to represent a significant hazard including an event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.4 Reporting Procedures

This study is a multi-site clinical trial. If an SAE occurs at a site other than the University of Utah, the site principal investigator must report to the University of Utah any SAE, 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 awareness of the event. Site investigators must also report any UP or any other AEs within 7 days of PI awareness. Participating sites 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, DSMB committee and PCORI within 3 days of the University of Utah PI becoming aware of the event.
- Other unanticipated problem will be reported to the IRB, DSMB committee, and PCORI within 7 days of the University of Utah PI becoming aware of the event.
- Adverse events that are anticipated do not need to be reported to the IRB or PCORI, including protocol deviations, but will be reported to DSMB in annual reports.

Should an unanticipated problem need to be reported to the IRB it will be reported to the site IRB and University of Utah IRB operating the single IRB for the study. A record of all reportable unanticipated problems will be maintained at the coordinating site and reported during annual DSMB 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 DSMB 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, investigators and the DSMB 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 Follow-up for Adverse Events

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

7.6 Safety Monitoring

The multi-site scope and the purpose of this study requires a data and safety monitoring board (DSMB) as specified by PCORI. The DSMB will be established based on the PCORI guidelines and commensurate with the level of risk, size, and complexity of this study.

Composition of the DSMB: The DSMB 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. The DSMB will have an executive secretary who is not otherwise involved in the study or with the study team. One member of the DSMB will be appointed the Chair.

Frequency and Character of DSMB: Because this study involves procedures with minimal risk, we propose to conduct DSMB meetings via conference call on an annual basis. Each DSMB meeting will begin with an open session that will be attended by study Investigators, Coordinators and PCORI program staff. 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 PCORI staff or others as invited by the DSMB. The closed session will be used to discuss data to which the Investigators must remain blinded such as grouped data. A closed executive committee session may be used if necessary to provide an opportunity for discussion among DSMB members without any other individual present.

Content of DSMB Meeting Reports: DSMB reports will be prepared for Open and Closed Sessions by members of the SDBC at the University of Utah. Reports will describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population. Other general information on study status will be presented. Listings of adverse events and serious adverse events as well as any other information requested by the DSMB will be included. Reports for the Open Session will not include identifying or unblinding information and no results will be presented by treatment group. Reports for the Closed Session may provide results by treatment group and include identifying information.

Following each DSMB meeting a report will be produced that reviews topics discussed at the meeting with respect to study procedures, accrual and retention, data management, etc. The DSMB report will include a recommendation concerning continuation of the study. Each DSMB 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 PCORI program staff, the University of Utah and site 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 assessment. If a participant is discontinued, we will continue to collect self-report outcomes if possible.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We will use a SMART study design (fig. 1). We will compare the effectiveness of Phase I treatments for chronic LBP: PT or CBT. Phase I treatment will be 8 weeks in duration with re-evaluation at 10-weeks post-enrollment to allow time to initiate and complete treatment. At the 10-week assessment we will evaluate if the participant has responded to initial treatment using a validated definition of a treatment responder based on achieving a 50% or greater improvement on the ODI from baseline. Patients who are responders to Phase I treatment will receive up to 2 additional sessions of the same treatment to assist with transition to self-management. Non-responders will be re-randomized to a second, Phase II treatment. Phase II treatment will be either Switching initial treatments (e.g., swtiching to PT if CBT was Phase I treatment or *vice versa*) or Mindfulness. Phase II treatment is 8 weeks in duration. Patient-reported outcomes will be collected again at 6 months (post-Phase II treatment) and 12 months after enrollment.

Our primary aims are to compare the effectiveness of Phase I treatments; and of Phase II treatments among Phase I non-responders. Our secondary aim will compare the effectiveness of each Phase I treatment when followed by Mindfulness or when followed by Switching to the alternative Phase I treatment. As exploratory aims we will seek to identify the 2-stage imbedded treatment regime which provides the optimum average outcome across the four 2-stage treatment strategies, and evaluate the primary and secondary treatment comparisons in pre-specified sub-groups.

9.2 Sample Size and Randomization

Sample size estimation is based on an estimated 85% project retention across the follow-up period. We have designated the ODI and pain intensity ratings as our co-primary outcomes. We assume standard deviations (SD) for ODI and pain of 12.5 and 2.2, respectively and we assume serial correlations of 0.13 and 0.23 for ODI and pain respectively between baseline and follow-up based on our past work.[59] Power and minimum detectable effects assume Phase I responder rates of 30% and 45%.[40,121] Response rate assumptions are used only for the power calculations; our data analyses will account for actual Phase I response rates. Each study treatment is an active intervention hypothesized to be beneficial. Thus, we base our power calculations on minimal clinical important differences (MCID) in ODI (6 pts) and pain (2 pts)[17,19] instead of directional hypotheses for comparisons against control groups. All comparisons have sufficient power to determine if one treatment is clinically superior to the other or if the mean difference between treatments is sufficiently small that the treatments can be considered clinically equivalent.

Hypothesis tests for aims 1 and 3A/B use a 2-sided α=0.04 for the ODI and α=0.01 for pain to assure an overall Type 1 error ≤ 0.05 accounting for evaluation of co-primary endpoints. We allocate a larger α for the ODI because the MCID for pain (2) is a larger fraction of the assumed SD (2.2) than is the case for the ODI. For aims 1 and 3A/B we did not implement additional multiple comparison adjustment within each aim to account for analyses of the other aims, as each of these aims addresses a fundamentally distinct clinical question. For Aim 2, if the response rate is 30%, the design provides 80% power with 2-sided α=0.05 to detect mean differences in the ODI and pain of 3.76 and 0.77 points, respectively, at 1 year among phase 1 non-responders between patients assigned to Mindfulness vs switching to the alternative Phase I intervention in phase II. If the response rate is 45%, the design provides 80% power with 2-sided α=0.05 to detect mean differences in the ODI and pain of 4.25 and 0.87 points, respectively, at 1 year among phase 1 non-responders between patients assigned to Mindfulness vs switching to the alternative Phase I intervention in phase II.

Table 1 – Power and Detectable Effect Sizes

Comparisons of Specific Aims	Outcome Variable	2-sided α	Min detectable effect, 80% power if response rate = 0.30	Min detectable effect, 80% power if response rate = 0.45
1: Mean difference in co-primary outcomes at wk 10 between Phase I treatment with CBT vs. PT (Co-Primary)	**ODI**	**0.04**	3.04	3.04
	Pain	**0.01**	0.62	0.62
1i: Mean differences in PROMIS measures at wk 10 between Phase I treatment with PT vs. CBT (Secondary)	PROMIS Measures	0.05	0.24	0.24
1ii: Mean difference in co-primary outcomes at wk 10 between Phase I treatment with PT vs. CBT in subgroup with 50% prevalence (Secondary)	ODI	0.04	4.31	4.31
	Pain	0.01	0.88	0.88
2: Mean difference in co-primary outcomes at 1 yr between Phase II treatment with Mindfulness vs. switching to the alternative phase 1 intervention among non-responders to either Phase I intervention (Co-Primary)	**ODI**	**0.04**	3.76	4.25
	Pain	**0.01**	0.77	0.87
2A/B: Mean difference in co-primary outcomes at 1 yr between Phase II treatment with Mindfulness vs switching to the alternative Phase I intervention, among non-responders to a specific Phase I intervention (Exploratory)	ODI	0.04	5.34	6.04
	Pain	0.01	1.09	1.24
2C: Mean difference in co-primary outcomes at 1 yr between Phase II treatment with Mindfulness vs switching to the alternative Phase I intervention, among non-responders to either Phase I intervention in subgroup with 50% prevalence (Exploratory)	ODI	0.04	5.34	6.04
	Pain	0.01	1.09	1.24
2D: Mean difference in PROMIS measures at 1 yr between Phase II treatment with Mindfulness vs. switching to the alternative Phase I intervention among non-responders to either Phase I intervention (Secondary)	PROMIS Measures	0.05	0.29	0.33
3A: Mean difference in co-primary outcomes at 1 yr between the Phase I treatments, with Mindfulness in Phase II (Secondary)	ODI	0.04	4.10	3.92
	Pain	0.01	0.84	0.80
3B: Mean difference in co-primary outcomes at 1 yr between the Phase I treatments, with Switching at alternative Phase 1 treatment in Phase II (Does order of PT & CBT matter? (Secondary)	ODI	0.04	4.10	3.92
	Pain	0.01	0.84	0.80
3Ai/3Bi. Mean difference in PROMIS measures at 1 yr between the Phase I treatments, with Mindfulness in Phase II (3Ai); Also applies to 3Bi with Switching treatment in Phase II (Secondary)	PROMIS Measures	0.05	0.32	0.31

Statistical Power and Minimum Detectable Effects for the Primary and Secondary Hypotheses. Power calculations assume standard deviations (SD) of 12.5 and 2.2 for the ODI and pain. The assumed ODI SD of 12.5 exceeds the median SD reported in 10 previous studies conducted in the United States reporting Oswestry scores and requiring patient consent, and exceeds the SDs of all the previous studies that restricted the ODI range at entry similar to our design. The assumed pain SD of 2.2 exceeds the SDs for pain in 9 of the 10 previous studies. We hypothesized effect sizes correspond to the MCID's of 6 for the ODI and 2 for pain for a patient population with a high rate of adherence to treatment visits; given the pragmatic nature of the study design plausible hypothesized effects are approximately 3 to 4 points for the ODI and approximately 1 point for pain. The power calculations assume 75% retention at Week 10 and 70% retention at subsequent assessments. Based on a study of 131 patients,[59] we assume serial correlations of R = 0.13 and R = 0.23 in ODI and Pain scores. Power calculations for PROMIS scores make no assumptions concerning serial correlations and are thus conservative.

9.2.1 Handling of Missing Data

This study is designed to minimize missing data through patient contact, remunerating time to complete PROs and reminders to patients who miss a follow-up. We will record reasons for missing data and attempt to contact lost-to-follow-up patients to determine reasons. To assess risk of bias from missing data, patterns of missingness across follow-ups will be displayed for all outcomes. We will compare baseline levels of prognostic variables between patients with and without missing data to assess deviation from missing at random (MAR) pattern. Longitudinal analyses will employ either restricted maximum likelihood estimation or weighted GEE which provide approximately unbiased results in the presence of missing data if missingness has a MAR pattern after accounting for non-missing measures of included variables.[90] If we find > 15% of patients have missing data we will consider applying multiple imputation.[91] If used, imputation models will include all variables in the analysis and any considered likely to predict outcome and likelihood of missingness.

9.2.2 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 (University of Utah, Johns Hopkins or Intermountain). The second randomization will also be stratified by Phase I treatment group (CBT or PT). Randomization will be done through the project's REDcap site using the Randomization module. Randomization assignments will be programmed in REDcap by individuals not involved in the study prior to any participant enrollment.

Based on the pragmatic nature of this project, participants cannot be blinded to study treatments and we will not use placebos or attempt to balance clinician time. Randomization assignment will not be revealed until baseline assessment is complete to reduce potential bias by either the participant or researcher. Follow-up assessments will be performed by a Research Assistant who will be blind to participants' treatment assignments. Clinicians providing treatment cannot be blinded. The use of standardized training and guidelines for all treatments and provider-compliance checklists throughout the project will permit the opportunity to assess differential treatment application and explore any influence on outcomes. The site PIs of the project 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 to guide primary analyses 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.

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 procedures for any 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 DSMB and PCORI program staff representatives.

9.5 Outcomes

Outcome measure for the primary and secondary hypotheses of the study are outlined below.

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 and at the 8-week, 6- and 12-month assessments.

Primary Outcomes: The study has two co-primary outcomes; function and pain. We will use the Oswestry Disability Index (ODI), a well-validated, reliable and responsive patient-reported measure of LBP-related function[67] recommended by the NIH Back Pain Task Force.[26] We will assess pain intensity with 0-10 ratings ('0' - no pain and '10' - worst imaginable pain).[68] Separate ratings are made for current, worst and best pain over the past 24 hours with an average computed to represent pain intensity.[69]

Secondary Outcomes: We are usingshort form versions from the Patient-Reported Outcomes Measurement Information System (PROMIS®) to assess health constructs most relevant to patients with chronic LBP as secondary study outcomes. We are using PROMIS short forms because they have been developed and validated with rigorous methods[131] and they assess universally-relevant (e.g., physical function, pain interference, etc.) instead of disease-specific constructs permitting comparisons with different chronic disease conditions.[132] We will use PROMIS measures assessing physical function, pain interference, sleep disturbance, fatigue, depression, anxiety and depression. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and standard deviation of 10. Higher scores indicate greater levels of the construct being evaluated.

Additional secondary outcomes are long-term opioid use and healthcare utilization collected by patient self-report supplemented by EHR data as available. For long-term opioid use we will ask patients at each assessment if they have used opioids for their LBP in the past 90 days, and if so whether or not opioids were used for their LBP "daily or near daily in the past 90 days". Daily or near daily use of opioids over at least 90 days will define long-term opioid use.[80] Healthcare utilization outcomes of interest include Emergency Department visits, imaging, injections and surgical procedures for LBP.

9.6 Data Analyses

Analyses will be carried out by the Study Design and Biostatistics Center, the biostatistics core of the University of Utah Center for Clinical and Translational Science. We will monitor data quality and completeness during the study so discrepancies can be resolved in real time. Intention-to-treat principles will guide primary analyses with all patients evaluated based on randomized assignment regardless of compliance. Skewed outcomes may be transformed to approximate normality. Analyses for each aim of the project are outlined below.

Aim 1: Compare effectiveness of initial treatment on co-primary outcomes: We will fit separate longitudinal linear models to relate repeat assessments of function and pain to Phase I treatment (PT vs. CBT) controlling for baseline outcome score. An unstructured covariance matrix will be used to account for repeated measures. Model parameters, including Phase I treatment effects at each follow-up, will be estimated using normality restricted maximum likelihood estimation.[82] An advantage of this approach is treatment effect estimates remain consistent and approximately unbiased if missing data follow a missing-at-random pattern. Mean differences in pain and function at 10 weeks between PT and CBT represent our primary

assessment because the measures occur prior to Phase II and reflect Phase I treatment effects. Secondary comparisons between PT and CBT at later assessments will evaluate average long-term effects of Phase I treatment in the context in which non-responders are assigned a Phase II treatment with equal probability.

Aim 1i: Compare effectiveness of initial treatment with PT vs. CBT for main secondary outcome of long-term opioid use and explore differences in other secondary outcomes: We will use weighted generalized estimating equations[83] to relate Phase I treatment to binary indicator variables for opiod use during successive intervals across the 1-year follow-up under a generalized linear model for binary outcomes. GEE analyses will use robust standard errors for statistical inference and inverse probability of censoring weights to account for missing data. The 10-week assessment will again be the primary evaluation of Phase I treatments, with subsequent follow-up providing secondary comparisons of Phase I treatments in the context of Phase II interventions for non-responders. Additional secondary outcomes (PROMIS-29 subcales) will be compared as exploratory analyses between PT and CBT using similar longitudinal linear models to those described above. Hypothesis tests for secondary outcomes will be performed on a comparison-wise basis without adjustment for multple comparisons.[84]

Aim 1ii: Compare effectiveness of initial treatment with PT vs. CBT in pre-specified sub-groups: Sub-group analyses for the Phase I treatment will be performed by repeating the longitudinal analyses of Aim 1 within each pre-specified subgroup, and by extending the statistical models in Aim 1 by adding interactions between the Phase I treatment and the subgroup factors. We will display forest plots of estimated Phase I treatment effects within each subgroup with p-values for the Phase I treatment by subgroup factor interactions indicated on the plots. Results of subgroup analyses will be assessed primarily based on the treatment by subgroup interactions, using 2-sided $\alpha = 0.04$ for function and 0.01 for pain to account for two co-primary outcomes, but without adjustment for multiple subgroups.

Aim 2: Among Phase I non-responders, compare effectiveness of switching treatments or mindfulness: We will compare the effectiveness in Phase II of Mindfulness vs. switching to the alternative Phase I intervention in Phase I non-responders by fitting a longitudinal linear model to relate the randomized Phase II treatments to ODI and pain co-primary outcome measures at 6 and 12 months, with the Phase I randomized treatment and the 10-week outcome level included as a covariate to account for the effects of Phase I treatment and serve as the baseline for comparing the Phase II treatments. The longitudinal model will estimate mean differences between the Phase II treatments at both 6 and 12 months, with the 12-month comparisons serving as the primary analyses.

Aim 2A/B: Among Phase I non-responders, compare effectiveness of switching treatment vs. mindfulness: We will compare the effectiveness of Mindfulness vs. switching to CBT for Phase I non-responders to PT (aim 2A), and of Mindfulness vs. switching to PT for Phase I non-responders to CBT (aim 2B), as exploratory analyses by fitting separate longitudinal linear models to relate the randomized Phase II treatments to ODI and pain co-primary outcome measures at 6 and 12 months, with the 10-week outcome level used as a covariate to account for the effects of Phase I treatment and serve as the baseline for comparing the Phase II treatments. The longitudinal models will estimate mean differences between the Phase II treatments at both 6 and 12 months, with the 12-month comparisons serving as the primary analyses.

Aim 3A: Compare the effectiveness of the Phase I treatments (PT vs. CBT) with Mindfulness as Phase II treatment: Aim 3A analyses will be performed in randomized patients who respond to their Phase I treatment or who do not respond and are randomized to Mindfulness in Phase II. The secondary analyses will apply weighted GEE with robust standard errors to compare the ODI and pain at week 10 and at months 6 and 12 between the patients initially randomized to PT or CBT in Phase I, with co-variate adjustment for baseline level of the outcome. The 12-month assessment will serve as the primary comparison. Inverse probabilty weighting will account for nonresponders being re-randomized and thus split in two groups and underrepresented relative to responders. We will apply inverse probability of censoring weights to account for missing data. We note the Phase I treatment in an optimal 2-stage sequence may differ from the Phase I treatment optimizing outcome at the end of Phase I (aim 1). For example, CBT may be superior to PT following Phase I, but a sequence of PT followed by Mindfulness may be the preferred 2-stage sequence. The longitudinal analyses for the co-primary outcomes will be adapted analogously to those of Aim 1 to estimate the effects of the Phase I treatments followed by mindfulness on secondary outcomes and perform subgroup analyses.

Aim 3B: Compare the effectiveness of the Phase I treatments (PT vs. CBT) with Switching as Phase II treatment. Analyses for aim 3B will be performed in randomized patients who respond to their Phase I treatment or who do not respond and are randomized to Switching in Phase II. Analyses for aim 3B will be analogous to those of aim 3A, and will address if the order in which PT and CBT are administered matters when applying these interventions sequentially.

Aim 4: Determine the optimal 2-stage treatment strategy with the best average outcome. Aim 4 compares four embedded 2-stage strategies: *a*) PT followed by CBT in non-responders, *b*) PT followed by Mindfulness in non-responders, *c*) CBT followed by PT in non-responders, and *d*) CBT followed by Mindfulness in non-responders. The analyses will apply weighted GEE to estimate the mean ODI and pain for all 2-stage strategies at week 10 and months 6 and 12. The dataset will be augmented by including each patient either once or twice depending on whether treatment is consisent with one or two strategies[85,86] (e.g., the sequence of a patient who responds to PT in Phase I is consistent with both *a* and *b* above). As in aims 3A/B, we will employ inverse probabilty weighting to account for non-responders being re-randomized and thus split in two groups and under-represented relative to responders. We will use robust standard errors to account for entry of some patients twice in the augmented dataset. Our design provides good power to identify the optimal 2-stage strategy which provides the best average outcome if there is a clinically relevant difference in outcomes between the best and second best strategy. If two or three strategies provide similarly beneficial outcomes, with the remaining strategies providing poorer outcomes, the analysis will identify the set of strategies with favorable outcomes.

Aim 5: Determine optimal 2-stage treatment strategy for sub-groups based on primary outcomes. Aim 5 applies Q-learning methods to investigate more complex treatments than the strategies examined in aim 4 to estimate an optimal intervention in which Phase I and II treatments are tailored to patient sub-group characteristics. We have designated ODI at 1-year as the primary outcome for the Q-learning procedure, but will repeat the procedure for the co-primary pain outcome and earlier time points as secondary assessments. We will implement Q-learning[87] by defining subject data as O_1, A_1, O_2, A_2. O_1 designating patient subgroup factors

available prior to Phase I (age, gender, opioid use, psychosocial risk); A_1 is Phase I treatment (PT, CBT); O_2 is response to Phase I treatment (responder, non-responder); A_2 is Phase II treatment for non-responders (switching, mindfulness). Q-learning uses two regression models corresponding to the two treatment Phases to determine the optimal sequence where the selection of Phase I treatment (A_1) takes into account subgroup factors (O_1), and Phase II treatment (A_2) takes into account subgroup factors (O_1), Phase I treatment (A_2) and response to Phase I (O_2). The Phase I regression model includes the interaction between O_1 and A_1. The Phase II model includes interactions of O_1 with A_1, A_1 with A_2, and O_2 with A_2 to account for heterogeneity of Phase I and II treatment effects. The optimized 2-stage sequence depends on the regression coefficients for the models corresponding to the two Phases. Statistical inference will be performed using soft-thresholding[88] or the m-out-of-n bootstrap.[89] The ultimate result will be an estimate of the optimal 2-stage treatment sequence for each combination of values for the patient subgroup factors.

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. Confidentiality of participant's records will be protected by storing all electronic information on encrypted, password-protected computers. The study database will be kept on a server supplied by the University of Utah Health Sciences (UUHS) and managed by the SDBC. The UUHS 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 UUHS Information Technology Support. All programming for the analyses will also be stored on the same server and coordinated through the SDBC. Source documents not stored electronically will be maintained in locked cabinets within the personal offices of the site Principal Investigator or study coordinator.

Provider-reported measures of treatment session compliance will be recorded in the EHR for each study site. Smart forms including core component checklists and free-text comment fields will be integrated into EPIC (University of Utah and Johns Hopkins) and Cerner (Intermountain) EHRs. Provider-reported information will be downloaded from the sites' EHRs and transferred to the SDBC on a weekly basis for integration into the study database.

10.2 Data Management

Each participant enrolled in the study will receive a site-specific unique Patient Identifier that will be generated prior to beginning the study. Once a participant 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 participant. The link between the Patient Identifier and the participant's Personal Health Information will be maintained by Investigators at each study site, and will be available only to the site's Study Coordinators and Investigators. After the Patient Profile is created, the participant will be able to input all self-report data directly into

REDCap using a computer or laptop with a web-based interface. All data entered by the participant 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 with information input into the REDCap study database by investigators.

All self-report data will be collected using the REDCap data collection platform. Additional participant information (e.g., informed consent documents, demographic and physical examination forms completed by a Research Assistant) will be entered into REDCap by the Study Coordinator or Research Assistant as appropriate. The Data Coordinating site for this project is the University of Utah SDBC under the direction of Dr. Tom Greene. The University of Utah SDBC will download study data monthly from REDCap once enrollment begins. This information will not include any patient identifying information.

Clinical sites participating in the project will be responsible for collecting electronic data from subjects using REDCap. Any source documents not stored electronically will be maintained in locked cabinets within the personal offices of the site PI or study coordinator. Any electronic documents outside of REDCap (e.g., participant contact information, etc.), will be kept in an encrypted file, on a password-protected and encrypted computers maintained by a member of the research team. The local site PI will be responsible for security and confidentiality of information maintained at each study site. The University of Utah SDBC will be responsible for maintaining and analyzing the overall study database.

10.3 Quality Assurance

10.3.1 Training

Study investigators will conduct training sessions for all research assistants and clinicians who will provide study interventions. Training will consist of in-person, didactic instructions, written instructions for the performance of study-related interventions, and hands-on practice as appropriate. Detailed study manuals and protocols for each intervention will be compiled and made available to providers. Providers will receive training in reporting of adverse events or unanticipated problems to investigators within appropriate time frames.

All research staff will receive instruction in administrative aspects of the study (informed consent, subject recruitment, data and safety monitoring and subject confidentiality issues, etc.). Training goals will be accomplished by providing theoretical and practical information related to this project and the procedures employed. Required certifications in Good Clinical Practice and Human Subjects Research will be completed. 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 Quality Control Committee

Quality control for study-related participant data input through REDCap will be monitored and overseen by the University of Utah SDBC, the Data Coordinating Center for the project, which is overseen by Dr. Tom Greene with support from Dr. Jincheng Shen and Molly McFadden. Quality control for study-related treatment session data input into site EHR as intervention core component checklists will be monitored during the project by the site PI and research team members at each site as overseen by the site PI.

10.3.3 Quality Control Metrics

Quality metrics for study-related participant data include counts and percentages of missing or incomplete responses and protocol deviations will be reported at least annually on DSMB reports for open and closed sessions. Quality metrics for study-related treatment data will examine the proportion of intervention sessions including all core components. The goal for each provider of study interventions is $\geq$ 90% compliance with providing core components at study treatment sessions.

10.3.4 Protocol Deviations

All protocol deviations and adverse events will be recorded at each study site as outlined in Section 7. Deviations or adverse events will be reported in a timely manner to the study PI and to the IRBs of the participating institutions as required. Annually, a report will be compiled for review by the DSMB and PCORI representatives. The DSMB may request more frequent reviews if necessary.

10.3.5 Monitoring

Protocol deviations are monitored at each study site and are overseen by the site PI. Protocol deviations will be reported to the University of Utah from each site PI. As specified in Section 7, any protocol deviation that is also an adverse event (e.g., incorrect randomization, failure to obtain informed consent, etc.) will be reported to the site and central IRB as well as the DSMB and PCORI project staff within 7 days of awareness. Protocol deviation that do not qualify as adverse events (assessments occurring outside the specified time window, participants receiving prohibited interventions, etc.) will be reported to the University of Utah from each site PI in quarterly monitoring reports. A report of all protocol deviations occurring across study sites will be maintained by the University of Utah and reported annually on the DSMB report.

We have developed the study procedures to minimize data quality concerns. Study data is be collected using the RedCap platform. The platform includes functionality that permits limiting data ranges and types, thus reducing the chance for input of out-of-range values or incomplete responses. Restrictions available within RedCap also provide identification verification through login and passwords, required field verification, and prevent duplicate records to minimize the chance for data input errors. In addition to passing point-of-entry edits, all study data entered to the central RedCap database will be subjected to extensive monitoring procedures on a routine basis by the SDBC. The SDBC will internally review distributions of baseline and follow-up variables to detect extreme values or inconsistent results and will notify the PI if problematic data are detected.

Study-related treatment data from core component checklists will be reviewed at each site to monitor for protocol deviations. Site researchers will review at least 25% of treatment session checklists for each study provider. Once a provider reaches 90% fidelity to key components we will continue to monitor at least 10% of the provider's sessions. We will provide feedback to providers whose fidelity falls below 90%.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents from each study site and any subsequent modifications will be reviewed and approved by the single IRB at the University of Utah and the

study sites' IRBs.

11.2 Informed Consent Forms

Informed consent 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 provide consent. The consent cover letter form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Documentation of consent is retained in the participant's study record with an electronic copy made available to participants.

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 will be obtained by the respective IRBs coordinated through the University of Utah single IRB. Consent forms that identify a participant 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 the participant. The data file linking names and unique identifiers will be accessible only to the site PI or Study 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, the DSMB and PCORI staff.

11.4 Study Discontinuation

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

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APPENDIX I

Intervention Training Manuals

Physical Therapy

Cognitive Behavioral Therapy

MORE Mindfulness