PACBACK Clinical Study Protocol

Spinal Manipulation and Patient Self-Management for Preventing Acute to Chronic Back Pain (PACBACK)

FULL PROTOCOL TITLE

Spinal Manipulation and Patient Self-Management for
Preventing Acute to Chronic Back Pain (PACBACK):
A Randomized Clinical Trial

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Version 8

Tool Revision History

Version Number: 3
Version Date: January 2019
Summary of Revisions Made:

- Added Dr. Ryan Eskuri to study staff list
- Remove STarT Back screening tool from in-person screening visit. This is captured at the initial screening survey only.
- Visit 2 for MC care can now occur (in-person or via phone) within 7 business days of visit 1 (changed from 1-2 days by phone)
- Changed eligibility criteria:
  "Acute or subacute LBP: At the time of randomization, the participant's current episode of LBP (period of LBP preceded by at least 1 month without bothersome LBP) must be between 2 and 12 weeks duration and the participant must report experiencing LBP that interferes with regular daily activities on less than half of the days over the past 6 months." was changed to

  "At the time of randomization, the participant's current episode/aggravation of LBP must be between 2 and 12 weeks duration.

  Participants with no LBP, mild LBP, or moderate LBP on average in the month preceding their current episode are eligible.
    - The current episode/aggravation has to be a new episode or a worsening of the existing LBP."
- Added "Average LBP characterized as severe in the month preceding the current episode/aggravation" to the exclusion criteria
- Chronic interference with daily activities added as a secondary outcome at months 6 & 12.

Version Number: 4
Version Date: March 2019
Summary of Revisions Made:

- Updated interventions to reflect DCs and PTs offering SMT and SSM at both CCCs
- Updated Milestone dates (i.e., date of transition and end of UG3 phase)

Version Number: 5
Version Date: October 2019

- Modifications to personnel
- Visual trajectory questionnaire for pain collected at baseline and M12
- Heal measure-Month 2: Remove PPC, HCE, TEX; Month 12: add POS
- Intervention uptake (SSM, SSM+SMT participants only) will be collected at M6 & M12
- Exacerbation of low back pain added as an expected AE to all treatment groups (natural history of the condition); further defined 'awareness' in the "PACBACK: Report AEs, Unanticipated Problems, and Protocol Noncompliance" to include 'awareness after talking with the participant to gather more information.'
- Frequency of intervention fidelity assessment updated to monthly for all treating clinicians for six months, quarterly thereafter.

- 5x sit to stand test added to baseline and W9 assessment
- Implementation measures: participating clinicians will complete surveys prior to intervention training, at the end of intervention training, annually and at the end of the UH3 trial.
  Added definition of loss to follow-up

Version Number: 6
Version Date: August 2020
Summary of Revisions Made:

- Updated non-key University of Pittsburgh personnel
- Added Phase 3 disruption due to Covid-19
- Added Partial Randomization Period(s) & Full Randomization Period(s)
- Added Plans for Covid-19 monitoring
- Added remote baseline screening procedures
- Updated delivery of SSM and MC interventions
- Added option to conduct informed consent via videoconference & document participant consent electronically in REDCap
- Participants at all sites will be given information related to Covid-19
- Added Covid-19 impact questionnaire & Telehealth Usability Questionnaire (TUQ)
- Hypertension screening procedures updated
- Analysis section updated to reflect partial randomization period
- Virtual fidelity assessments can be recorded on Zoom

Version Number: 7
Version Date: August 2021
Summary of Revisions Made:

- Aim #1 was updated to "Prevention of cLBP at 12 months as measured by LBP Impact (from Promis-29) scale: 8-50 (Analysis of AUC for months 10-12)."Analysis section updated to reflect this modification. A rationale for this change is included.
- Secondary Outcomes updated to include Prevention of cLBP at 12 months, as measured by the proportion of patients in each group meeting the definition by the NIH Task Force on Research Standards for Chronic LBP (i.e., ongoing LBP on ≥50% of days over past 6 months). Analysis section updated to reflect this modification.
- Update Linda Hanson's role and remove Co-Investigator Joel Stevens.
- Update non-key personnel
- Update Steering Committee members to include Drs. Roni Evans and Carol Greco
- TUQ: all participants enrolled in the 2-arm phase will complete the TUQ at predefined time points. Participants who engage in virtual study visits will complete the TUQ.
- Update UMN Research Clinic location
- Updated UPITT research team Suite #
- NSAID creams added as an allowed MC intervention

Version Number: 8
Version Date: June 2023
Summary of Revisions Made:

- Added Amy Perkins, Carly Thiner, Lynn Winkel, Aditi Das, Tracey Murray, Erin Rozwat, Leslie Lesoon (non-key personnel)
- Removed Mary Greer, Shane Conley, Donna Schneider, Heidi Mendenhall and Ryan Eskuri (non-key personnel)
- Removed UPMC Centers for Rehab Services
- Added Pete Murray, NCCIH Program Officer
- Updated Wendy Weber, NCCIH study role
- Robin Boineau's role as NCCIH project scientist was taken over by Wendy Weber
- Change in sample size from n=1180 to n=1000
- Update study location to include Homewood Community Engagement Center Wellness Pavilion
- Update pregnancy test requirements
- Statistical analysis plan updated

TABLE OF CONTENTS

Page

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PRÉCIS

Study Title

Spinal Manipulation and Patient Self-Management for Preventing Acute to Chronic Back Pain (PACBACK)

Objectives

Primary Objective
Our long-term objective is to reduce overall lower back pain (LBP) burden by testing scalable first-line non-pharmacologic strategies that address the biopsychosocial aspects of acute/sub-acute LBP and prevent transition to chronic LBP (cLBP). We will assess the effectiveness of Spinal Manipulation Therapy (SMT), Supported Self-Management (SSM), and SMT+SSM relative to Medical Care (MC).

Secondary Objective
To facilitate translation and dissemination across health professions and other clinical settings we will gather contextual data using mixed methods guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE- AIM) framework. Qualitative data will lend context regarding patients', staff, providers' and health system leaders' perceptions of barriers and facilitators associated with the interventions; quantitative data collection will provide insight into intervention application, adherence, fidelity, and provider confidence.

Design and Outcomes

This is multi-site, predominantly pragmatic, phase III randomized trial using a 2x2 factorial design. Participants will be randomized to one of the following treatment groups: (1) SMT, (2) SSM, (3) the combination of SMT+SSM, or (4) MC. Physical therapists (PTs) and chiropractors (DCs) will deliver SMT and SSM, and medical providers will deliver the MC. The study has 2 primary effectiveness research questions with different time frames:

1. Prevention of cLBP at 12 months as measured by LBP Impact (from Promis-29) scale: 8-50 (Analysis of AUC for months 10-12)

2. Average pain intensity and low back disability over 1 year as measured by weekly NRS and monthly RMDQ scores.

Secondary outcome measures include: recovery, NIH minimal dataset including the Patient Reported Outcome Measurement Information System-29 (PROMIS-29) and other measures of LBP burden (e.g., productivity loss, health care and medication use, including opioids).

Interventions and Duration

All participants will be followed for 12 months after randomization. The initial treatment period is 8 weeks. Decisions regarding visit frequency will be made collaboratively by the provider and participant, as is typical in real-world stings. Participants will be required to attend ≥ 75% of the prescribed intervention visits to be considered compliant. In addition, participants have the option to receive additional treatment in the group to which they were randomized if they experience a recurrence of an acute LBP episode during the 10-month follow-up period. Specifically, if the patient experiences a recurrence of bothersome low back pain (e.g., a "flare up" lasting more than two weeks) the provider will assess the patient and decide if additional visits are necessary over the 12 month research study.

Sample Size and Population
A total of 1000 patients age 18 and above will be enrolled with nonspecific LBP of 2-12 weeks duration, at medium or high risk of developing cLBP. The randomization will use 2 strata: Site and Risk of chronicity (medium or high).

1. STUDY OBJECTIVES

The US is in the midst of an unprecedented pain management crisis, with chronic pain impacting more Americans than heart disease, diabetes, and cancer combined.[1] Low back pain (LBP) is the most common chronic pain condition in adults and one of the leading cause of disability worldwide.[2-4] Evidence based guidelines have recommended non-pharmacological treatments like spinal manipulation and behavioral approaches for LBP for nearly a decade,[5] however uptake in practice has been poor. Further, little is known about the role of these treatments in secondary prevention of chronic LBP (cLBP), especially for patients with biopsychosocial risk factors. With burgeoning costs of cLBP and mounting evidence of ineffectiveness and harms of commonly used drug treatments, including opioids,[6-8] there is a critical need for research on non-pharmacological treatments for cLBP prevention that can be readily translated to practice.

Our long-term objective is to reduce overall LBP burden by testing scalable first-line non-pharmacologic strategies that address the biopsychosocial aspects of acute/sub-acute LBP and prevent transition to cLBP. We will assess the effectiveness of Spinal Manipulation Therapy (SMT), Supported Self-Management (SSM), and SMT+SSM relative to Medical Care (MC) in a randomized trial using a 2x2 factorial design. A total of 1000 patients will be enrolled with nonspecific LBP of 2-12 weeks duration, at medium and high risk of developing cLBP using the Subgroups for Targeted Treatment (STarT) Back Screening Tool (SBST). Physical therapists (PTs) and chiropractors (DCs) will deliver SMT and SSM, and medical providers will deliver the MC. This multi-site, predominantly pragmatic, phase III trial has two main objectives:

1.1 Primary Objective

EFFECTIVENESS will be determined via three primary outcomes measures:

1. Prevention of cLBP that is impactful at 10-12 months follow-up (8-50, LBP Impact scale using mean from months 10-12). The LBP impact scale includes measures of pain intensity, pain interference, and physical function from the PROMIS-29 Profile v2.0)
2. Average pain intensity over 12 months post-randomization (0-10 numerical rating scale (NRS))
3. Average disability over 12 months post-randomization (0-24 scale, Roland Morris Disability Questionnaire (RMD))

Our hypotheses are informed by our prior research.[7 9-23] Hypothesized quantifiable differences are outlined in the statistical considerations section.

Secondary effectiveness objectives will assess: a) secondary outcomes including but not limited to recovery, the Patient Reported Outcome Measurement Information System-29 (PROMIS-29), and other measures of LBP burden (e.g., productivity loss, health care and medication use, including opioids); b) primary outcomes in pre-specified subgroups of acute vs. sub-acute and medium vs. high risk of cLBP using the SBST; and c) the effect of key psychosocial mediators on primary outcomes.

1.2 Secondary Objective

IMPLEMENTATION data related to the SMT, SSM, and SMT+SSM interventions will be collected and described using mixed methods about important influences that could affect future implementation and interpretation of results.[24] Qualitative data will lend context regarding patients', staff, providers' and health system leaders' perceptions of barriers and facilitators associated with the interventions; quantitative data collection will provide insight into intervention application, adherence, fidelity, and provider confidence. This will inform the dissemination and implementation plan championed by an experienced, multidisciplinary team, uniquely suited to facilitate translation across health professions.

For **implementation**, we will gather contextual data using mixed methods to facilitate later translation to other real-world clinical settings, and aid in the interpretation of trial results. This aim is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE- AIM)[25] framework. It serves as a complement to PRECIS[26] in providing richer information regarding potentially important influences on the effectiveness of the intervention from patient, staff, provider, and health system leadership perspectives.[25]

The trial will use a two-phased approach. An initial UG3 planning and pilot phase will include development of the detailed study protocol, the data safety & monitoring plan, the Study Accrual and Retention Plan, obtaining IRB approval, and training of study staff and providers. In addition, during the UG3 planning and pilot phase 92 participants were enrolled into the trial to assess performance milestones focused on key areas of recruitment, enrollment, patient intervention adherence, provider intervention fidelity, and data collection. Criteria for including the 92 participants from the pilot phase as part of the total sample size were met, and the subsequent UH3 phase will enroll an additional 908 participants. (See section 3.6.2 for further detail).

2. BACKGROUND AND RATIONALE

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

The United States is in the midst of an unprecedented pain management crisis, with chronic pain impacting over ⅓ of the US population, and affecting more individuals than heart disease, diabetes, and cancer combined.[1 27] With mounting concerns about the efficacy of commonly used pain interventions,[28 29] and estimated pain-related costs of $560 to $635 billion per year,[1] the prevention of chronic pain has become one of the most significant public health challenges of our time. While preventing chronic pain could result in huge public health benefits, there has been scant research focused on interventions targeting the secondary prevention of pain and the transition from acute to chronic.[30]

This research aligns with the National Center for Complementary and Integrative Health's (NCCIH) Strategic Plan 2016[31] by focusing on the investigation of non-pharmacologic pain management strategies that can improve first-line LBP management, including the reduction of opioid use. Specifically, this large, pragmatic study addresses the secondary prevention of cLBP, the most common chronic pain condition in American adults.[2]

LBP is one of the most common and burdensome pain conditions worldwide with an estimated 40-80% of adults experiencing LBP at some point in their lives.[32 33] LBP related disability has increased an alarming 42% over the past two decades, making it the leading cause of disability globally.[4] Approximately 20% of acute cases will become chronic,[34] and it is these individuals that bear a disproportionate share of LBP associated burden.[35] Spinal pain accounts for 9% of total US healthcare expenditures [8] and costs US employers an estimated $19.8 billion per year due to lost productivity.[36] While there is a wide range of treatments available for LBP, the majority of cases are not optimally managed.[37] There is also a growing

awareness that primary care physicians are under-trained in pain management, and do not have ready access to interdisciplinary treatments that could address LBP from a biopsychosocial perspective.[38] This is evidenced by the persistent use of marginally effective and potentially harmful therapies that largely ignore the psychosocial aspects of LBP. For example, the use of epidural injections, opioid prescriptions, and spinal surgeries for LBP has doubled over the past decade with little positive impact on patient outcomes.[28 39] Of growing concern, is the over reliance on opioids. An estimated 40% of LBP patients use opioids making them the most commonly prescribed medications for LBP.[35 40] This occurs despite LBP guidelines suggesting other pharmacologic and non-pharmacologic treatment options [5] and mounting recognition of opioid misuse, addiction, and fatal overdose.[6] The recently released AHRQ review[41] largely confirmed the main conclusions of previous reviews[42] regarding the benefits and harms of pharmacologic therapies. For acute or subacute LBP, NSAIDs, opioids, and skeletal muscle relaxants were associated with only small effects for pain compared to placebo; no benefits were found for systemic corticosteroids or acetaminophen (which due to new evidence, differed from previous reviews). There was also increased risk of adverse events (AEs) compared to placebo for all pharmacological therapies.

The overreliance on ineffective, costly and at times harmful treatments suggests a serious deficiency in the uptake and translation of research based guidelines.[43-45] The 2017 American College of Physicians LBP guidelines recommended clinicians select non-pharmacologic treatments including spinal manipulation for acute LBP and consider pharmacological treatment if desired.[46] Poor adherence to research based guidelines is endemic across health professions.[47] There are several barriers to research uptake at physician and health system levels including knowledge deficiencies,[48-50] poorly aligned incentives,[51] and organizational factors.[52 53] There is also recognition that most research has been insufficiently pragmatic to meet the needs of its end-users.[24] To speed the translation of research to practice there has been increasing interest in research designs and strategies that work to balance methodological rigor with generalizability. This includes the emergence of hybrid effectiveness-implementation designs,[24] and other frameworks,[25 26] which blend rigorous clinical research approaches alongside implementation research methods to facilitate adoption by providers and systems. While such approaches are gaining traction in other health fields,[54-56] there have been few studies in the LBP arena[57] which have used such an approach.

There is growing evidence that physical and psychosocial risk factors can predict progression of acute LBP to chronic.[34 58] This has led to recommendations for trials to focus enrollment on participants at higher risk of chronicity, limiting the testing of interventions to those in need, and excluding those with a more favorable natural history.[30] There is also evidence that treatments addressing psychosocial risk factors in patients with increased risk of chronicity are more effective than usual care.[59] However, most clinical trials to date on acute and subacute LBP populations have tested interventions irrespective of prognosis, limiting the ability to make confident conclusions about their effectiveness.[30] Consequently, there is a need for research that can more rigorously assess the potential of promising interventions to prevent acute LBP from progressing to chronic by appropriately targeting those at higher risk.

To reduce cLBP burden, patients should have greater access to front-line care addressing both their physical and psychosocial needs. This will require the integration of psychosocial interventions with traditional biologically based pain management approaches.[60] Physical therapists (PTs) and chiropractors (DCs) are the most common providers of non-pharmacologic treatment for LBP in the U.S., with approximately 39% of LBP patients seeking treatment from DCs and 34% from PTs.[40] Both PTs and DCs help patients manage symptoms and aid in the restoration of movement and functional ability. They are thus well suited to integrate psychosocial strategies with biological/physical approaches,[60 61] and play an essential role in the frontline management of LBP.[62 63]

2.2 Study Rationale

2.2.1 Preliminary Studies

Collectively, the investigative team has experience conducting multi-site, comparative effectiveness studies. Findings from their research have informed several aspects of the study design including recruitment and enrollment,[10-12 64-66] risk stratification,[67] intervention design,[10-16 18-22 64 68] and mixed methods data collection.[69-71] Their research has also demonstrated that SMT, SSM (incorporating several evidence based behavioral elements), and their combination, are viable treatment options for LBP in different populations.[9-12 14-16 18-22 64 66 68 72]

Further, investigators Bronfort, Delitto, Chou, George, Licciardone, Schneider, and Turk are actively involved in a broad range of influential professional activities. These have helped prioritize the research questions most relevant to health professions involved in LBP care delivery, and enhance the likelihood of future translational success. This involves participation on the NIH LBP Task Force,[73] Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group (IMMPACT),[30 74-81] Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, and Opportunities Network (ACTTION), public-private partnership with the FDA,[79 82-87] and physician,[5] physical therapy,[17] osteopathic,[88] chiropractic,[89] and cross-disciplinary guidelines[6 23 41 42 90] and systematic reviews.[41 91-94] Cumulatively, the investigators' research findings and professional experiences have contributed substantially to the design of the study and enhance the likelihood of successful project completion and effective dissemination.

2.2.2 Interventions

The study uses several approaches to enhance the likelihood of advancing LBP research and shifting the sub-optimal management of acute and sub-acute LBP that currently exists in primary care.

1) This study is the first to assess the effectiveness of SMT, SSM and SMT+SSM relative to MC for the secondary prevention of cLBP that is impactful.

2) The comprehensive quantitative data collection throughout the follow-up year addresses several currently unanswered questions regarding the treatment of acute LBP. This includes how SMT, SSM, and SMT+SSM affect time to recovery from acute LBP, the trajectory of pain and disability over time, as well as the effects of and impacts on psychosocial outcomes.

3) We will address both effectiveness and implementation within our trial. We consider this an efficient, low risk, and potentially high yield tactic, which maintains the rigor required for assessing effectiveness,[26] while simultaneously adding key contextual information to speed implementation to other real-world settings.[25]

4) By training both DCs and PTs to deliver SSM (either alone or in combination with SMT) there is potential for these providers to have a larger and more impactful role in the frontline management of LBP. This may shift the current clinical practice paradigm away from an over-reliance on opioids and other marginally effective medications, to accessible and integrated biopsychosocial approaches.

5) This study will be the first in the U.S. to involve collaboration between influential researchers from medicine, psychology, and all three licensed provider groups of SMT (chiropractic, physical therapy, and osteopathy), increasing the likelihood of widespread translational success.

Spinal manipulation therapy (SMT) is a physical modality used by both DCs and PTs and is well accepted by patients as indicated by relatively high utilization and patient satisfaction relative to usual

medical care.[95] Further, the American College of Physicians and the American Pain Society highlight SMT as one of the recommended non-pharmacologic therapies for acute and sub-acute LBP.[46]

The recently released Agency for Health Research and Quality (AHRQ) comparative effectiveness review provides the most up-to-date synthesis of research regarding SMT for acute LBP.[41] This review builds upon a 2012 Cochrane systematic review,[64 96-98] plus three additional trials that have been published since.[64 97 98] The AHRQ review found some evidence that SMT is associated with beneficial effects for acute LBP compared to sham therapy, no intervention, or usual medical care.[41] Importantly, the side effects associated with SMT are overall benign, with approximately 50% of patients reporting one reaction, most commonly local discomfort which resolves within a day.[99-102] There is stronger evidence supporting the use of SMT in cLBP populations where patients have more complicated physical and psychological phenotypes.[103] This provides a rationale for applying SMT early during the clinical course of patients with increased risk of chronicity based on physical and psychosocial risk factors (e.g., leg pain, comorbid pain, catastrophizing, fear, anxiety, and depression).[104]

Overall, SMT's low risk profile and evidence of benefit lend support for it to be better integrated into primary care settings in an effort to diminish reliance on pharmacologic and other more invasive treatments for acute and sub-acute LBP. It is noteworthy that most studies assessing SMT for acute and sub-acute LBP have primarily assessed pain and disability outcomes in the short-term. In light of the enormous burden imposed by LBP of longer duration, a more relevant question appears to be, "Can SMT prevent acute and sub-acute LBP from transitioning to chronic?" Sufficiently large, adequately powered studies are needed to address this very timely and important issue.[96]

Supported Self-management (SSM). Self-management is widely advocated for LBP and other pain conditions.[1 5] We have adopted the definition proposed by Carnes et al,[105] which is consistent with the study and application of self-management for other musculoskeletal pain conditions.[106-108] Defined as a structured or semi-structured instructional program, self-management includes multiple, distinct components aimed at improving patients' ability to effectively care for themselves on a daily basis.[105] Components can include psychological strategies (e.g., behavioral or cognitive); mind-body approaches (including relaxation, meditation or guided imagery); physical activity (e.g., exercise); lifestyle advice (e.g., for sleep, daily activities, social support); and pain education (e.g., pain theories, prognosis, and pain management tips).[105] While patients recognize the need for self-management strategies for pain, often they need the support and validation of health care providers to initiate and maintain optimal self-care.[109 110] In light of increasing calls for PTs and DCs to play a larger role in addressing the psychosocial aspects of LBP, a natural avenue is through structured self-management (SSM), using evidence-based behavioral strategies that educate, motivate and support patients.

The most recent AHRQ review by Chou et al, found psychological/behavioral based strategies, as well as psychological approaches with exercise, yielded small to moderate benefits for cLBP; insufficient evidence however was available to determine effects in patients with acute LBP.[41] These findings are similar to systematic reviews for other chronic musculoskeletal pain conditions which have found behavioral based strategies to be beneficial;[111 112] importantly, patient education on its own has been found to be insufficient.[113 114] Further, there is some evidence that shorter programs (no longer than 8 weeks), and delivery by health professionals (versus lay persons) are effective.[105] Research has shown that healthcare providers other than psychologists can be trained to confidently deliver SSM programs similar to the one proposed.[106 108 115]

While most research to date has focused on SSM for chronic pain management, acute suffers are also likely to benefit from cognitive and behavioral skills for pain management. To this end, a noteworthy review by Brunner et al, found that a form of cognitive behavioral therapy, is a promising strategy that can be integrated into ambulatory PT practices for the prevention of cLBP.[61] This suggests that by

addressing the very psychosocial factors implicated in pain (e.g., fear avoidance, social isolation, etc.) well-delivered SSM programs for acute and sub-acute LBP patients could play an important role in cLBP prevention, and therefore warrant further study.

Rationale for combining SSM and SMT: Consistent with NCCIH's strategic objective to examine the interactions of non-pharmacologic interventions for additive effects,[31] the research will examine the effectiveness of combining SSM and SMT. Historically, the predominant part of a PT and DC practice has focused on the biological or physical aspects of LBP,[60] with a separation of mind and body, and consequently a distinction between physical and psychological treatments.[116 117] However, the biopsychosocial model suggests a shift away from this dualism.[116] There is an opportunity to advance LBP care by exploring how PTs and DCs (and others) can play a role in addressing the complex factors implicated in the transition to LBP chronicity.[109 110 118] As noted above, patients with increased risk of chronicity have different combinations of physical and psychosocial obstacles to recovery.[104] Given that SMT and SSM target complementary mechanisms (SMT primarily biological and physical, and SSM primarily psychological and social), we anticipate that the combination will promote LBP recovery and prevent LBP chronicity to a greater degree than usual medical care or either monotherapy alone. Further, there are pragmatic advantages to having both treatments delivered by a single practitioner, particularly DCs and PTs, including improved accessibility and integration.[106] Findings from a recent study by the investigators demonstrated the addition of SMT to home exercise and advice (incorporating several behavioral elements included in the SSM) reduced pain and disability in adults with back-related leg pain.[11]

Medical Care (MC) The medical care treatments are informed by the American College of Physicians guidelines on noninvasive treatment for LBP[46] and reflect what is delivered in primary care clinics. Medical care will be provided by licensed physicians or advanced practice nurses with a minimum of 3 years managing musculoskeletal pain patients. Decisions regarding medical care (e.g., pharmacological management) and visit frequency will be made collaboratively by the provider and patient, as normally occurs in clinical practice. Care will be provided within research clinics, outpatient clinics, or virtually using HIPAA compliant Zoom, affiliated with the Universities of Pittsburgh and Minnesota.

3. STUDY DESIGN

3.1 Trial design

This is a two-site randomized trial with a 2x2 factorial design. A total of 1000 individuals with acute or subacute non-specific LBP, at medium or high risk for persistent disabling LBP, will be randomized to either SMT, SSM, SMT+SSM, or MC . The trial uses a hybrid design to address both effectiveness and implementation.[24]

The PRECIS-2 tool has been used to guide the description of the study design and provide clarity regarding the pragmatic and explanatory features of the study.[26] This hybrid study design can best be characterized as rather pragmatic. By design, there will be no attempt to control for non-specific effects due to intervention group differences in time and attention.

Specific design features that are very pragmatic include:

- use of outcomes that are patient-oriented
- use of all data in an intention to treat analysis

Specific design features that are close to or equally pragmatic and explanatory include:

- broad inclusion and narrow exclusion criteria within the subgroup at increased risk of chronicity
- expanded recruitment from the general population and clinical settings

- conduct in outpatient research clinics
- minimal additional resources to organize and deliver the interventions with the exception of SSM training
- flexibility in experimental and comparator intervention delivery
- methods to ensure patient compliance with interventions

Specific design feature that is very explanatory include:

- close follow-up of participants monthly for one year

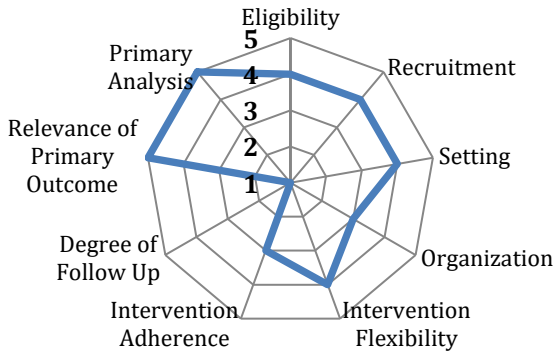

Figure 3.2. Mapping to PRECIS-2 Domains (scores: 5=fully pragmatic, 1= fully explanatory)

Table 3.1 – PRECIS-2 Domain Definition

Domain	Criteria
Eligibility	To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
Organization	How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?
Flexibility (delivery)	How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?

Flexibility (adherence)	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
Follow-up	How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
Primary outcome	To what extent is the trial's primary outcome directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

3.2 Primary and secondary outcomes

Primary and secondary outcomes will be collected predominantly using web-based self-report tools (for details see section 6.1 Schedule of Evaluations and section 10 Data Collection & Quality Assurance).

Primary effectiveness outcome measures are: (1) prevention of cLBP that is impactful at 10-12 months follow-up (LBP impact from the PROMIS-29 Profile v2.0); (2) average pain intensity over 12 months post-randomization (pain, numerical rating scale); (3) average low back disability over 12 months post-randomization (Roland-Morris Disability Questionnaire). Secondary outcomes include: recovery, PROMIS-29 Profile v2.0 measures to assess pain interference, physical function, anxiety, depression, fatigue, sleep disturbance, and ability to participate in social roles and activities. Other patient-reported measures include LBP frequency, medication use, healthcare utilization, productivity loss, STarT Back screening tool status, patient satisfaction, prevention of chronicity, adverse events, and implementation measures. Objective measures include the Quebec Task Force Classification, Timed Up & Go Test, the Sit to Stand Test, and the Sock Test assessed by clinicians blinded to the patients' intervention assignment.

Prevention of chronic LBP will be measured using the patient-rated LBP impact measure described by the NIH RTF[73] which is a quantitative measure derived from subsets of the PROMIS-29. It is scored on a scale of 8-50 (8-27: Mild; 28-34: Moderate and >34: Severe). We will measure LBP Impact on a monthly basis using the area under the curve for Month 10-12 as the primary endpoint.

There is evidence on reliability, validity, and responsiveness and its prognostic value to support the use of the impact measure. (Dutmer 2019)

Important note: The chronic LBP impact measure was collected as a secondary outcome measure from the start of the trial but was adopted as a primary outcome in July 2021 with approval from the trial DSMB and by NIH. At the time of the change in primary endpoint less than 25% of the total participants had been recruited into the trial. Under the supervision of the data coordinating center no interim analysis was planned or conducted and none of the investigators have had access to outcomes data.

When recruitment in the UG3 phase started in October 2018 we were using the published NIH RTF new definition of chronic LBP: "a back pain problem that has persisted at least 3 months and has resulted in pain on at least half of the days in the past 6 months." Specifically, this will be assessed with two NIH RTF minimum dataset items: 1) LBP duration and 2) proportion of days that LBP has been a problem over the past 6 months.[97] The chronicity status at 12-month follow-up is based on patients' recall of their low back pain being present on more or less than half the days during the preceding 6 months.

Since the initial approval and funding of our project by NCCIH in August 2017, important published information has been accumulating regarding the importance of measuring the impact of chronic pain

including chronic LBP[73] (von Korff 2020, Herman 2019, Dahlhamer 2018, Dutmer 2019, Pitcher 2019). This body of literature prompted us to reevaluate the adequacy of our primary chronicity outcome measure. We were aware that the original NIH RTF chronicity outcome measure has several recognized limitations: It is a dichotomous outcome that does not incorporate pain severity, pain interference with daily activities, limitations of physical function, and is not able to quantitatively overall LBP impact. It also has limited statistical power to conduct pre-specified pairwise comparisons among the four groups. To date no data in the literature is available on the prevalence LBP chronicity using the RTF definition. The chronicity status at 12-month follow-up based on patients' recall of their low back pain being present on more or less than half the days during the preceding 6 months.

References in paragraphs above on this page:

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Herman 2019 - Exploring the prevalence and construct validity of high-impact chronic pain across chronic low-back pain study samples Patricia M.Herman, Nicholas Broten et al. The Spine Journal Volume 19, Issue 8, August 2019, Pages 1369-1377

Pitcher 2019 - Prevalence and profile of high-impact chronic pain in the United States MH Pitcher, M Von Korff, MC Bushnell, L Porter - The Journal of Pain, 2019 Volume 20, Issue 2, February 2019, Pages 146-160

Von Korff 2020 - Graded chronic pain scale revised: mild, bothersome, and high impact chronic pain M Von Korff, LL DeBar, EE Krebs, RD Kerns, RA Deyo et al. Pain, March 2020 - Volume 161 - Issue 3 - p 651-661

3.3 Study location

The University of Minnesota (UMN) and the University of Pittsburgh (UPITT) will serve as the Clinical Coordinating Centers (CCC), with the UMN serving as the primary institution providing overall project coordination. The University of Washington (UWA) will serve as the Data Coordinating Center (DCC). Screening of potential study candidates and treatment of enrolled participants will be coordinated by the CCCs and will occur at University-affiliated research, outpatient clinics, or virtually using HIPAA compliant Zoom.

3.4 Intervention administration

SMT, SSM, and SMT+SSM will be provided by PTs and DCs in Pittsburgh and in Minnesota. Medical providers will provide MC. Since the PTs and DCs will follow the same treatment protocols, there is no need or plan to assess differences in outcomes based on provider type. The primary goal of SMT is to address the biological and physical aspects of LBP (e.g., spinal dysfunction) with the intention of restoring maximum movement and functional ability of the spine. The goals of SSM are to primarily address the psychosocial aspects of acute and sub-acute LBP, by providing patients the opportunities to develop their capacity and motivation to self-manage their LBP in an adaptive manner.[108 121] The goals of the MC group will be to provide care for acute and subacute LBP using evidence based guidelines for primary care.

3.5 Randomization, stratification, and blinding

Patients will be randomized to one of the following treatment groups within the 2x2 factorial design: (1) SMT, (2) SSM, (3) the combination of SMT+SSM, or (4) MC. From January 2021 to October 2021, patients were randomized to remote-delivery of (1) SSM or (2) MC due to the COVID-19 pandemic.

The DCC will perform blocked randomization (using variable block sizes of 12 or 16) following stratification by site and baseline risk for cLBP according to the SBST (medium or high). The computer-generated random assignments will be conveyed electronically from the DCC to each clinical site.

Blinding of treatment providers and participants is not feasible. However, the following steps will be taken to minimize potential bias and enhance study rigor: a) all study personnel involved in screening and enrollment will be masked to upcoming randomization assignments; b) all study personnel involved in outcome assessment will be independent of intervention delivery, blinded to intervention arm, and trained in ensuring unbiased data collection until after database lock; c) only a single member from the DCC will be unblinded and have access to treatment group assignment for the purpose of creating closed DSMB reports; and d) participants will be queried in self-report questionnaires as to whether or not anybody attempted to influence their responses.

3.6 Trial phases

The trial will use a two-phased approach. An initial UG3 planning and pilot phase will include study start-up activities including completion of study related documents in collaboration with NCCIH (e.g., study protocol, data safety & monitoring plan), obtaining IRB approval, and training of study staff and providers. In addition, during the UG3 planning and pilot phase 92 participants were enrolled into the trial to assess performance milestones focused on key areas of recruitment, enrollment, patient intervention adherence, provider intervention fidelity, and data collection. The milestones and threshold criteria for transition from the UG3 planning and pilot phase to the main UH3 phase of the trial where the remaining 908 participants will be enrolled are provided in section 3.6.1. In addition, the criteria for not including the UG3 phase participants in the main UH3 phase of the trial are provided in section 3.6.2.

3.6.1 Milestones for transition from UG3 to UH3

Table 3.2 -- Transition Milestones

Milestone	Milestone Description	Expected Date of Completion
CCC/DCC #1	Develop and finalize UG3/UH3 NIH approved documents: -Study Accrual and Retention Plan (SARP); includes plans for women and minorities, adherence and retention (CCC) -Study Protocol (CCC) -Data & Safety Monitoring Plan; includes plan for SAE reporting (DCC) -Informed Consent Documents (CCC) Final NIH-approved documents for Protocol Review Committee (PRC) due by expected completion date.	Prior to Pilot Study enrollment AND at least 6 months prior to transition request For UG3 documents: First half of September, 2018 approved to start (completed site initiation visit)
CCC/DCC #2	Obtain IRB approval; coordinate site approvals with central IRB for the UG3 pilot study.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019

CCC/DCC #3	Finalization of NIH-approved case report forms.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
CCC #5/ DCC #11	Develop and finalize Manual of Operations	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
DCC #5	Develop Study database and finalize data management and data quality plan. Version for PRC due by expected completion date	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
CCC #6/ DCC#10	Recruit and complete regulatory work and contracts at 4 sites needed for the UH3 phase with high likelihood of adequate patient recruitment, retention, intervention delivery, and data quality (see Criteria for Transition below). A list of back up sites will be made available. IRB and other necessary approvals/contracts will be obtained for recruitment in all sites.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
CCC #7/ DCC #12	Develop and finalize training and fidelity monitoring plans and materials. The CCC will assume responsibility for training material associated with screening and enrollment of subjects and completion of study procedures. The DCC will develop training materials for use of the research portal (study management and data collection).	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
DCC #7	Develop and finalize safety surveillance plan and site monitoring plan.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019
CCC #8/ DCC #12	Develop and finalize recruitment plan and patient recruitment materials. The CCC will assume responsibility for training, recruitment, and fidelity material associated with recruitment of subjects and completion of study procedures.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019

DCC #8/ CCC #9	Develop ancillary study policy document.	By date of transition request May 1, 2019
DCC #9/ CCC#10	Create an NIH-approved resource and data-sharing plan.	By date of transition request May 1, 2019
CCC #11/ DCC #15	Submit transition request for UH3 including: annual milestones, updated timeline, an updated detailed budget.	By date of transition request May 1, 2019
CCC #12/ DCC #14	Update and finalize UH3 NCCIH/DSMB approved study documents: SARP Protocol DSMP ICF The CCC will assume primary responsibility for completion of the SARP, Study Protocol, and Informed Consent Document, while the DCC will assume the lead on completion of the Data & Safety Monitoring Plan.	By date of transition request April 1, 2019
CCC #13	Meet additional threshold criteria for transition* (see separate table).	By date of transition request May 1, 2019
DCC #13	Develop study web page / portal with links to participant screening, enrollment, randomization, and electronic data capture tools.	Prior to Pilot Study enrollment: First half of September, 2018 AND by date of transition request May 1, 2019

Threshold Criteria for Transition (UG3 to UH3)

Table 3.3

Criteria (Indicator)	Criterion Description	Expected Date of Completion
A (Clinical Sites)	A total of 4 clinic sites (2 at UMN, 2 at UPITT) participate.	By the end of the UG3 Pilot Study April 15, 2019
B (Recruitment & Retention)	Total of 80 participants are enrolled in the Pilot Study.	By the end of the UG3 Pilot Study April 15, 2019

		Reporting on available follow-up data for all participants will be provided at the time of transition request May 1, 2019.
C (Recruitment & Retention)	An average total of ≥ 24 participants are enrolled per month in the two highest enrollment months of Pilot Study.	By the end of the UG3 Pilot Study April 15, 2019
D (Recruitment & Retention)	≥85% of enrolled participants are retained for the primary outcome, measures of pain and disability at the 8 week time point. Note: chronicity at 1 year which is part of the primary outcome, cannot be assessed in the pilot study due time constraints.	At the end of the 8-week intervention phase for all intervention groups in the entire 80 participants enrolled in the UG3 Pilot Study
E (Intervention Adherence)	≥80% of enrolled participants engage in the assigned treatment (defined as attending ≥75% of prescribed intervention visits).	In the entire 80 participants enrolled in the UG3 Pilot Study
F (Intervention Contamination)	≤10% of participants cross contaminate defined as receiving unassigned intervention or part of unassigned intervention during the 8 week treatment phase (due to outside care, or provider contamination of the interventions, as measured on patient self-report questionnaires).	Within the 8 week intervention phase in the entire 80 participants enrolled in the UG3 Pilot Study
G (Intervention Contamination)	≤10% of audited visit records exhibit cross contamination defined as delivering unassigned intervention or part of unassigned intervention during the 8 week treatment phase (as measured on provider record).	Within the 8 week intervention phase in the entire 80 participants enrolled in the UG3 Pilot Study
H (Safety & Adverse Events)	≤5% of participants experience an unexpected, related, moderate or greater adverse event. <2% SAE overall unexpected and related to the intervention (no more than 1 participant).	In the entire 80 participants enrolled in the UG3 Pilot Study

3.6.2 Criteria for not including participants from UG3 in the UH3 analysis

Study data from the UG3 pilot phase and the UH3 full-scale phase will be combined for analysis unless the UG3 planning and pilot phase leads to changes in the following:

- Design (e.g., the addition or removal of a trial arm)
- Inclusion/exclusion criteria (would apply to participants from the Pilot Study that would not qualify for the full-scale phase)
- Outcome measures (e.g., the addition of outcome measures or timing of administration)
- Interventions or their delivery (e.g., protocol modification of the interventions or type of provider delivering them)

NCCIH, and the DSMB reviewed and approved combining data for the UG3 and UH3 phases at the end of the UG3 phase.

3.6.3 UH3 Phase disruption due to COVID-19

In March 2020, the COVID-19 global pandemic resulted in a temporary suspension of the trial, including recruitment, enrollment, intervention delivery, and the collection of objective secondary outcomes. In response to increased severity of the COVID-19 pandemic, including increased rates of community spread, hospitalization and death rates and a rapidly changing environment, we made important modifications to the trial protocol.

Two of the trial arms (SMT and SSM+SMT) required face-to-face contact with study participants. In order to avoid physical interaction, we updated the protocol to allow for remote assessments and interventions in a partial 2 group randomization period during which participants were randomized only to MC or SSM, delivered using HIPAA-compliant videoconferencing technology. In order to accomplish this, several modifications were made including: transitioning to an electronic consent process; updating study protocols and training staff to assess eligibility criteria, deliver SSM and MC virtually, and objective measures via telehealth; addition of secondary outcome measures regarding COVID-19 impact and telehealth usability; modifications to randomization scheme for the partial 2-group randomization period; and implementation of active COVID-19 monitoring at participating sites. The partial 2-group randomization period began in December 2020.

In November 2021, when conditions were met to safely return to in-person activities, we returned to full 4 group treatment allocation. Clinic activities that were suspended at UM Epidemiology Clinical Research Center due to COVID-19 were moved to the Berman Center for Outcomes and Clinical Research. In order to account for potential period-effects, we updated our statistical analysis plan to include an adjustment for partial randomization time periods in all analyses. Since November 2021, all trial procedures have been compliant with Covid mitigation rules (masking, distancing, and sanitation of surfaces) established by the Universities of Minnesota and Pittsburgh. All modifications were planned by the principal investigative team, reviewed and approved by the DSMB and the funding agency, and reported within the trial registration at ClinicalTrials.gov.

3.6.3.1 Covid-19 Monitoring

The DCC will proactively monitor local COVID related trends from the clinical sites' recruitment catchment areas, including number of infections, and hospitalization and death rates. This information is used to guide decisions on trial conduct.

3.7 Enrollment period and follow-up

Participant enrollment will take approximately 4 months for the UG3 planning and pilot phase and approximately 4-5 years for the main UH3 phase of the trial. Individual participants will be followed on a weekly basis for 52 weeks from randomization.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria:

- 18 years of age or older prior to participating in study procedures.
- At the time of randomization, the participant's current episode/aggravation of LBP must be between 2 and 12 weeks duration.
- Participants with no LBP or less than severe LBP on average in the month prior to the current episode/aggravation are eligible.
- Average LBP severity ≥3 on the 0-10 numerical rating scale (NRS) over 7 days
- Medium or High Risk for persistent disabling back pain according to the STarT Back screening tool
- Ability to read and write fluently in English

4.2 Exclusion Criteria

Candidates meeting any of the following exclusion criteria at baseline will not be enrolled:

- Average LBP characterized as severe in the month preceding the current episode/aggravation
- Specific non-mechanical causes of LBP (e.g., infection, cancer)
- Contraindications to SMT or SSM (e.g,. spinal fracture, progressive neurological deficits, inflammatory arthropathies of the lower back, surgical fusion of lumbar spine)
- Active management of current episode of LBP by another healthcare provider. Participants must stop management with their current provider to enroll in the study (e.g., SMT, PT, prescription medication, CBT, a structured program led by a healthcare provider that may include pain education, mind-body practices, coping strategies etc).
    - Participants taking prescription opioid medication for LBP are required to obtain a note from a prescribing/medical provider to confirm they have safely discontinued their opioid medication.
- Serious comorbid health condition that either requires medical attention (e.g., severe hypertension, inadequately managed serious mental health conditions, substance abuse), or has a risk for general health decline over the next year (e.g., Parkinson's disease, Multiple Sclerosis, organ failure, Dementia, Alzheimer's disease).
- Pregnancy, current or planned, and nursing mothers during the study period.
- Inability or unwillingness to give written informed consent.

4.3 Study Enrollment Procedures

4.3.1 Recruitment methods

Trial participants will be recruited from the Twin Cities (Minneapolis and St. Paul, MN), Pittsburgh, PA, and surrounding metropolitan communities using methods described in the Study Accrual and Retention Plan. These include identifying LBP patients at risk for developing cLBP from existing electronic health records, cultivating relationships with local providers (e.g., MDs, DCs, PTs) to obtain participant referrals, and distributing recruitment materials to participating health systems' clinics and providers via regular communication channels (e.g., electronic and print mailings, social media). Additionally, we will use print mailings to targeted demographic groups, mass media advertisements (e.g., minority-oriented community newspapers), and we will work with minority leaders and groups in respective cities (e.g., Urban League, Indian Health Board). Finally, we will utilize recruitment resources from the UMN and UPITT Clinical Research and Translational Science Institutes (CTSI): CTSI PITT+ME (UPITT) research

patient registry, i2b2 Cohort Discovery tool and StudyFinder (UMN), and ResearchMatch (National Registry).

4.3.2 Documentation of reasons for ineligibility and for non-participation of eligible candidates

A comprehensive list of all candidates who were screened, whether or not they were enrolled, and the reasons for ineligibility or non-participation (if applicable) will be maintained electronically. A summary of the number of candidates screened and enrolled with reasons for ineligibility or non-participation will be monitored by the CCC and DCC at routine operational meetings.

4.3.3 Consent procedures

A full description of the consent process is described in section 6, Study Procedures. All participants will provide written consent prior to enrollment.

4.3.4 Baseline screening procedures

Screening consists of a preliminary web-based survey, followed by a phone screen with study staff and an in-person visit to confirm eligibility.

4.3.5 Randomization procedures

We will use block randomization within site using variable blocks of size 12 or 16 participants (since 4 study groups). Using block randomization ensures that equal numbers are randomized to the control and intervention arms, and that the intervention groups are balanced at periodic enrollment intervals. Randomization will be stratified on site and on baseline STarT Back screening tool risk status (medium risk, or high risk of cLBP).[58 104] The study web portal will be available 24 hours a day, 365 days a year, for screening and randomization. In the event of planned or unplanned portal downtime, a telephone-based backup protocol will be administered by the DCC. From January 2021 to October 2021, patients were randomized to remote-delivery of (1) SSM or (2) MC due to the COVID-19 pandemic.

5. STUDY INTERVENTIONS

Patients will be randomized to one of the following treatment groups within the 2x2 factorial design: (1) SMT, (2) SSM, (3) the combination of SMT+SSM, or (4) MC. The initial treatment period is 8 weeks. Decisions regarding visit frequency will be made collaboratively by the provider and patient, as is typical in real-world settings. Participants will be required to attend 75% of prescribed intervention visits to be considered compliant over the 8-week period. In addition, participants have the option to receive additional treatment in the group to which they were randomized if they experience a recurrence of an acute LBP episode during the 10 month follow-up period. This additional treatment will occur in the same study clinic, or virtually using HIPAA compliant Zoom, with the same provider when possible. Participants will not be offered the option to receive treatment delivered in any of the other 3 study groups.

The primary goal of SMT is to address the biological and physical aspects of LBP (e.g., spinal dysfunction) with the intention of restoring maximum movement and functional ability of the spine. The goals of SSM are to primarily address the psychosocial aspects of acute and sub-acute LBP, by providing patients' the opportunities to develop their capacity and motivation to self-manage their LBP in an adaptive manner.[45 108] The goals of the MC group will be to provide care for acute and subacute LBP as it would typically be delivered in primary care settings.

5.1 Interventions, Administration, and Duration

5.1.1 Spinal manipulation therapy (SMT)

The SMT techniques are based on those used in the UK BEAM Trial[122] and agreed upon by PT, DC, and osteopathic professional groups. SMT will be provided by licensed physical therapists (PT-MPT's and DPTs) and licensed doctors of chiropractic (DCs) at the UMN and UPitt who have a minimum of 3 years clinical experience. Decisions regarding visit frequency will be made collaboratively by the provider and patient, as is typical in real-world settings. SMT will be provided within research and outpatient clinics affiliated with the UPITT and UMN. Dedicated clinics in Pittsburgh (Physical Therapy Clinical and Translational Research Center (PT-CTRC) and Homewood Community Engagement Center Wellness Pavilion and Minnesota (The Berman Center for Outcomes and Clinical Research and Hennepin County Medical Center Integrative Care Clinic) will function as the main clinics for the trial. In case of a recurrence of an acute LBP episode during the 10 month follow-up period participants have the option to continue to receive spinal manipulation therapy; this treatment will occur in the study clinics with the same provider if possible. They will not be offered the option to receive treatment delivered in any of the other 3 study groups.

SMT is considered safe for the treatment of LBP, but side effects associated with SMT are common and benign. Approximately 50% of patients report one reaction, most commonly local discomfort which resolves within a day.[7 99-102] Serious adverse events (SAEs) following lumbar SMT are rare[7] and are estimated to occur once per million to several million visits and include cauda equina syndrome, disc herniation, fracture, hematomas or hemorrhagic cysts.[123]

5.1.2 Supported self-management (SSM)

The goals of SSM are to primarily address the psychosocial aspects of acute and sub-acute LBP, by providing patients' the opportunities to develop their capacity and motivation to self-manage their LBP in an adaptive manner.[108 124] The program is theory informed and evidence based. It is adapted from previous SSM programs delivered by PTs, DCs, and other professionals for musculoskeletal and LBP conditions.[11 106-108 124] SSM will be provided by licensed physical therapists (PT-MPT's and DPTs) and licensed doctors of chiropractic (DCs) at the UMN and UPitt who have a minimum of 3 years clinical experience. PTs and DCs will be trained to deliver the SSM program; it includes the following components:

- Psychological/behavioral strategies (e.g., pleasant activity planning, pacing, cognitive restructuring, problem solving).
- Mind-body approaches (e.g., muscle relaxation, breath awareness, focused attention, guided imagery, simple symptom management, postural awareness and strengthening LBP exercises).
- Lifestyle advice (e.g., sleep, daily activities, prevention of social isolation).
- Pain education (e.g., pain theories, prognosis, and evidence based pain management tips).[105]

One-on-one sessions, will be provided by licensed PTs and DCs via HIPAA compliant video conference (e.g., Zoom) or at dedicated clinics in Pittsburgh (Physical Therapy Clinical and Translational Research Center (PT-CTRC) and Homewood Community Engagement Center Wellness Pavilion and Minnesota (The Berman Center for Outcomes and Clinical Research and Hennepin County Medical Center Integrative Care Clinic). Session frequency will be decided collaboratively by the provider and patient depending on the patient's needs and abilities. [107] Informational and instructional materials including, audio recordings and a workbook (intended for use by patients on their own at their preferred pace) will be provided.[108]

At the first visit, the PT/DC will provide an overview of the SSM program, and together the clinician and patient will assess which psychological, lifestyle and behavioral strategies would benefit the patient. This will be done using a quick, interactive assessment that serves to educate, motivate and develop the patient-practitioner bond. The assessment will address common impacts of pain including mood, social connections, relationships, thoughts about LBP and their current situation, activities, sleep and stress. The PT/DC will also perform a simple and repeated movement assessment (flexion/extension, side gliding) to determine if directional preferences exercises (as a form of symptom self-management) would be helpful.

If needed, postural awareness exercises (neutral spine, abdominal curl ups, side planks, and quadruped) will be prescribed to support neutral spine posture, and will include breath awareness to facilitate the mind-body connection. Strengthening exercises to support daily living (bridging, squats and lunges, all done with 'spine sparing' postures) will also be prescribed if necessary.

In case of a recurrence of an acute LBP episode during the 10 month follow-up period, participants have the option to continue to receive the supported self-management treatment; this treatment will occur in the study clinics with the same provider if possible. They will not be offered the option to receive treatment delivered in any of the other 3 study groups.

Side-Effects: Risks associated with the supported self-management group are considered extremely rare. No SAEs were reported in trials including physical and biopsychosocial treatment components.[7] Participants may experience emotional discomfort as a result of discussing the impacts of their pain (e.g., mood, social connections, etc.). Participants may also experience physical discomfort as a result of the directional preference, postural awareness, and strengthening exercises. All of these side effects are expected to be temporary and short-lasting.

5.1.3 Combined SMT and SSM

The goals of the combined SMT+SSM group are to address the biological/physical and psychosocial components of LBP in an accessible and integrated manner. Delivery of SMT and SSM will be by the same provider (licensed PTs or DCs) over an 8-week period using the protocols described above. In case of a recurrence of an acute LBP episode during the 10 month follow-up period participants have the option to continue to receive this combined treatment; this treatment will occur in the study clinics (Physical Therapy Clinical and Translational Research Center (PT-CTRC) and Homewood Community Engagement Center Wellness Pavilion and Minnesota (The Berman Center for Outcomes and Clinical Research and Hennepin County Medical Center Integrative Care Clinic), or virtually using HIPAA compliant Zoom, with the same provider if possible. Trial participants will not be offered the option to receive treatment delivered in any of the other 3 study groups. Descriptions of these interventions are described above.

5.1.4 Medical care

Medical care is informed by the American College of Physicians guidelines on noninvasive treatment for LBP[46] and reflect what is delivered in primary care clinics. Medical care will be provided by licensed medical providers (e.g., MD, APN, PA) with a minimum of 3 years managing musculoskeletal pain patients. Decisions regarding medical care (e.g., pharmacological management) and visit frequency during the initial 8-week intervention period will be made collaboratively by the provider and patient, as normally occurs in clinical practice. Care will be provided via HIPAA compliant video conference (e.g., Zoom), within outpatient clinics affiliated with UPITT and UMN, and/or over the phone: the Physical Therapy Clinical and Translational Research Center, Homewood Community Engagement Center Wellness Pavilion and the Berman Center for Outcomes and Clinical Research , respectively. In case of a recurrence of an acute LBP episode during the 10 month follow-up period participants have the option to continue to receive medical care; this treatment will occur in the study clinics with the same provider if possible. They will not be offered the option to receive treatment delivered in any of the other 3 study groups during this follow-up period.

Medication Delivery: Medication will be prescribed topically and/or orally, in tablet form. Participants can purchase over-the-counter (OTC) medications (e.g., Ibuprofen, 4% lidocaine patches); however, these will be paid for by the study. Prescription medications (see Required and Allowed Interventions) will be sent to the patient's preferred pharmacy by the provider or research staff.

- The first visit will occur in the clinic or via virtual HIPAA compliant videoconference (Zoom). Clinicians will review information collected during the screening phase, and conduct their own medical history and exam as needed. A treatment plan will be established, and the provider will follow-up with the participant (in-person, via videoconference or by phone) within 7 business days of the initial visit.

- The second and subsequent encounters between the provider and participant may occur in the clinic, virtually using HIPAA compliant Zoom, or over the phone. During this encounter the provider will get a sense of how the patient is responding to the treatment. Medication adjustments, including class, dose, and frequency can be made based on the participant's current presentation and response. As described above, the need for subsequent in-person, videoconference visits, and/or phone calls will be made collaboratively between the provider and participant.

Side-Effects [125]: Pharmacological therapies are associated with increased AEs compared to placebo.[7] Several protections are in place to minimize risks, including reminding participants to take their medication as prescribed and to contact the study clinician if there are changes to their medication regimens to avoid drug-drug adverse interactions. Also, clinicians will assess the potential for risk factors based on the patient's medical history prior to prescribing/recommending (prescription and OTC) medications and will suggest the lowest effective dose(s) for the shortest time necessary.

- Allergic reaction
- Cardiovascular symptoms: hypotension, edema, flushing,
- Central nervous system: dizziness, weakness, ataxia, fatigue, drowsiness, headache, stimulation, insomnia, sedation, tremor, syncope
- Chemical dependence
- Dermatologic: itchy skin, rash, sweating
- Endocrine & Metabolic: weight gain
- Gastrointestinal symptoms: nausea, vomiting, dry mouth, abdominal pain, dyspepsia, diarrhea, GERD, constipation, bleeding
- Kidney failure (excessive NSAIDs use)
- Liver failure (excessive Acetaminophen use)
- Ophthalmic: visual field loss, blurred vision
- Respiratory: depression, arrest, apnea

5.2 Handling of Study Interventions

5.2.1 Spinal manipulation therapy

Required Interventions

Overall, the SMT protocol is largely pragmatic as it includes core manipulative practices with sufficient flexibility to be representative of the professions most commonly delivering SMT.[122]

- SMT will be applied to the spine (below the fifth thoracic vertebrae), and sacroiliac joints.
- SMT will consist of mobilization (low velocity, low-high amplitude passive movements) and/or manipulation (high velocity, low amplitude thrust) at the clinician's discretion.
- SMT may be applied unilaterally or bilaterally at one or more locations.

Allowed Interventions

- Soft tissue techniques which include cross-fiber stretch, longitudinal stretch, direct pressure, and deep friction applied to soft tissue from the lower ribs to the gluteal folds.
- Lumbar neural mobilization

- Clinicians may use heating pads for up to 10 minutes to facilitate the delivery of SMT.

Prohibited Interventions
Clinicians applying SMT are prohibited from providing the following:
- SMT to the neck or upper thoracic spine (above the sixth thoracic vertebrae)
- SMT directed at extremity joints (e.g., hip joint)
- Instrument assisted SMT (e.g., activator)
- Applying passive modalities other than heat (e.g., TENS & ice)
- Lumbar belts, strapping, taping etc.
- Recommending bed rest
- Exercise recommendations beyond those described in section 5.3
- Educational materials or recommendations for self-care/self-management beyond those described in section 5.3
- Recommendations to use Mind-body practices (e.g., yoga, Tai Chi, meditation) or intervention elements described in the SSM protocol
- Assessment of need for symptom management exercises (flexion/extension, side gliding, postural awareness exercises, and strengthening exercises)

Training
Clinicians providing SMT will be required to attend at least 2, 2-hour training sessions prior to delivering study interventions. Refresher training sessions during the treatment phase will be conducted annually thereafter. Training sessions will be led by study investigators and will cover the goals of the SMT intervention, including hands-on demonstration and practice, and required, allowed, prohibited interventions as outlined in the protocol, and the importance of maintaining equipoise to avoid contamination between the SMT and SSM groups. It will include a combination of in-person (e.g., videoconference) and interactive workshops, webinars and online training formats. Monthly video and/or audio conferences will be held to build a community of practice to problem-solve and facilitate a degree of consistency between providers and across sites.

5.2.2 Supported self-management
Required Interventions
The following are considered standard elements of the SSM intervention:
- Presenting rationale for biopsychosocial approach to pain management and performing assessment of need for other psychological/social/behavioral strategies (see options below)
- Pain theories
- Favorable prognosis
- Evidence- based pain management tips
- Relaxed breathing, progressive muscle relaxation, mental imagery
- Encourage activities of daily living
- Encourage regular physical activity
- Postural awareness (neutral spine)
- Acknowledging/problem- solving challenges of integrating SSM strategies into life
- Encouragement/reassurance

Allowed Interventions
The following summarizes optional SSM elements (based on patient needs):
- Cognitive restructuring (shifting thoughts and attitudes to reduce balance out catastrophizing)
- Problem- solving as needed (around pain impacts to maximize well being)
- Pleasant activity planning (helpful for those who have depressive symptoms)

- Pacing (having an awareness of up/down time needed, plan activities to manage with pain)
- Symptom management exercises (flexion/extension, side-gliding)
- Postural stabilization exercises (abdominal curl-ups, side planks, and quadruped)
- Strengthening exercises to support activities of daily living (bridging, squats and lunges, all done with 'spine sparing' postures)

Prohibited Intervention
SMT providers delivering the SSM intervention are prohibited from delivering:
- SMT as described in section 5.2.1
- Applying passive modalities (e.g., TENS, heat, ice)
- Exercise recommendations, including rehabilitative exercises that fall outside of what is described in the SSM allowable interventions
- Educational materials and recommendations for self-care beyond those described in section 5.3 and what is described in the SSM allowable interventions
- Recommendations to use mind-body practices not described in required or allowable SSM interventions
- Lumbar belts, strapping, taping, etc.
- Recommending bed rest

Training
The goal of SSM training is to facilitate providers' confidence and ability to act as an effective coach for patients' in their self-management. Clinicians providing SSM will be required to complete online training materials covering information in the key SSM content areas. In addition, they will be required to attend face-to-face training sessions (e.g., via Zoom) led by Drs. Greco, Evans, and other investigators. Face-to-face training sessions will be highly interactive, and focus on the application of assessment and intervention elements of SSM, including delivering SSM in the remote environment. Prohibited interventions and other study specific related procedures (e.g., intervention documentation) will also be addressed. Monthly video and/or audio conferences will be held to build a community of practice and to problem-solve and facilitate a degree of consistency between providers and across sites. Refresher training sessions during the treatment phase will be conducted annually thereafter.

5.2.3 Medical care
Required Interventions
Participants are required to meet with their medical provider to discuss treatment options.

Allowed Interventions
The evidence-informed medical care intervention is largely pragmatic as it includes different OTC and prescription drug classes and doses, reflective of what is available in clinical practice.
- The clinician and patient should select OTC or prescription nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants (SMRs)[46] as first-line treatment in this study.
- The choice between NSAIDs and SMRs should be individualized on the basis of patient preferences and likely individual medication risk profiles.
- In addition, providers may recommend the use of heat, massage, or acupuncture; however, no formal referrals will be made.

Additional recommendations for commonly used OTC and prescription drug options that are not supported by good data are permissible for participants who are unresponsive to or unable to tolerate first-line medications:
- Acetaminophen
- Lidocaine patches

- NSAID creams
- Opioids
- Benzodiazepines
- Antiseizure medications
- Tricyclic antidepressants
- Selective Serotonin Reuptake Inhibitors and/or Serotonin Norepinephrine reuptake inhibitors

Prohibited Interventions/Recommendations
Medical providers are prohibited from recommending the following interventions:

- Medication(s) different from what is described in allowed interventions above.
- Referral for physical therapy, manual treatment, cognitive behavioral therapy, or any treatments provided by a PT, DC, or psychologist.
- Referral for interventional procedures (e.g., epidural steroid injections, intramuscular and facet joint injections)
- Exercise recommendations beyond those described in section 5.3
- Educational materials or recommendations for self-care beyond those described in section 5.3
- Recommendations to use Mind-body practices (e.g., yoga, Tai Chi, meditation) or intervention elements described in the SSM protocol
- Lumbar belts, strapping, taping etc.
- Recommending bed rest

Training
Clinicians providing medical care are required to attend at least 2, 2-hour training sessions prior to delivering study interventions. Training will focus on the medical care protocol (e.g., what is required, allowed, prohibited, safety assessments, and AEs), the operating procedures at each respective clinic, and delivering MC via videoconference when applicable. Refresher training sessions during the treatment phase will be conducted annually thereafter. Training sessions will be led by study investigators and cover required, allowed, and prohibited interventions as outlined in the protocol. Monthly video and/or audio conferences will be held to build a community of practice to problem-solve and facilitate a degree of consistency between providers and across sites.

5.3 Concomitant Interventions

Required Interventions
All participants will receive basic standardized information regarding the generally favorable prognosis of acute and sub-acute LBP. We will provide patients with an updated version of the Back in Action book [11] [44] in print and/or electronic formats. The Back in Action book:

- Encourages patients to engage in their normal activities as soon as possible, even if it causes some pain.
- Encourages general aerobic exercise like walking, swimming, bicycling.
- Provides a very brief summary of the general causes of LBP, reassurance that it is rarely due to a serious problem, and that the majority of cases do not require specialty care or imaging.
- Emphasizes the patient's role in facilitating their own recovery by providing some general recommendations for symptom management (e.g., use of heat, changing positions frequently).

Allowed Interventions
Participants will be allowed to use OTC medications as needed during the course of the study. In addition, participants will be allowed to continue self-care practices (e.g., heat, stretching) for LBP they used prior to the study. Participants not assigned to MC who experience a significant worsening of LBP symptoms that cannot be managed by the assigned and concomitant interventions will be referred to the study's

medical care provider for a short-course of 'rescue medications', using a protocol successfully implemented, but rarely required, in previous studies by the investigators.[10 11] See section 5.5.

Treating clinicians, in consultation with the PIs, may refer in the case of AEs or if LBP complications develop that cannot be adequately managed with the assigned intervention (e.g., disc herniation with progressive neurological deficits). Participants will be informed to seek any required care for all conditions unrelated to the study.

Prohibited Interventions
Participants will be asked to limit treatment to their assigned intervention for the length of the initial 8-week intervention period; similarly providers will be taught to refrain from delivering interventions that fall outside the scope of the study protocols (see above). However, participants retain the right to discontinue care at any time.

5.4 Adherence Assessment

The total number of treatments will be decided by the treating clinician based on each individual participant's clinical presentation and response to care, as is done in clinical practice. We anticipate 4-6 visits being prescribed for most participants receiving SMT, 4-8 visits for most participants receiving SSM, and 2-4 visits for most participants receiving medical care. Participant adherence to assigned interventions will be documented at each visit in the clinical notes.

Treatment adherence has been defined in the Threshold Criteria for Transition as attending ≥75% of prescribed intervention visits. We have expanded on this definition by including a minimum number of visits for each intervention and requiring participants not drop out of active care to be considered adherent. A minimum of 2 sessions will be required for participants in SMT and MC, and minimum of 4 for the two groups receiving SSM, but additional sessions may be needed.

Intervention fidelity will be assessed by review of treatment visit activities that address required, allowed and prohibited interventions. In addition, fidelity will be assessed by video/audio recordings or in person observations of randomly determined intervention visits. Fidelity assessments will occur monthly, for six months, on each provider currently treating patients, then quarterly thereafter. If concerns arise during quarterly reviews, the provider may resort back to monthly fidelity checks as needed. The DCC will monitor the treatment administered forms for activities defined as 'out of scope' for the defined intervention (e.g., spinal manipulation delivered to a participant assigned to structured self-management). Out of scope activities indicating potential crossover will be flagged through automated real-time alerts created by the DCC which will immediately be sent to the relevant site's PI and study coordinators. The site study coordinators are best suited for contacting providers, as they will be familiar to them and will have developed collaborative working relationships that ensure successful project implementation. Additional actions would include remedial training for the providers and potential removal from providing study care.

5.5 Rescue Medication
Participants not assigned to MC who experience a significant worsening of LBP symptoms that cannot be managed by the assigned and concomitant interventions will be referred to a study medical care provider for a short-course of rescue medications. Skeletal muscle relaxants and non-steroidal anti-inflammatories are the first line rescue medications that will be offered based on the participant's individual medication risk profile. Additional medication may be used when first line rescue medications are contraindicated or do not sufficiently manage the participant's pain (e.g., opioids, benzodiazepines, antiseizure medications).[46] Use of rescue medication will be monitored and differences across intervention arms will

be compared. Further, medical providers should make reference to the Back in Action booklet and reinforce its content (e.g., the favorable prognosis for acute/subacute back pain and the importance of staying active).

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

See Table on next page

Assessment	Initial Screen	Baseline/ Enrollment (Day 0)	Intervention Visits (Months 0-2)	Weekly Follow-Up (Weeks 1-52)	Follow-Up (Week 2)	Monthly Follow-Up (Months 1-12)	Follow-Up (Month 1)	Follow-Up (Month 2)	Follow-Up (Month 6)	Follow-Up (Month 12)
Informed Consent	x	x								
Demographics	x	x								
Medical History & Current Medications		x								
Physical Exam including objective outcomes		x						x		
Inclusion/Exclusion	x	x								
Technology Assessment**		x								
COVID -19 Impact		x						x	x	x
TUQ**		x					x	x		
STarT Back Screening Tool Status	x							x	x	x
Chronic LBP status (NIH RTF definition)	x	x							x	x
Chronic interference with daily activities	x	x							x	x
LBP intensity	x	x		x						
LBP frequency		x		x						
Pain Trajectory		x								x
Implementation Measures	x	x						x	x	x
Randomization/Enrollment		x								
Treatment Administered (booster sessions allowable in months 3-12)			x							

Intervention Uptake							x	x	x	x
Disability, PROMIS, healthcare and medication use, and productivity loss		x				x				
Adverse events*		x	x			x				
Satisfaction and global improvement								x	x	x
Non-specific factors (HEAL)		x			x		x	x	x	x
Psychosocial Mediators (self-efficacy, coping, kinesiophobia, and pain catastrophizing)		x						x	x	x
Participant Close Out										x

*Participants can also report adverse events to the PI's or study staff at any point during the trial
** Technology Assessment and the Telehealth Usability Questionnaire (TUQ) will be administered to participants who are enrolled in the 2-arm study only. Technology Assessment and the Telehealth Usability Questionnaire (TUQ) may be administered to participants in the 4-arm study if applicable (e.g., if screening and/or treatments are done virtually).

6.2 Description of Evaluations

6.2.1 Screening Evaluation

The following evaluations will occur to determine if the candidate is eligible for the study.

Consenting Procedure

- Potential participants will consent at 3 different time points: the initial screen online, phone screen, and at an in-person or videoconference baseline screening appointment.

Initial screening

- Potential participants will read a brief online description of the study, including the purpose, study design and procedures to help them decide if they want to complete the initial screen. Consent is provided by checking a box that will allow them to proceed with the initial screening.
- Phone Screening

Baseline Screening Appointment

- Potential participants will be given a copy of the consent form to review on their own that will describe the screening and study procedures. See Section 11.2 for a full description of the consent form. They will be given ample time to review the form on their own and ask questions.

- The Principal Investigators, or designee (i.e., research staff) will review the consent form, section by section, one-on-one with each potential participant; participants will be invited to ask questions as they proceed through each section.

- Informational materials (e.g., flow chart or PowerPoint) will be used to facilitate understanding.

- All participants will be given information related to the COVID-19 pandemic and potential risks associated with research participation

- A signed and dated consent form will be obtained from each study candidate and research staff conducting the consent process will sign as a witness. All participants will be given a copy of the signed consent form for their personal records. Participants will provide electronic consent (e-Consent in REDCap) or written consent.

- Original signed consent forms will be secured in the respective participants' research file at each of the respective clinical coordinating centers or in REDCap. Scanned consent forms will be sent electronically to the DCC for monitoring.

- Only individuals who demonstrate comprehension will be considered eligible to participate. Persons who are not able to read and write in English or consent for themselves are ineligible.

Training

All research staff obtaining informed consent are required to undergo project specific human subjects training that addresses the essential components to the informed consent process. See Section 11.2 for

additional information about the consent form. In addition, staff will complete human subjects training in accordance with the IRB of record and/or the staff member's institutional human subject training requirements.

Changes to the Informed Consent Form

In the event the informed consent form changes, following necessary IRB approvals, study staff will meet with the PI or designee and review changes to the form prior to conducting consent with a potential participant. See the Participants and Confidentiality section for additional information.

If potential participants need to be informed of specific changes in the risks or benefits of study participation, an addendum consent will be used. This addendum will be used to inform enrolled participants about significant new findings that may have a bearing on their willingness to continue participation in the study. The addendum consent will be given to the participant at a study visit or mailed to the participant's home.

Screening

Screening will occur at 2 time points: an initial screen (online and phone) and a face to face (e.g., in-person or videoconference) baseline screening appointment.

Initial Screening (Online/Phone)

- Following consent, potential participants will be asked a series of self-report questions to screen basic eligibility. Persons who meet basic inclusion criteria (e.g., age, medium or high risk on STarT Back Screening Tool, LBP intensity of 3 or higher, English literacy) and who otherwise have no obvious exclusions (e.g., pregnancy, history of surgical fusion of lumbar spine) will be contacted by study staff, who will ask specific health-related, questions pertaining to inclusion (e.g., LBP episode duration).

- In-person or videoconference screening appointments will occur as soon as possible, but must occur within 30 days of completing the phone screen; otherwise, the initial phone screen will be redone.

Baseline Screening (In Person/Videoconference)

- Written or e-informed consent will be collected from participants prior to any screening procedures at this visit.

- Participants will complete self-report questionnaires to determine eligibility that include:

    - Demographics

    - Current back pain intensity and duration

    - Diagnosis of serious mental health disorders and related treatment; if major depression is suspected or reported by the participant, the Patient Questionnaire-2 (PHQ-2)[126] will be administered; a score of greater than or equal to 3 will lead to additional screening for suicidality. Suicidal ideation will be collected using question 12 from the Quick

Inventory of Depressive Symptomatology-Self Report (QIDS-SR)[127] and a score of greater than or equal to 2 warrants exclusion and referral.

- Substance abuse. All participants who indicate they drink alcohol will be asked if they drank more alcohol than intended in the previous 6 months. If affirmative, additional questions will be asked related to how often they have drunk 6 or more drinks on one occasion. Those who indicate having done so at least weekly will receive additional screening: the 10-item Alcohol Use Disorders Identification Test (AUDIT) for alcohol.[128] Scores of greater than or equal to 20 on the AUDIT is exclusionary and warrants referral. AUDIT will be available to administer at any time if the clinician suspects a problem. Participants reporting the use of illegal drugs or prescription medication for nonmedical reasons in the last year will complete the 10-item Drug Abuse Screening Test (DAST)[129-131] for drugs. Scores of greater than or equal to 6 on the DAST is exclusionary and warrants referral. The DAST will be available to administer at any time if the clinician suspects a problem.
- Comorbidities

- A licensed healthcare provider (e.g., DC, PT, MD, advanced practice provider) will conduct a medical history and a focused low back physical exam that will include posture assessment, orthopaedic and neurological tests, palpation (in-person only) etc. Current medications and vitals (in-person only) will be collected. Participants undergoing screening assessment via videoconference will be asked additional screening questions regarding potential hypertension as remote assessment of blood pressure is not planned. Suspicion of declining cognitive function during clinical exam will lead to administration of the Mini-mental state examination. A score of 23 or below is exclusionary.[132]

- Women of childbearing age require a pregnancy test. Women who have had a hysterectomy or are postmenopausal will not require a pregnancy test. Persons who are in same sex relationships, transgender and/or transitioning, celibate, LBTGQ+, can refuse a pregnancy test and still be eligible to participate. For remote videoconference baseline appointments, participants will be mailed a pregnancy test and instructed to take the test during the baseline appointment and show research staff the result.

- Potential participants who present with signs and symptoms suggestive of a specific cause of LBP (e.g., nephrolithiasis, infection, fracture), contraindication to SMT or SSM (e.g., inflammatory arthropathies of the lower back), or other condition that warrants medical attention will be referred to their medical provider for follow-up and management.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment is defined as the date of randomization at which point all eligibility criteria are confirmed and the individual has agreed to participate; this is recorded on a case-report form. AEs will be collected after the participant is enrolled. Participants will be told to contact study staff and/or providers about any health related changes they experience. See Safety Assessments and the DSMP for additional details.

Baseline Assessments
For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments are performed against which to measure the study outcome. These will also ensure the groups are balanced with respect to baseline characteristics.

Primary and secondary outcomes will be measured using web-based, self-report questionnaires administered free of provider and investigator influence.

Baseline characteristics
Important baseline characteristics (e.g., demographics, past healthcare use, COVID-19 impact[190], LBP duration, prior episodes of LBP, visual trajectory questionnaire for pain[186], Quebec Task Force classification of spinal disorders[133]) will be collected through web-based, self-report questionnaires and the screening provider's medical history and physical exam. Baseline measures included in the NIH research task force's minimum dataset will be collected.[73]

Primary Outcome Measures
The following primary outcome measures will be collected during the baseline assessment.

- Low back pain impact is defined as a combination of pain intensity, pain interference with normal activities, and functional status, using 9 items of the 29-item PROMIS short form. These items have substantial research support to validate their discriminatory and prognostic importance. Scores on the 9 PROMIS-based items yielding Impact Stratification range from 8 (least impact) to 50 (greatest impact).[191]

- LBP Intensity: participants will be asked to rate their average LBP over the last week on an ordinal 11-box NRS (0=no LBP, 10=the worst LBP possible). Several studies have shown that ordinal pain scale measures perform as well as the 10-cm Visual Analog Scale (VAS),[134] a simple, frequently used valid assessment of variation in pain intensity[119 135] and a reliable measure of treatment efficacy.[136] The advantage of the 11-box scale over the VAS is that it is easier to administer and score.[119]

- Low back disability will be measured with the modified Roland Morris Disability Questionnaire, a 24-item questionnaire that measures the degree to which the low back problem or leg pain restricts patients' daily activities. It has a high level of internal consistency, construct validity, and responsiveness.[120]

Secondary Outcome Measures

- The PROMIS-29 Profile v2.0 Instrument (www.nihpromis.org) as recommended by the NIH RTF will be used with the exception of the question on pain intensity which is collected elsewhere on a weekly basis.[73] This includes the following measures: pain interference with normal activities, physical function, anxiety, depression, fatigue, sleep disturbance and the ability to participate in social roles and activities.

- LBP frequency will be collected by asking participants to report the number of days LBP has been a problem in the past 7 days.[73]
- OTC and prescription medication use for LBP, including class and frequency by class.
- Health care utilization including provider visits, ER visits, MRIs, injections, hospitalizations, and surgeries.
- Productivity loss related to LBP (e.g., missed work, reduced productivity while at work) will be assessed using questions from the Institute for Medical Technology Assessment's productivity cost questionnaire.[137]
- Physical exam objective outcome measures including QTF classification[133], timed up and go test, 5 times sit-to-stand test [185, 187, 188], and the sock test.[185]
- Chronic interference with daily activities assessed using "how often has low-back pain interfered with your ability to do regular activities over the past 6 months?" on a 3-item scale (less than half the days in the past 6 months, at least half the days in the past 6 months, every day or nearly every day in the past 6 months).
- Prevention of cLBP at 6 and 12 months, as measured by the proportion of patients in each group meeting the definition by the NIH Task Force on Research Standards for Chronic LBP (i.e., ongoing low back problem on ≥50% of days over past 6 months).

Psychosocial Mediator Measures

- Self- efficacy will be assessed using the 22-item Chronic Pain Self-Efficacy Scale that will be adapted for acute/sub-acute pain.[138]
- Coping will be assessed using an adapted version of the 28-item Brief COPE instrument.[139]
- Kinesiophobia will be measured using the 11-item Tampa Scale for Kinesiophobia demonstrated to have internal consistency, responsiveness and validity similar to the original 17-item instrument.[140]
- Catastrophizing (Pain Catastrophizing Scale[141]) is measured using the 13-item Pain Catastrophizing Scale; it uses a 5-item point scale (0=not at all, 4 all the time) and has internal consistency and validity.
- Measurement of key non-specific factors that may influence outcomes will be measured using the short forms for positive outlook (6-item) from the Healing Encounters and Attitudes Lists (HEAL)

Randomization

Randomization will precede intervention administration. Randomization will occur within 7 business days of finalizing eligibility determination. Persons who are not randomized within this time frame will repeat the in-person/videoconference screening. Interventions will be initiated within 7 business days of randomization/ enrollment.

6.2.3 Blinding

Blinded Personnel:
Blinding of treatment providers and participants is not feasible. However, the following steps will be taken to minimize potential bias and enhance study rigor:

a). all study personnel involved in screening and enrollment will be masked to upcoming randomization assignments;
b). all study personnel involved in outcome assessment will be independent of intervention delivery, and trained in ensuring unbiased data collection and blinded to study assignment until database is locked;
c). only a single member from the DCC will be unblinded and have access to treatment group assignment for the purpose of creating closed DSMB reports; and
d). participants will be queried in self-report questionnaires as to whether or not anybody attempted to influence their responses.

6.2.4 Follow-up Visits

Intervention Visits
The following information will be collected at each intervention visit, which will occur as needed throughout the one year as there is no set schedule of treatments:

- Treatment delivery format – in-person, videoconference or phone
- Treatment administered – provider's record treatment administered including required, allowed and prohibited treatments to assess treatment fidelity and adherence. (Clinical notes will be documented in the medical record as required for patient management and for compliance with provider licensing requirements).
- Adverse events (AEs) - participants will be asked about the occurrence of AE/SAEs by their treatment provider at each visit. The AE protocol described in section 7, Safety and Assessments will be initiated and adhered to for all AEs identified.

Weekly Follow-up
Weekly outcomes will be collected electronically via direct patient self-report; participants who are unable to provide electronic data will be contacted directly by blinded study staff who will ascertain outcomes. Additional information related to data collection and quality assurance is described in section 10.

The following outcomes will be collected on a weekly basis for one year (± 2 days):

- Primary outcomes
  - Pain intensity
- Secondary outcomes
  - LBP frequency

Monthly Follow-up

Monthly follow-up data (Months 1-12) will be collected electronically via direct patient self-report. Participants who are unable to provide electronic data will be contacted directly by blinded study staff who will ascertain outcomes, or they will be mailed a paper copy of the questionnaire to complete and return to the study team. Additional information related to data collection and quality assurance is described in section 10.

The following outcomes will be collected on a monthly basis for one year (± 7 days):

- Primary outcomes
  - Disability - Roland Morris Disability Questionnaire
  - Low Back Pain Impact - subset of PROMIS-29

- Secondary outcomes
  - PROMIS measures, additional healthcare use, medication use, and productivity loss
  - AEs -participants will be queried about AEs associated with study interventions (e.g., increased pain, neurological symptoms, medication side effects etc.). [11] [142] [143] The AE protocol described in section 7, Safety and Assessments will be initiated and adhered to for all AEs identified.

Week 2 Follow-up

In addition to outcomes collected weekly, the following outcomes will be collected at week 2 (± 7 days)

- Psychosocial mediator measures
  - Measurement of key non-specific factors that may influence outcomes will be measured using the short forms for patient-provider connection (7-item), healthcare environment (6-item), and treatment expectancy (6-item) from the Healing Encounters and Attitudes Lists (HEAL)

Month 1 Follow-up

In addition to outcomes collected weekly and monthly, the following outcomes will be collected at month 1 (between -7 and +14 days)

- Psychosocial mediator measures
  - Measurement of key non-specific factors that may influence outcomes will be measured using the short forms for patient-provider connection (7-item), healthcare environment (6-item), treatment expectancy (6-item), and positive outlook (6-item) from the Healing Encounters and Attitudes Lists (HEAL)
- Intervention uptake (SSM, SSM + SMT participants only)
  - To measure patient's use of recommended activities we will document in patient self-report questionnaires the use of the main SSM components using the following question: How many days in the past week did you use: the mind-body skills (like relaxed breathing, progressive muscle relaxation) recommended by your provider; the exercises recommended by your provider; the postural awareness suggestions (like neutral spine) recommended by your provider; other

tips recommended by your provider (like suggestions for sleep, communicating with others, etc.); the workbook.

- Telehealth Usability Questionnaire (TUQ)

Month 2 Follow-up

In addition to outcomes collected weekly and monthly, the following outcomes will be collected at month 2 (between -7 and +14 days)

- Low back physical exam objective outcome measures
- Secondary outcomes
  - Patient satisfaction will be measured using a 7-point Likert scale (from completely satisfied to completely dissatisfied).[144]
  - Global improvement will be measured using a 9-point scale ranging from completely recovered to vastly worse.[145]
  - SBST status
- Psychosocial mediator measures
  - Measurement of key non-specific factors that may influence outcomes will be measured using the short forms for positive outlook (6-item) from the Healing Encounters and Attitudes Lists (HEAL) .
  - Self-efficacy, Coping, Kinesiophobia, Pain Catastrophizing
- Intervention uptake (SSM, SSM + SMT participants only)
- COVID-19 impact & Telehealth Usability Questionnaire (TUQ)

Month 6 Follow-up

In addition to outcomes collected weekly and monthly, the following outcomes will be collected at month 6 (between -7 and +14 days)

- Secondary outcomes
  - Satisfaction, global improvement, chronic interference with daily activities and SBST status
  - Prevention of cLBP will be measured using the NIH RTF definition of cLBP "a back pain problem that has persisted at least 3 months and has resulted in pain on at least half of the days in the past 6 months." Specifically, this will be assessed with NIH RTF minimum dataset items 1 (LBP duration) and 2 (proportion of days that LBP has been a problem over the past 6 months).73
- Intervention uptake (SSM, SSM+SMT participants only)
- Psychosocial mediator measures
  - Self-efficacy, Coping, Kinesiophobia, Pain Catastrophizing, and HEAL positive outlook measure.
- COVID-19 impact

6.2.5 Completion/Final Evaluation

Month 12 Follow-up
In addition to outcomes collected weekly and monthly, the following outcomes will be collected at month 12 (between -14 and +28 days)

- Secondary outcomes
  - Satisfaction, global improvement, chronic interference with daily activities, visual trajectory questionnaire for pain [186] and SBST status
  - Chronic LBP status as determined by NIH RTF questions
- Psychosocial mediator measures
  - Self-efficacy, Coping, Kinesiophobia, and Pain Catastrophizing measures
  - Measurement of key non-specific factors that may influence outcomes will be measured using the short form positive outlook (6-item) from the Healing Encounters and Attitudes Lists (HEAL)
- Intervention uptake (SSM, SSM+SMT participants only)
- COVID-19 impact
- Participant Close-out
  - Final participation will be used to record participant status

All efforts will be taken to facilitate participant's completion of the study interventions. In the event a participant must discontinue the intervention early (see also Intervention Discontinuation), participants will be asked to complete follow-up electronic self-report questionnaires to the extent possible. Potential reasons for early termination include:

- Participant develops a competing comorbid health condition that precludes adherence or makes it unsafe for them to proceed with their assigned treatment.
- A change in the participant's life (e.g., participant moves, dies, has other personal matters to attend).
- Participant chooses to discontinue on their own for any reason (e.g., participant is not responding to care or getting worse).
- Study closure by institute or oversight body.

Additional information related to intervention discontinuation is described in Section 8.

6.2.6 Additional Evaluation Related to Hybrid Effectiveness/Implementation Design, RE-AIM and PRECIS Frameworks

Implementation Measures
Mixed-methods data collection (qualitative and quantitative) will be used to collect contextual information addressing dimensions outlined by the RE-AIM framework. These data will inform future implementation and aid in the interpretation of effectiveness results.[25]

Screening

- Qualitative survey questions (open-ended) will assess potential participants' views regarding barriers and facilitators to participating in the study and study interventions.
- Quantitative data regarding reasons for exclusion will also be collected

Months 2, 6, and 12 Follow-Up

- Qualitative surveys will address enrolled participants barriers and facilitators to engaging in the interventions as recommended, including barriers and facilitators for engaging in telehealth visits.
- Satisfaction
- HEAL Positive Outlook

Additional contextual data will be collected from the participating practitioners to inform future implementation in other settings. Prior to training, prior to the start of the UG3 pilot phase, at the completion of the UG3 pilot phase, pre and post UH3 training, annually during the UH3, and at the completion of the UH3 randomized controlled trial, self-report questionnaires will be administered to all participating practitioners. Questionnaires will include qualitative survey questions that address practitioners' views regarding the interventions, including perceived barriers and facilitators and their confidence in the interventions and in delivering care remotely[189]. The Pain Attitudes and Beliefs Scale (PABS)[43] and additional questions regarding practitioner confidence (using a 0-10 NRS) will also be assessed quantitatively in the self-report questionnaires.

Qualitative data will also be collected from purposeful samples of health providers' and health system leaders using data collection methods that meet their needs and preferences (e.g., qualitative surveys, interviews and field notes). Additional details regarding assessment of implementation measure data collection is provided in the manual of operations.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Following enrollment, participants will be asked about the occurrence of AE/SAEs by their treatment provider at every visit. In addition, participants will be informed to report AE/SAEs directly to study staff throughout the study period and will also be asked if they experienced any AE/SAEs associated with study interventions on monthly self-report surveys. Events will be followed for outcome information until resolution or stabilization. The PI or designee will record all reportable events with start dates occurring any time after enrollment until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

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

Spinal manipulation therapy (SMT) is considered safe for the treatment of LBP, but side effects associated with SMT are common and benign. Approximately 50% of patients report one reaction, most commonly local discomfort that resolves within a day.[7 99-102] SAEs following lumbar SMT are rare[7] and are estimated to occur once per million to several million visits and include cauda equina syndrome, disc herniation, fracture, hematomas or hemorrhagic cysts.[123]

Risks associated with the supported self-management group are considered extremely rare. No SAEs were reported in trials including physical and biopsychosocial treatment components.[7] Participants may experience emotional discomfort as a result of discussing the impacts of their pain (e.g., mood, social connections). Participants may also experience physical discomfort as a result of the directional preference, postural awareness, and strengthening exercises. All of these side effects are expected to be temporary and short-lasting.

Pharmacological therapies delivered as part of medical care are associated with increased AEs compared to placebo.[7] Several protections are in place to minimize risks, including reminding participants to take their medication as prescribed and to contact the study clinician if there are changes to their medication regimens to avoid drug-drug adverse interactions. Also, clinicians will assess the potential for risk factors based on the patient's medical history prior to prescribing/recommending (prescription and OTC) medications and will suggest the lowest effective dose(s) for the shortest time necessary.

Below is an alphabetical list of expected AEs for each study intervention.

Supported Self-Management

- Emotional discomfort
- Exacerbation of low back pain
- New or increased leg pain
- Numbness or tingling
- Soreness or stiffness

Medical Care

- Allergic reaction
- Cardiovascular symptoms: hypotension, edema, flushing,
- Central nervous system: dizziness, weakness, ataxia, fatigue, drowsiness, headache, stimulation, insomnia, sedation, tremor, syncope
- Chemical dependence
- Dermatologic: itchy skin, rash, sweating
- Endocrine & Metabolic: weight gain
- Exacerbation of low back pain
- Gastrointestinal symptoms: nausea, vomiting, dry mouth, abdominal pain, dyspepsia, diarrhea, GERD, constipation, bleeding
- Kidney failure (excessive NSAIDs use)
- Liver failure (excessive Acetaminophen use)
- Ophthalmic: visual field loss, blurred vision
- Respiratory: depression, arrest, apnea

Spinal Manipulation Therapy

- Cauda equina syndrome
- Disc herniation
- Exacerbation of low back pain
- Fracture
- Hematoma
- Hemorrhagic cyst
- New or increased leg pain
- Numbness or tingling
- Soreness or stiffness

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

AE is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. AEs are to be recorded regardless of their relationship to the study intervention.

The following scale will be used to grade AEs:
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.

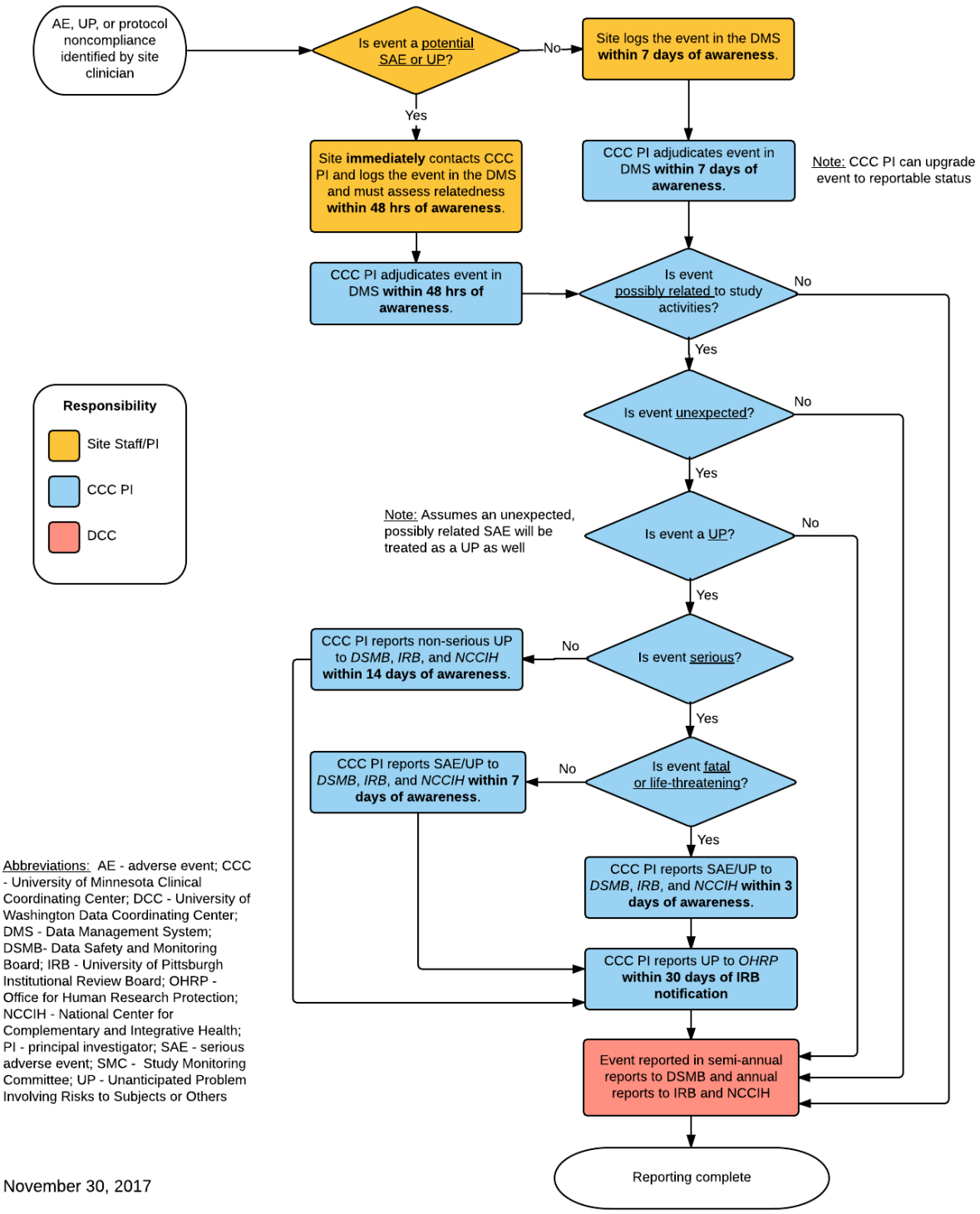
We will measure and compare rates of AEs across the four treatment arms. We will specifically look for common treatment-related AEs that include: LBP, soreness at the treatment site, gastrointestinal symptoms, emotional discomfort, and other events. We will capture AEs prospectively from study participants through monthly surveys and at in-person/videoconference/telephone visits. Each unique occurrence will receive a separate ID in order to avoid duplication in documentation.

SAE is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

We will collect SAEs both passively through ad hoc reporting and through systematic evaluation at study visits. Given the nature of the interventions we do not anticipate any specific treatment-related SAEs and therefore focus on standard and LBP-specific serious events: death; severe or permanent disabilities; life-threatening conditions; hospitalizations; other important medical events; progressive neurological deficits, or cauda equina syndrome.

7.4 Reporting Procedures

Procedures and responsibilities for reporting AEs and SAEs are outlined in the figure below. “Awareness” in the figure below is defined as the date at which the research team is able to contact the participant to gather additional information about the event.



If an AE occurs at a CCC where the PI is not available, the PI at the other CCC institution will be notified and the AE reporting protocol will be initiated. If both PIs are not available, a clinical Co-Investigator

will be notified, and the above protocol will be initiated. Once a PI is available, the PI will assume responsibility for reporting.

7.5 Follow-up for Adverse Events

AEs/SAEs will be identified during the intervention phase at study visits and during the study follow-up phase using monthly self-report questionnaires (surveys) or through direct contact with study staff. Events will be followed until resolution or stabilization, whichever occurs first; resolution and stabilization will be determined by the PI with input from the study clinician when appropriate.

If an AE/SAE occurs during the intervention phase, the study clinician will monitor the AE/SAE while the participant is under their care, this will include a medical evaluation and treatment, or modifications to treatment as necessary to protect the participant and minimize harm. If warranted, referral to an outside provider will be made.

If an AE/SAE occurs during the follow-up phase, study staff will be in regular contact with the participant as the event permits.

7.6 Safety Monitoring

A data safety monitoring board (DSMB) will be created to review the accruing data quarterly to:

1) Ensure that the study is adequately enrolling
2) Ensure data acquisition and protocol adherence rates are acceptable
3) Ensure that there are no serious safety concerns.

The DSMB will be assigned by NCCIH in coordination with the DCC. SAEs will be brought to the attention of the IRB and the DSMB in writing. As part of the Data Safety and Monitoring Plan (DSMP) we will perform continuous and interim analysis of accruing safety data. We have defined potentially treatment related SAEs (SAEs) that will be monitored throughout the course of the study.

The following guidelines will be used when considering halting the trial for safety: 1) > 5% of participants experience an unexpected, related, moderate or greater adverse event; 2) ≥2% SAE overall that are unexpected and related to the intervention. The DSMB will consider this guidance when making recommendations regarding trial continuation.

8. INTERVENTION DISCONTINUATION

Criteria for Discontinuation

Participants will be discontinued from their assigned intervention if the study interventions become contraindicated, for example:

- A serious adverse event related to treatment occurs and thus makes it unsafe to continue with the assigned intervention.
- The participant has a specific cause of back pain and was erroneously diagnosed during screening.
- New evidence emerges and suggests it is unsafe for the participant to proceed with the intervention.

Due to the pragmatic nature of this study, interventions can be modified to accommodate patients and their needs (e.g., mobilization can be used in lieu of manipulation, or medication changes can be made in the medical care group to mitigate drug-induced side effects).

Criteria for discontinuation are met when the event is classified as serious and it is determined by the provider and/or the PI that it is unsafe to continue with the study intervention, or when a diagnosis for a specific cause of LBP is made.

Reasons for Discontinuation
All efforts will be taken to facilitate participant's completion of the study interventions. Potential reasons for early termination include:

- Participant develops a competing comorbid health condition that precludes adherence or makes it unsafe for them to proceed with their assigned treatment.
- A change in the participant's life (e.g., participant moves, dies, has other personal matters to attend).
- Participant chooses to discontinue on their own for any reason (e.g., participant is not responding to care or getting worse).
- Study closure by institute or oversight body.

With their permission, participants will continue to be followed if the study intervention is discontinued. Participants who have discontinued treatment will be asked to complete weekly and monthly self-report questionnaires (months 1-12), if possible. Efforts will be made to accommodate participant compliance (e.g., paper or electronic questionnaires, or data can be collected by phone).

If participants are unwilling to complete the entire self-report questionnaires during the follow-up phase, they will be asked to complete the primary outcome measures (e.g., pain intensity and frequency, low back disability) on a monthly basis. This can be further modified to include, at a minimum, measures at 2, 6 and 12 months.

Temporary Discontinuation of the Intervention
Potential reasons for temporary intervention discontinuation include:

- An acute health problem arises and prohibits their ability to attend the intervention (e.g., hospitalization). The length of discontinuation will be addressed on a case-by-case basis. All attempts will be made to minimize this discontinuation.
- Participant has a scheduled vacation. Participants will be asked to limit their vacation time to 1 week.

9. STATISTICAL CONSIDERATIONS

Modifications to Statistical Analysis Plan Regarding the Sample Size and Power
(edited February 2023)

In consultation with NCCIH program staff and the DSMB in December 2022 we have modified the target enrollment to n=1000 participants (reduced from original n=1180). Our rationale for the modification is based on alignment with our updated primary outcome on chronicity. We have conducted extensive evaluation of power to detect meaningful effects using the LBP-Impact measure and our other primary outcomes. We have determined that it is appropriate to reduce the target sample size.

Modifications to Statistical Analysis Plan Regarding Primary Analysis and Treatment of Multiple Comparisons

(edited September 2022)

The trial initially had three main effectiveness objectives: (1) prevention of chronic LBP at twelve months; (2) recovery from acute/sub-acute LBP at six months; (3) Average of pain and disability over twelve months. In 2021, the NIH statistician overseeing the trial raised the question of the adequacy of the planned adjustment for multiplicity given the trial's three main effectiveness objectives and accompanying four primary outcome measures. In response to this concern, the lead investigators recommended the recovery objective be changed to a key secondary outcome. Early in the conduct of the trial it was decided and approved as a protocol change to include patients that had an acute aggravation of ongoing LBP, if the ongoing pain was not rated as severe in the month prior to the aggravation. This protocol change substantially lowers the proportion of patients that can be expected to recover according to our criteria (pain severity = 0 and RMD score ≤ 2). Given this change, the recovery outcome was less appropriate as a primary effectiveness objective and demoting it to a secondary outcome mitigates the concern of cross-objective control.

In consultation with NCCIH program staff and the DSMB in 2022 we have outlined our planned publications for presenting our main results and have revised the primary statistical test that would be used to evaluate differences in mean outcomes across the treatment groups. Specifically, rather than conduct individual tests of SMT alone, SSM alone, and the combination against medical care with adoption of a multiple comparisons correction for three tests we will now use an overall test of equality across the four groups to conduct a single omnibus hypothesis test followed by the estimation of key group comparisons using Fishers least significant difference methods to construct individual nominal 95% confidence intervals with reporting of the induced simultaneous coverage. These methods will be used for primary analysis of the 3 primary effectiveness outcomes : LBP-Impact and pain and disability.

We plan to present principal findings in two key publications. The first publication would focus on average pain and disability over 1-year as the multiple primary outcomes and present recovery at 6-months (previously a primary outcome) as one of the secondary outcomes. A second paper will focus on LBP Impact averaged over months 10-12 as the primary outcome .

Modifications to Statistical Analysis Plan Regarding Primary Outcome
(edited July 2021)

In consultation with the NCCIH program staff and DSMB in the Spring of 2021 we have changed our primary outcome for assessment of treatment impacts on chronicity prevention. Specifically, we have replaced our original NIH Task Force on Research Standards for Chronic LBP (referred to as RTF) dichotomous chronicity measure with the RTF quantitative impact measure. The LBP-Impact outcome measure is a subset of the Promise 29 measures, **which is already being collected at baseline and every month during the follow-up year from the start of the trial**. As a secondary outcome measure, we will compare differences across treatment groups in the distribution of patients with mild, moderate, and severe impact.

Modifications to Statistical Analysis Plan in Response to COVID-19 Impacts
(edited August 2020)

In Spring 2020 we suspended new enrollment into our study due to the COVID-19 pandemic. We continue to follow our participants and to maintain high-quality data collection. In order to resume trial enrollment, we are making adjustments to both care delivery and research data collection, and we have a modification to the enrollment and randomization that is responsive to risk mitigation. The key design and analysis modifications include:

- We will initially restart with restricted randomization to the MC and SSM groups. We will resume full factorial randomization once it is safe and appropriate. Specifically, in order to restrict physical interaction, we will conduct both remote assessment and intervention in a partial randomization period during which participants are randomized only to Medical Care (MC) or Supported Self-Management (SSM). Although we hope that partial randomization will only occur for the Fall of 2020, we recognize the need to be flexible by being able to consider reverting to restricted partial randomization during any future periods when physical contact is precluded. Since all possible randomization groups contribute to the ultimate effect estimates, the partial randomization period data is informative and can be combined with the pre-COVID data and the full factorial randomization data. In order to account for potential period-effects, we will modify all analyses to include adjustment for partial randomization time periods.
- Our statistical analysis will now adjust for study period (PERIOD) which is appropriate to account for our initial trial phase (UG3 and UH3 before March 2020), our restricted randomization phase, and resumption of full factorial randomization.
- Although we will ultimately have more subjects enrolled into the UMC and SSM groups due to restricted randomization we will not change our parameter of interest which is defined as the linear contrast capturing the equally weighted average of the SSM intervention effect combined from no-SMT and SMT strata, and similarly the equally weighted average of the SMT intervention effect combined from the no-SSM and SMM strata. (please see below for details)
- We have evaluated the impact on the power of our study subject to the potential for up to 240 subjects enrolled during restricted randomization. In our original protocol we focused sample size on obtaining adequate power for the Aim 1 chronicity endpoint assuming treatment relative risks of 0.70 (a 30% relative reduction), no interaction between treatments, and a control rate of 0.20. For this original scenario we used simulations to compute a power of 81% for either the overall SSM effect or the overall SMT effect. With partial randomization and an upper bound of n=240 subjects allocated during this period we obtain 78% power to detect an overall SSM effect and 77% power to detect an overall SMT effect. Therefore, the impact of altering the design to permit partial randomization is anticipated to have a minor reduction in power for our binary endpoints. In addition, the planned design will result in a minimum of n=30 per protocol pre-COVID subjects in the SMT and SSM+SMT groups combined with a full factorial randomization allocation of n=188 will permit a total of n=30+188=218 subject per group to evaluate mean differences in pain and disability scales across the four treatment groups. For MC and SSM groups we expect to have an upper bound of n=45 pre-COVID, n=120 partial randomization, and n=188 full factorial randomization subjects or n=45+120+188=354 total subjects per group. Our original balanced allocation would have produced n=1180/4= 295 subjects/group.

Statistical Analysis Plan

Introduction: A factorial trial is ideal when the two treatments under study are thought to act independently via different mechanisms .[146] Our interventions focus on a physical treatment approach (SMT) and a psychological intervention (SSM) for addressing acute LBP. A factorial design allows an efficient evaluation of each of these modalities using fewer subjects than would be required by separate trials. In addition, a crucial advantage of a factorial trial is the ability to evaluate whether the beneficial effects of each treatment modality combine in an additive, antagonistic, or synergistic fashion through evaluation of treatment interaction.[147]

The trial was originally powered to detect meaningful differences in two dichotomous primary outcome measures, chronicity and recovery. These two outcomes are now secondary effectiveness measures.

Figure 9.1: The 2x2 factorial design (n=1000)

	SMT Intervention	**No SMT Intervention**
SSM Intervention	SMT + SSM Group **A**	SSM only Group **B**
No SSM Intervention	Group **C** SMT only	Group **D** Usual Medical Care

For the 3 quantitative primary outcomes collected longitudinally, RMDQ, Pain NRS and LBP-Impact we will conduct detailed analysis of the four groups formed by the factorial design since we have excellent power for such endpoints with our revised sample size of 1000 subjects. However, McAlister et al.[146] comment that "the most powerful analysis of a factorial trial is performed at the margins" and we adopt such an approach for our secondary binary chronicity and recovery outcomes. We explicitly define the separate treatment effects for SMT and SSM as the overall or average treatment effect that is obtained from pooling comparisons over strata defined by the other treatment approach (i.e., the SMT treatment effect obtained by pooling over strata with and without SSM). In particular, we define the parameter of interest as a linear combination (contrast) of parameters from an appropriate regression model that acknowledges the potential for SMT and SSM interaction. Therefore, our proposed analyses for binary outcomes do not make any additive assumptions and is quite generally valid for creating meaningful overall effect summaries. Furthermore, by collecting detailed outcomes and health care utilization through one year we can conduct thorough mediation analyses and careful evaluation of concomitant treatment.

Our statistical analysis plan focuses on the effectiveness evaluation detailed under the Primary Objective in the protocol, We also provide a plan for mixed methods analyses (qualitative/quantitative) associated with the Secondary Objective: implementation.

Primary Effectiveness Outcome # 1: prevention of cLBP that is impactful at 10-12 months follow-up (LBP Impact scale (min 8 - max 50) using mean from months 10-12). The LBP impact scale includes measures of pain intensity, pain interference, and physical function from the PROMIS-29 Profile v2.0) we will determine the effectiveness of SMT, SSM, and the combination of SMT+SSM relative to medical care (MC)

LBP Impact Effectiveness Hypothesis: SMT alone will decrease the impact of low back pain with at least a moderate effect size of 0.3 standard deviations (Cohen's d). Similarly, SSM alone will decrease the impact of low back pain with at least a moderate effect size of 0.3 standard deviations. The combination SMT+SSM will lead to a stronger but not necessarily additive net reduction compared to the individual component interventions.

Design: As shown in Figure 9.1, we plan to enroll a total of 1000 subjects randomized to one of four treatment groups using a factorial design: medical care (MC); spinal manipulation therapy alone (SMT); supported self-management alone (SSM); and combined SMT+SSM.

LBP Impact Primary Analysis: Our primary analysis will compare each of the treatment groups to MC using an adjusted regression analysis. Specifically, Let Y_{ij} denote the primary outcome variable (average of LBP-Impact over months 10-12) for subject i in site j, and let *Site(2)* be an indicator variable used to code the two recruitment sites. All analyses will adjust for site and the baseline risk status represented by *RiskGroup* (0=medium risk; 1=high risk). In order to code the treatment groups we use the variables *SMT-Only* (0=no; 1=only spinal manipulation therapy), *SSM-Only* (0=no; 1=only supported self-management), and SMT-and-SSM (0=no, 1=both SMT and SSM). Given interruption by COVID-19 and an associated period of restricted randomization we will also adjust for this modified randomization using the variables *Period(k)* which will be an indicator for: 1=UG3 and UH3 through March 2020; 2=calendar period of restricted randomization; and 3=calendar period of resumed full factorial randomization. We will use an adjusted linear regression model with robust standard error to make inference regarding treatment groups using the following structure where X_{ij} denotes the covariates for subject i:

$$E(Y_{ij} \mid X_{ij}) = \beta_0 + \beta_1 \cdot Site(2)_j + \beta_2 \cdot RiskGroup_{ij} + \beta_3 \cdot SMT\text{-}Only_{ij} + \beta_4 \cdot SSM\text{-}Only_{ij} + \beta_5 \cdot SMT\text{-}and\text{-}SSM_{ij} + \beta_6 \cdot Period(2)_{ij} + \beta_7 \cdot Period(3)_{ij}$$

In the primary regression model the parameters of interest are:

β_3 = adjusted mean difference comparing SMT Only to UMC;
β_4 = adjusted mean difference comparing SSM Only to UMC;
β_5 = adjusted mean difference comparing combined SMT and SSM to UMC.

Our primary analysis will test the global hypothesis that these three treatment comparisons are all null using a multivariate Wald test with 3 degrees of freedom and alpha=0.05. We will then provide individual confidence intervals for each coefficient that compares an intervention group to medical care based on Fishers least significant difference methods which provide individual nominal 95% confidence intervals and also estimates the simultaneous coverage probability.

Power and Sample Size for Primary Outcome of LBP Impact: To characterize the power of our primary analysis (an overall F-test) we provide a summary table that considers potential standardized mean differences comparing the individual intervention arms to medical care. For a small effect size (Cohen's d of 0.2) and an additive effect we have greater than 90% power to reject the null. However, additivity may not hold so we also consider sub-additive scenarios, and the scenario where only one intervention is effective. For small to moderate effect sizes (0.2 – 0.3 standard deviations) we have >90% with our proposed design. We assume n=1000 enrolled with a realistic 90% follow-up that yields 900 evaluated subjects. We also account for the

imbalanced design due to restricted randomization that will yield approximately 300 subjects in the UMC and SSM alone groups and 200 subjects in each of the SMT and SMT+SSM groups. Power is calculated based on 5,000 simulation replications for each scenario and presented in Table 9.1.

The current design is robust to the enrollment target and follow-up assumptions. For example, with an enrollment of n=1000 subjects and 85% follow-up we would have 90% power for our expected alternative scenario with small treatment effects (0.30 standardized mean difference) that are not additive (sub-additive 1).

A secondary evaluation will consider whether the separate effects of SMT and SSM are potentially additive and this will be done using a formal test for interaction:

Interaction Model: $$E(Y_{ij} \mid X_{ij}) = \beta_0 + \beta_1 \cdot Site(2)_j + \beta_2 \cdot RiskGroup_{ij} + \beta_3 \cdot SMT_{ij} + \beta_4 \cdot SSM_{ij} + \beta_5 \cdot SMT_{ij} \cdot SSM_{ij} + \beta_6 \cdot Period(2)_{ij} + \beta_7 \cdot Period(3)_{ij}$$

Table 9.1: Chronicity based on LBP-Impact averaged over months 10-12 of follow-up. Power for the overall F-test of equality of means under various alternative scenarios. (alpha = 0.05)

Alternative	SMT Alone	SSM Alone	SMT + SSM	Power
Additive	0.20	0.20	0.40	**93%**
Sub-Additive 1	0.25	0.25	0.35	**91%**
Sub-Additive 2	0.30	0.30	0.30	**94%**
Sub-Additive 3	0.25	0.25	0.25	**81%**
Single effect 1a	0	0.30	0.30	**98%**
Single effect 1b	0.30	0	0.30	**94%**
Single effect 2a	0	0.25	0.25	**91%**
Single effect 2b	0.25	0	0.25	**80%**

In this model a test of H0: β5=0 allows us to determine if there is strong evidence for synergistic or antagonistic effects associated with combined treatment.

Secondary Effectiveness Outcome of Chronicity: Chronic back pain: For a subject to be classified as a chronic back pain patient at the 1-year assessment they must endorse having "a back pain problem that has persisted at least 3 months and has resulted in pain on at least half of the days in the past 6 months". This outcome is based on specific items from the NIH Research Task Force recommended minimal data set:[73] Question 1 on LBP duration; and Question 2 on the proportion of days that LBP has been a problem in the past 6 months. To evaluate chronic back pain we will consider the 1-year status as a key secondary outcome for chronicity prevention, and will use the 6-month status as another key secondary outcome.

Chronicity Hypothesis: SMT alone will decrease the rate of cLBP by 6-9% from a baseline MC level anticipated to be 20% or higher. Similarly, SSM alone will decrease the rate of cLBP by 6-9%, and the combination of SMT+SSM will lead to an additive net reduction.

Secondary Chronicity outcome Analysis: The analysis of the secondary binary outcome will use parallel marginalized tests of the average SMT treatment effect and the average SSM treatment

effect using linear contrasts from a logistic regression model. Specifically, we will use two separate Wald tests based on logistic regression, with stratification by recruitment site and baseline risk group (medium, high). Let Y_{ij} denote the primary outcome status (0=not chronic; 1=chronic) for subject i in site j, and let *Site(2)* be an indicator variable used to code the two recruitment sites. All analyses will adjust for site and the baseline risk status represented by RiskGroup (0=medium risk; 1=high risk). In order to code the treatment groups we use the variables *SMT* (0=no; 1=spinal manipulation therapy), and *SSM* (0=no; 1=supported self-management). Given interruption by COVID-19 and period of restricted randomization we will adjust for this using the variables *Period(k)* which will be an indicator for: 1=UG3 and UH3 through March 2020; 2=calendar period of restricted randomization; and 3=calendar period of resumed full factorial randomization. Regression models for the outcome are used to structure the probability of chronic back pain as follows:

Additive Model

$$logit[\ P(Y_{ij}=1 \mid X_{ij})\ ] = \beta_0 + \beta_1 \cdot Site(2)_j + \beta_2 \cdot RiskGroup_{ij} + \beta_3 \cdot SMT_{ij} + \beta_4 \cdot SSM_{ij} + \beta_5 \cdot Period(2)_{ij} + \beta_6 \cdot Period(3)_{ij}$$

Full Model

$$logit[\ P(Yij=1)\ ] = \beta_0 + \beta_1 \cdot Site(2)_j + \beta_2 \cdot RiskGroup_{ij} + \beta_3 \cdot SMT_{ij} + \beta_4 \cdot SSM_{ij} + \beta_5 \cdot SSM_{ij} \cdot SMT_{ij} + \beta_6 \cdot Period(2)_{ij} + \beta_7 \cdot Period(3)_{ij}$$

Our original application proposed using an additive model to generate a single summary parameter that describes the SMT effect (β3) and the independent SSM effect (β4). However, the additive model uses an assumption that the effect of one intervention is independent of whether the other intervention is delivered. Such an assumption is not necessary, and a full model can be used to make inference on a single linear contrast for each treatment that represents an average treatment effect.

The "Full Model" can then be used to derive an overall or average effect of SMT, and an overall or average effect of SSM. Specifically, focusing on the effect of SMT the model yields:

SMT effect when SSM=0:	β3
SMT effect when SSM=1:	β3 + β5
Average SMT effect:	½ β3 + ½ (β3 + β5) = β3 + ½ β5

Our original analysis plan used an additive regression model that did not include the interaction term in order to generate a model-based average effect of SMT. By using the full model, we are not making any assumption of constancy of SMT effect across the two strata defined by SSM, and are directly calculating the average of the two treatment effects as the linear contrast that will be used to summarize the overall effect of SMT. The model can similarly be used to derive a linear contrast the represents the average SSM effect:

SSM effect when SMT=0:	β4
SSM effect when SMT=1:	β4 + β5
Average SSM effect:	½ β4 + ½ (β4 + β5) = β4 + ½ β5

The overall SMT summary (β3 + ½ β5) estimates a common or average effect of SMT by pooling across sites, across risk groups, and across the two SSM arms (see figure 9.2). Similarly, β4 + ½ β5 estimates a common or average effect of SSM by pooling over the site, risk group, and SMT strata. Such analysis leverages the factorial design to permit separate estimates for each component of intervention. Notice that an additive model would use only 2 coefficient parameters to code the four treatment groups by assuming that the combined SMT+SSM group will have a treatment effect that is the sum of the effect for each individual component. Our analysis does not make any additive assumptions but rather directly defines a summary contrast for each treatment modality as the parameter of interest. Factorial designs are particularly efficient when evaluating two treatment modalities that work in complementary domains such as SMT (physical) and SSM (psychological) and permit separate assessment of each intervention. Formally, our primary analysis will separately test the null hypothesis H0: (β3 + ½ β5) = 0 denoting no average effect of SMT, and H0:(β4 + ½ β5) = 0 denoting no average effect of SSM. Each primary test will use a significance level of 0.05 without correction since each test evaluates a separate intervention. Finally, evaluation of the interaction term using $SMT_{ij} \cdot SSM_{ij}$ *permits a formal evaluation for non-additivity by testing the interaction* coefficient H0: β5=0 (interaction model described below).

Power and Sample Size for Secondary Outcome of Chronicity: In order to determine the necessary sample size for effectiveness evaluation we need to formulate assumptions for the binary secondary outcome rate in the treated and untreated groups. Chou and Shekelle[34] review six studies conducted in primary care that focused on pain, functional status, or mixed outcomes. Using results from this paper we conservatively assume a rate of cLBP of 20% at 1 year. In order to formulate appropriate effect estimates we consider detection of a relative risk of RR=0.70 for each of SMT and SSM individually implying a reduction of the rate from 20% to 14% for these intervention groups. Based on the Cochrane Back Review Group[148] a relative risk of 0.70 is a clinically relevant and medium in size intervention effect, while the assumption of additive effects on the probability scale would lead to a cLBP rate of 8% among those randomized to SMT+SSM, which is considered a "large" treatment effect (RR=0.40). Therefore, we seek to design our study to detect and medium sized treatment effects, and consider power under a collection of plausible scenarios. A recent cohort study of acute LBP patients in primary care reported a similar proportion of patients with cLBP at 2 years, but noted the estimate varied based on the case definition[149] and estimates based on the NIH RTF definition are not yet available. Relative to general LBP patients, we expect a rate of chronicity in the MC group to be larger since we are enrolling subjects at an increased risk of chronicity. Accordingly, we increased the estimated proportion with cLBP in the MC group to be 30 and 40% and determined the magnitude of treatment effects for which we have ≥ 80% power. At 1 year, we assume that we will have at least 88% follow-up based on prior studies conducted at the clinical research sites and studies[11 150] with similar incentives[151]. Thus, with n=1000 enrolled subjects we expect at least n=880 total subjects available for primary analysis.

Our original sample size was chosen as n=1180 (since modified to n=1000) to ensure 80% power assuming an additive model with a chronic rate of 20% in UMC and a medium relative risk (RR) of 0.70. To evaluate power we conducted simulations using the R statistical package. We generated data under various additive assumptions. For analysis we first considered a single

likelihood ratio test of one treatment modality (either SMT or SSM). For simulations we considered crude analysis while our formal analysis will additionally adjust for site and baseline risk and therefore improve power since these are variables that only predict outcome and are not related to treatment group. For each scenario we simulated 5,000 data sets and empirically calculated power as the percentage of replicates in which the null hypothesis was rejected.

Using simulations with n=1000 subjects, 90% follow-up, and accounting for our imbalanced allocation due to COVID interruption we compute power for analyses that consider individual marginal treatment effects for both SMT and SSM. If we assume a UMC chronicity rate of 20% and a relative risk of 0.65 (rate under treatment = 20% * 0.65 = 13%, or an absolute risk reduction of 7%) then we have >85% power to detect average SSM or SMT effects. If we a smaller effect corresponding to a relative risk of 0.70 (rate under treatment = 20% * 0.70 = 13%, or an absolute risk reduction of 7%) then we have approximately 70% power to detect average SSM or SMT effects of this magnitude (specifically accounting for imbalance power is 72% for SSM and 70% for SMT). Power is greater for any relative risk when the UMC rate is increased to 30% or 40%. These relative risk effect sizes equate to medium effect sizes and are considered clinically important by Cochrane's Back Review Group.[148] We have not powered the study to detect interaction for the binary chronicity endpoint, but rather have powered the study to detect interaction on the underlying function and disability scales (see below).

Furthermore, we have excellent power to detect interaction effects where the effect of SMT and SSM may be synergistic or antagonistic, and using alpha=0.05 we have >80% to detect a X-point difference in LBP Impact treatment effects of one modality across the strata defined by the other treatment modality.

Secondary Effectiveness Outcome of Recovery: Determine the effectiveness of SMT, SSM, and the combination of SMT+SSM relative to medical care (UMC) in promoting recovery from acute or subacute LBP at 6 months.

In 2021, the NIH statistician overseeing the trial raised the question of the adequacy of the planned adjustment for multiplicity given the trial's three main effectiveness objectives and accompanying four co-primary outcome measures. In response to this concern, the lead investigators recommended the recovery objective be changed to a key secondary outcome. Early in the conduct of the trial it was decided and approved as a protocol change to include patients that had an acute aggravation of ongoing LBP, if the ongoing pain was not rated as severe in the month prior to the aggravation. This protocol change substantially lowers the proportion of patients that can be expected to recover according to our criteria (pain severity = 0 and RMD score $\leq$ 2). Given this change, the recovery outcome was less appropriate as a primary effectiveness objective and demoting it to a secondary outcome mitigates the concern of cross-objective multiplicity control.

In 2022 NCCIH and the DSMB approved that the recovery effectiveness objective, formally one of the 3 primary effectiveness objectives, will be designated as a key secondary outcome.

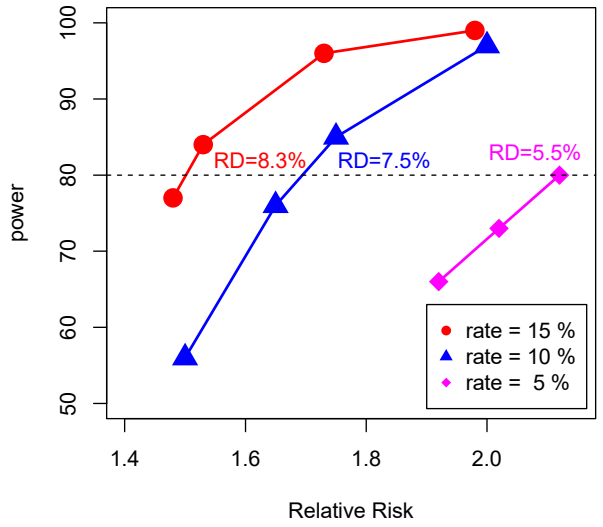
Recovery Effectiveness Hypothesis: SMT alone will increase the rate of recovery by 5.5-7.5% or more from a baseline MC rate of 5%-15%. Similarly, SSM alone will increase the rate of recovery from 5.5-7.5%, and the combination of SMT+SSM will lead to an additive net increase in the recovery rate.

Recovery outcome definition: For a patient to be classified as recovered at the 6 month or 1 year assessment they must endorse both an NRS of 0, and an RMDQ of <= 2.[152] To evaluate recovery we will consider the 6-month status first and use the 1-year status second.

Recovery Analysis: The primary analysis will be two parallel tests of the average effects of SMT and SSM in a full logistic regression model for the primary outcome (recovery at 6 months). The primary analysis for recovery will use pre-specified linear contrasts for hypothesis testing regarding overall or average effects.

Power and Sample Size for the Recovery Outcome: In order to determine the necessary sample size for effectiveness evaluation we need to formulate assumptions for the primary outcome rate in the treatment and control groups. Bronfort et al.[11] compared SMT plus Home Exercise with Advice (HEA) to HEA alone among subacute and chronic patients and find complete recovery from leg pain in 20% of SMT+HEA versus 5% of HEA at 12 weeks, and 23% versus 12.5% respectively at one year (RR=1.84) providing evidence that relative risks in the range of 1.5-2.0 are plausible. The recovery rate at 6 months was estimated based on studies by Kamper et al.[152] and members of our investigative team,[153] which used the same strict definition for recovery. Kamper et al.[152] summarize recovery rates and criteria based on both NRS and RMDQ from four studies with acute and subacute subjects. Recovery rates range from 7% to 12%. A recent study by George et al.[153] reported a 5% recovery rate within a mixed population of sub-acute and chronic patients with increased risk for cLBP. Given the potential uncertainty in the recovery rate for the MC group, we varied the expected recovery rate from 5-15% and determined the magnitude of treatment effects for which we have ≥80% power.

Figure 9.2: Power of a single marginal treatment effect test as a function of relative risk (assumed equal for SMT and SSM), and recovery rate with UMC.



For simulations we considered crude analysis while our formal analysis will additionally adjust for site and baseline risk yielding improved power since these are variables that only predict outcome and are not related to treatment group. For each scenario we simulated 5,000 data sets and empirically calculated power as the percentage of replicates in which the null hypothesis was rejected.

Figure 9.2 shows the power to test each intervention marginally. We see that we have >80% power to detect a relative risk of 1.75 associated with either SMT or SSM if the UMC recovery rate is 10%. If the UMC recovery rate is 5% then we have power to detect a 5.5% risk difference (RR=2.1), while if the UMC recovery rate is 15% then we have power to detect an 8.3% risk difference (RR=1.55). These effects are also medium in size and considered clinically important by Cochrane's Back Review Group.[148]

Primary Effectiveness Outcome # 2 and 3: Determine the effectiveness of SMT, SSM, and the combination of SMT+SSM relative to medical care (MC) in achieving improvements in average pain intensity and back-specific functioning cumulative through 1 year based on monthly measures of RMDQ and weekly Pain NRS scores.

Effectiveness Hypothesis: We will focus on parallel analyses for pain and function. We hypothesize that SMT alone will decrease average pain by at least 1 point, and average disability by 2 points. Similarly, SSM alone will decrease average pain by at least 1 point, and average disability by 2 points, and the combination of SMT+SSM will lead to an sub-additive net decrease of <2 points and <4 points respectively.

Primary outcome variables: We will derive measure of disability and pain by calculating the time-averaged patient outcome using the monthly measurements taken over the year of follow-up.

Primary Analysis: For quantitative outcomes we will focus on analyses that generally do not assume that the effects of SMT and SSM are additive since we have adequate power to evaluate specific group contrasts. We will use linear regression methods with robust standard errors to test for the difference in mean scores comparing each intervention group to MC. Let Y_{ij} denote the outcome of interest (either average pain or average disability for parallel analyses). Similar to our primary analysis of LBP impact 1 we will use a linear regression model with robust standard errors using the structure:

$$\textit{Four Groups Model: } E(Y_{ij} \mid X_{ij}) = \beta_0 + \beta_1 \cdot \textit{Site(2)}_j + \beta_2 \cdot \textit{RiskGroup}_{ij} + \beta_3 \cdot \textit{SMT-Only}_{ij} + \beta_4 \cdot \textit{SSM-Only}_{ij} + \beta_5 \cdot \textit{SMT-and-SSM}_{ij} + \beta_6 \cdot \textit{Period(2)}_{ij} + \beta_7 \cdot \textit{Period(3)}_{ij}$$

In the primary regression model the parameters of interest are:

β_3 = adjusted mean difference comparing SMT Only to UMC;
β_4 = adjusted mean difference comparing SMT Only to UMC;
β_5 = adjusted mean difference comparing combined SMT and SSM to UMC.

This model considers each treatment group separately using an indicator of SMT only (*SMT-Only*), an indicator of SSM only (*SSM-Only*), and an indicator of combined therapy with both SMT and SSM (*SMT-and-SSM*). We will also add the baseline outcome as a covariate to perform a variation of ANCOVA for repeated measures.

Table 9.2: Power for the overall F-test of equality of means under various alternative scenarios.
Average pain intensity & disability over 12 months post-randomization (alpha = 0.05/2)

Alternative	SMT Alone	SSM Alone	SMT + SSM	Power
Additive	0.20	0.20	0.40	**88%**
Sub-Additive 1	0.25	0.25	0.35	**85%**
Sub-Additive 2	0.30	0.30	0.30	**89%**
Sub-Additive 3	0.25	0.25	0.25	74%
Single effect 1a	0	0.30	0.30	**96%**
Single effect 1b	0.30	0	0.30	**88%**
Single effect 2a	0	0.25	0.25	**83%**
Single effect 2b	0.25	0	0.25	71%

Our primary analysis will test the global hypothesis that these three treatment comparisons are all null using a multivariate Wald test with 3 degrees of freedom and alpha=0.05/2 to account for the pair of primary outcomes (pain and disability). We will then provide individual confidence intervals for each coefficient that compares an intervention group to medical care based on Fishers least significant difference methods which provide individual nominal 95% confidence intervals and also estimates the simultaneous coverage probability.

A secondary evaluation will consider whether the separate effects of SMT and SSM are potentially additive, and this will be done using a formal test for interaction:

$$\textit{Interaction Model:} \quad E(Y_{ij} \mid X_{ij}) = \beta_0 + \beta_1 \cdot Site(2)_j + \beta_2 \cdot RiskGroup_{ij} + \beta_3 \cdot SMT_{ij} + \beta_4 \cdot SSM_{ij} + \beta_5 \cdot SMT_{ij} \cdot SSM_{ij} + \beta_6 \cdot Period(2)_{ij} + \beta_7 \cdot Period(3)_{ij}$$

In this model a test of H0: β5=0 allows us to determine if there is strong evidence for synergistic or antagonistic effects associated with combined treatment. Given that we evaluate interaction for both disability and pain we will use a Bonferroni corrected alpha of 0.05/2.

Power and Sample Size for primary effectiveness outcomes # 2 and # 3: See Table 9.2. We will conduct longitudinal analysis of the underlying RMDQ and Pain NRS scores. Specifically, we will conduct analyses using the mean area under the curve for both disability and pain and use linear regression to evaluate treatment effects on the native underlying scales. With n=1000 subjects evaluated through one year and using alpha=0.05/2 for the two outcomes and an overall F-test we have >80% power across a range of scenarios presented in the table below. To orient standardized effects a marginal 2-point mean difference on RMDQ for any treatment modality compared to UMC assuming a standard deviation of 6.5 or less,[149 153] corresponds to a Cohen's D of 2.0/6.5 = 0.31, and >80% power to detect a marginal 1-point difference on Pain NRS assuming a standard deviation of 3.0 or less corresponds to a standardized effect of 0.33.[149 153] Note that our outcome is the area under the curve through 12 months, which is a patient-level weighted average, and the standard deviation (SD) for this outcome will be less than the SD for a single measurement. Our power calculations are conservative since we use the SD for a single measurement. Although we have <80% power if SMT and SSM have small marginal effects of 0.25 SD and no additional benefit when combined (sub-additive 3 below) this scenario leads to no single treatment arm yielding an effect of 2 points on RMDQ (0.31 SD) or 1 point on Pain NRS (0.33 SD) and therefore suggests our design is appropriate for important and plausible effect sizes and not overpowered for effects that may not be meaningful.

Furthermore, we have excellent power to detect interaction effects where the effect of SMT and SSM may be synergistic or antagonistic, and using alpha=0.05/2 we have >80% to detect a 2.7-point difference in disability or 1.3-point difference in pain treatment effects of one modality across the strata defined by the other treatment modality.

Secondary Analyses of the 3 primary effectiveness outcomes and other secondary outcomes: We will conduct a number of pre-specified secondary analyses.

Subgroup/Moderator Analyses: We will consider two pre-specified subgroup analyses to look at treatment effects within: subjects who are medium risk based on STarT Back, and subjects who are high risk; and subjects stratified based on their duration of LBP. Subgroup analyses will use logistic or linear regression among restricted subsets to quantify specific treatment effects, and formal evaluation of differences in treatment effects across subgroups will be conducted using treatment by subgroup interactions. In addition to the pre-specified subgroup analyses we will also conduct exploratory analyses to evaluate the heterogeneity of treatment effects according to Gender, Race, and Ethnicity.

Responder Analysis: We will focus on evaluation of a >50% improvement in pain or function from baseline to six months, and from baseline to one year. We will also consider a >30% improvement, and a comprehensive responder analysis that looks at the cumulative percentage of subject achieving a range of improvement percentages as described in Farrar, Dworkin, and Max.[76]

Secondary Outcomes: We will assess secondary outcomes including the PROMIS-29 measure, productivity loss, healthcare utilization (e.g., opioid use, injection, MRIs), and AEs for the combined group (SMT+SSM) and each intervention alone relative to MC. We will use linear or logistic regression and the Four Group model structure given above and will use linear mixed models or generalized estimating equations (GEE) for longitudinal analysis of secondary outcomes.[154]

Time-until-recovery: An important class of secondary analyses will consider the time-until-recovery based on measurements taken every 4 weeks during the year of follow-up. Specifically, we can define the time-until-recovery as the assessment month in which the subject is first observed to achieve an NRS=0 and RMDQ <= 2. We will use discrete time (monthly data) cumulative incidence curves to show the percent of subjects in each treatment group who have achieved a first recovery by each follow-up time period. We recognize that recovery may not be maintained, and subjects may subsequently relapse so we will also display plots showing the percent of subjects who are currently in the recovered state as a function of time. Formal comparison of cumulative incidence curves can be obtained using the log rank test since in this situation the cumulative incidence is simply 1-survival as would be computed using Kaplan-Meier curves. In addition, we will use a model-based survival analysis.

Cross-sectional outcomes at 2, 6, and 12 months: We will also conduct analysis of change in pain NRS, RMDQ, and STarT Back status from baseline. Satisfaction will also be analyzed at these

time points. This analysis will evaluate the magnitude of short, medium, and long-term effects of treatment, which are traditionally used in systematic reviews and meta-analyses.

Mediation Analysis for Psychosocial Factors: Formal mediation analysis [155-157] will focus on characterizing the degree to which self-efficacy, coping, kinesiophobia, and pain catastrophizing measured at 8 weeks can explain treatment effects at 6 months, and whether these measures obtained at 6 months explain long-term treatment effects (1 year). We will quantify the percent of the treatment effect that is explained by changes in each scale individually, and in totality when included in a multivariate model for the outcome.[158] We will analyze mediation for cLBP, recovery at six months and change in pain NRS and RMDQ measured at 6 months and 1 year.

Longitudinal analyses of patient trajectories for pain and disability: We will use the monthly measures of disability and weekly measures of pain to conduct longitudinal analysis that characterizes the mean profile over time for each intervention group. Formal comparison of profiles will be based on linear mixed models or GEE. Furthermore, we will conduct exploratory analyses that assume latent classes with associated trajectories, and we can evaluate whether these groups differ across the intervention arms.[159] We have recently used these methods for analysis of the BOLD back pain cohort.[160]

Longitudinal Analysis Adjusting for Concomitant/Subsequent Therapy: Our first analysis will be a descriptive summary of the types and frequency of additional treatments received throughout the study. The initial study intervention occurs within the first two months and outcomes are collected through one year. Therefore, there is potential for variation in the treatment received according to randomized group or non-study interventions during months 3-12. Intermediate treatment received is a post-randomization variable and potential intermediate outcome that will be considered in mediation analysis. In addition, we can use structural nested mean models (SNMMs) or marginal structural models [161 162] to adjust for time-varying confounding (treatment contamination) associated with intermediate treatment received. For example, if we consider longitudinal concomitant treatment a_k, measured at times k=1, 2, …, m, then using SNMM notation we can define the 1-year counterfactual outcome for subject i as Yi(Z, a1, a2, …, am) which represents the potential outcome associated with baseline treatment Z and time-varying concomitant treatments. We can use either SNMMs or MSMs to estimate population mean outcomes under controlled concomitant treatment paths such as the expected outcome with treatment Z and no additional longitudinal treatments: mean of Yi(Z, 0, 0, …, 0). For these longitudinal analyses we will use the monthly measured RMDQ and Pain NRS as the outcomes in parallel regression analyses. We have previously conducted critical evaluation of such methods for the analysis of surgical non-compliance.[163]

Impact of cLBP & recovery definitions: The robustness of NIH RTF case definition of cLBP will be assessed using measures of pain frequency and LBP-related burden (pain, disability, productivity loss, healthcare utilization) by assessing differences between subjects meeting the case definition and those who do not. We will also explore the clinical and demographic characteristics of subjects with high LBP-related burden who fail to meet the case definition for cLBP in addition to the characteristics of subjects with low LBP-related burden who meet the case definition for cLBP. We will also assess the impact of an alternative definition of recovery (e.g., NRS <2 and RMDQ <3) on treatment effects at 6 and 12 months.

Sample Size for Seconday Objective of Implementation: Qualitative data collection associated with Aim 2 will require a minimum of 22-30 participants from each of the patient, facility, and organizational levels; this is the approximate number to reach 'saturation', or the point where no new themes emerge.[164 165]

Analysis plan for Implementation: Qualitative and quantitative analyses will be performed for data collected regarding contextual information that will inform future implementation and results interpretation, as described in Section 6.2.6. Qualitative data will be analyzed using template style qualitative content analysis using NVivo qualitative software or similar. Data collection and analyses will be performed by clinical site investigators and designees experienced in analysis of qualitative data using methods applied previously.[166-169] All qualitative analyses will begin with the creation of a working codebook, developed by reviewing samples of texts to gain a general understanding of the data and establish preliminary codes.[164 165 168] Representative quotations will be identified during the coding process; coded themes will be grouped into larger thematic categories. Themes will then be quantified by categorizing them as present or absent for each case, and presented as frequencies.[164] The DCC will oversee the conduct of validity checks of 10% of the analyzed cases to ensure consistency with the codebook. Quantitative analyses will be performed by the DCC and will include descriptive statistics data collected as described in Section 6.2.6. Independent t-tests (for means) and z-tests (for proportions) will be used to assess group differences when appropriate.

General Missing Data Considerations:
Missing data may include missing covariate information, study dropout, or missed and/or mistimed participant visits. While the PACBACK protocol includes procedures to ensure the most "complete" follow-up data on every enrolled participant, it is likely that some participants will have incomplete data. We will determine reasons for missingness, classifying each missingness pattern as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). The MCAR mechanism occurs when the probability of response is independent of both the observed data and the unobserved data[170]. All protocols will include recommended sensitivity analyses that will help determine the extent of potential biases that could affect the results.

In longitudinal analyses, likelihood-based analyses of complete-case data for the linear mixed-effects model, the generalized linear mixed-effects model, and the nonlinear mixed-effects model lead to valid inference under MCAR and MAR mechanisms, whereas the GEE analyses lead to valid inference only in the presence of MCAR mechanisms.[170 171] Statistical tests to assess the validity of the MCAR assumption in certain circumstances are available, but they are model-dependent and non-robust.[172-174] In general, we will advocate the use of multiple imputation (MI)[175] both to assess the sensitivity of results and to correct for bias from missing covariates. We will consider the missing data mechanism, analysis approach, and plausibility of the congeniality assumption.[176 177] If MNAR data are suspected, there are three basic approaches to address this challenge, namely, (1) selection models[178-180], (2) pattern-mixture models[181 182] and (3) MI.[175 183] We recommend MI because it appears to be more robust. We can apply MI using weights dependent on the probability of dropout to assess the dependence of results on dropout.

We will also consider selection models with varying dropout parameters in sensitivity analyses.[183 184]

Potential Problems & Alternative Strategies:
Factorial Model Assumptions: We have assumed both an additive data-generating model with small effects and alternative sub-additive scenarios with moderate effects for the three primary effectiveness outcomes. However, for the secondary binary outcomes and we have assumed additivity to assess power for SMT and SSM treatment main effects. For these binary outcomes it is possible that there is an interaction that is either synergistic or antagonistic (sub-additive). In this situation our proposed analysis will estimate an average treatment effect rather than a common treatment effect. A synergistic interaction however would suggest that SMT + SSM produce greater effects together, than when used alone. Conversely, an antagonistic interaction would suggest that their effects are less than additive. Both scenarios would provide new and important information and advance what is known about these therapies and how they should be applied for acute and sub-acute LBP. Importantly, even if an interaction is observed, we have >80% power to detect the following differences between the combined group or either of the single interventions alone compared to medical care: For prevention of chronicity, we will be powered to detect a reduction of 9% (RR=0.55) at an event rate of 20% in the MC group, a reduction of 11% (RR=0.63) if the event rate is 30%, and a reduction of 12% (RR=0.7) if the event rate is 40%. For recovery, we will be powered to detect an increase of 7% (RR=2.4) at an event rate of 5% in the MC group, 9% (RR=1.9) if the event rate is 10%, and 10% (RR=1.67) if the event rate is 15%.

10. DATA COLLECTION AND QUALITY ASSURANCE

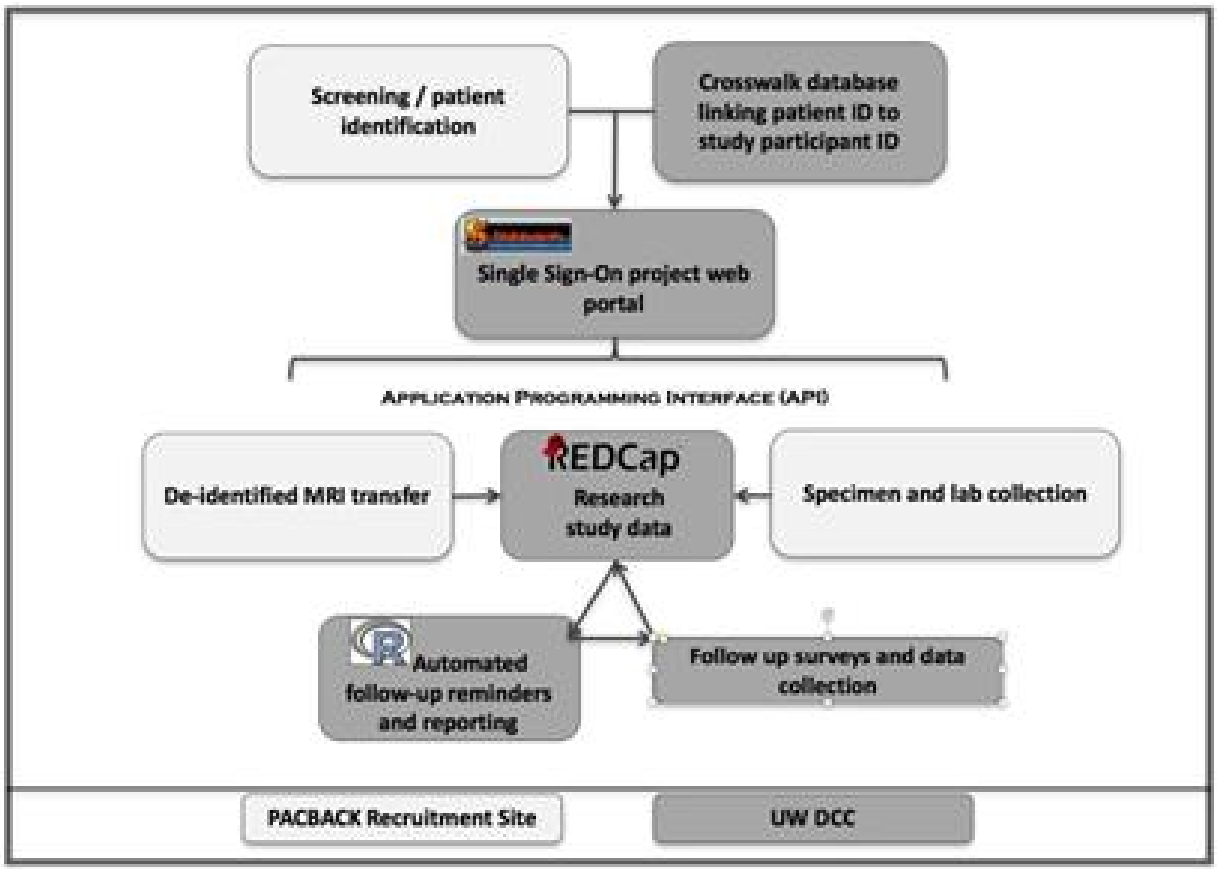
10.1 Data Collection Forms

Initial screening data will be directly entered by potential study participants via a web-based survey supplied by the DCC. Phone-based screening data and in-person/video-conference screening data obtained at the in-person/videoconference visit will be entered directly into the study portal by research staff at the sites to confirm study eligibility. For consented participants, protected health and contact information will be stored in a separate limited-access REDCap database and no research personnel will have data export rights in this database. Data collected as a part of the research study protocol database will be stored in a completely separate database, linked by study ID. A procedure/visit case report form will be filled out by research staff for every study-related visit and electronically entered directly into the web-based portal. Electronic web-based surveys will be sent to study participants on a monthly basis, with computer-assisted telephone interviewing or mailed surveys as a parsimoniously used back-up in cases where follow-up may be challenging. Printable CRFs will be made available for every study assessment.

10.2 Data Management

Data management in the LBP project will be almost exclusively web-based. The UWA DCC will support an https-secured web page (www.PACBACK.ORG) that provides a centralized location for public information about the project for potential subjects, investigators, and institutional agencies. The web page will contain a link to the project portal. Study personnel will log on to the private portal on the study web page with individual Shibboleth-based user names and passwords to securely perform study data management activities. Shibboleth is a standards-based, open source software package for web single

sign-on across or within organizational boundaries. An overview of the DCC responsibilities and data management system is presented below.



Study Integration: The UWA DCC team has extensive experience developing Application Programming Interfaces (APIs), which allow multiple software programs to seamlessly interact and communicate with one another in a simple and intuitive interface. The web portal API will serve as the wrapper for all data management tools and software utilized in the LBP project, including: study ID assignment, screening, centralized image storage (if needed), prospective data collection forms and surveys, and study operations reporting. Screening and eligibility will be determined centrally through the portal and all subjects screened under the LBP trial protocol will be assigned a sequentially generated study participant ID. The DCC will maintain an additional REDCap database to centrally and securely store identifiable patient information, separating patient contact information from research study data. For each REDCap database, the DCC will use distinct data access groups for clinical recruitment sites.

Electronic Data Capture: The UWA DCC supports its own installation of REDCap, which is software specifically designed for electronic data capture that we have used successfully in several multi-site clinical trials. REDCap features include differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes (http://www.project-redcap.org/software.php). REDCap will serve as the architectural backbone for all data captured prospectively in this study, with all data linked by study subject ID. The web-based data management portal allows for four participant contact methods: research coordinator data entry; electronic survey; computer-assisted telephone interviewing (CATI); or Short Message Service (SMS) text message. All survey modalities are customized to incorporate project logos and information to increase participant recognition and response rate. Furthermore, surveys may be

distributed on any time schedule (e.g., monthly for pain and disability), and in any designated survey format.

Access and Security: The DCC will invite each research staff member at the clinical recruitment sites to obtain a University of Washington NetID, which will be required to gain access to the secured study for screening, randomization, and data entry. Research staff will be grouped into data access groups whereby study participant data will be separated by site, as appropriate. The clinical recruitment sites are responsible for scheduling patient follow-up visits. REDCap databases are stored on a secure electronic server with username and passwords login for individual users and will be backed up nightly The REDCap servers are virtual machines (VMs) located on UW DCC hardware in a secure server room. Our server room meets the technical requirements for HIPAA compliance and hosts servers that do contain PHI. Storage for all study data is backed by (2) dedicated Network Appliance FAS2050 storage appliances. The filer provides highly fault tolerant storage using large RAID volumes, on-line hot-spare drives, and built-in, proprietary 'snapshot' file system technology that automatically creates hourly, daily, and weekly on-line backups of modified files.

10.3 Quality Assurance

10.3.1 Training

Training: Before any clinical recruitment site may begin recruitment for this study, the DCC will provide two training sessions on the data management system for all research staff. The first training session will be a GoToMeeting virtual tour of the data system conducted by the DCC protocol operations specialist; the second training is a GoToMeeting virtual training session where research staff are observed interacting with the system by a UWA DCC staff member and are required to demonstrate proficiency in key data management steps (screening, randomization, data entry, documentation of AEs, data management protocol compliance, etc.). As with most studies, there will likely be turnover in recruitment site personnel necessitating a process for ongoing training. The DCC will create data management system training videos that covers the material of the first training session. All new research staff will be required to view the suite of training videos and then complete a second virtual training session with the DCC protocol operations specialist prior to being given a log-in and access to the study portal.
Detailed communication about protocol and case report forms changes will come through the DCC through Basecamp (www.basecamp.com) notifications, a program used to facilitate project management and study-wide communication. The DCC will additionally develop a question-by-question (QxQ) document that outlines in detail the intent of each research staff-facing CRF question and response.

10.3.2 Quality Control Committee

Missing data reporting and other customized reports will be developed by the DCC in collaboration with the CCC and recruitment team in order to facilitate efficient work-flow and high-quality data capture. A subset of key personnel from the DCC and CCC will serve as an operations committee and review quality control reports on a weekly or biweekly basis, though quality control reports will be made available on a daily basis. CRF-specific follow-up rates will be tabulated on a nightly basis and reviewed during the weekly check-in meeting with each clinical recruitment site. Nightly, the DCC will generate graphs that monitor CRF-specific follow-up rates over time as well as data quality trigger rates over time to prospectively monitor potential issues that may develop gradually or acutely over time. A data query resolution dashboard will be available to each site on a continuous basis. In similar studies, we have found that establishing a fixed-day for a monthly review of all unresolved queries is an adequate balance of time to resolution and alert fatigue.

10.3.3 Metrics

For each monthly follow-up survey, we aim to achieve an 85% or higher follow-up rate. We will utilize a combination of web-based survey, telephone and text-based outreach, and mailed surveys to achieve maximal survey response – especially at the 6 and 12-month follow-up time points. Survey completion rates will be primarily based upon the completion of pain and functional outcome measures, but the DCC will additionally tabulate follow-up by each instrument to monitor and evaluate survey burden.

Loss to Follow-Up: Participants are considered loss to follow-up if a participant

1. Dies, or they
2. Missed 3 consecutive monthly surveys, and
3. Missed 4 consecutive weekly surveys (~ 1 consecutive month), and
4. 3 email/text auto or manual reminders and 3 phone calls result in no response from the participant

When criteria 2-4 are met, the DCC will stop (turn off) the weekly and monthly surveys with the exception of the 6 and 12 month surveys (primary outcome). Study staff will contact participants prior to request they provide data at these time points.

Participants' status may be adjusted if the participant contacts the study and begins participating in data collection activities.

10.3.4 Protocol Deviations

Study deviations and violations will be tracked prospectively at the participant-level on an ongoing basis in the study portal, and will be reviewed during the annual in-person site monitoring visit. During in-person monitoring visits, every study participant will be 100% monitored for the presence and absence of a priori defined protocol violations.

10.3.5 Monitoring

On the portal Reports page, missing data and data quality reports are provided by the DCC on a nightly basis and reviewed weekly by the DCC protocol operations specialist. Free text data collection from study participants will be minimized to the extent possible and field masking and automated out of range checks will be implemented where applicable.

For ongoing data querying and cleaning, the DCC will implement and utilize a query resolution dashboard where the protocol operations specialist will visually review 100% of all data entered in the previous week and provide documentation that each participant-CRF has been reviewed. On a nightly basis, the DCC will also generate a comprehensive data quality report to flag unusual data and will be made broadly available to the study team. The protocol operations specialist will flag any data that trigger a review through logic-based checks, visual checks, or intermittent missing data. Research staff at the recruitment sites will be asked to review each outstanding query and respond with "confirmed" or "corrected" and may provide a comment beside each query to note relevant details. Each query will be closed by the DCC protocol operations specialist.

During annual site monitoring visits to the clinical recruitment sites, the DCC will conduct 100% monitoring of in-person/videoconference screening data, informed consent documentation, and fidelity with the portal-assigned randomized treatment. In addition to the previously described study-wide data quality reports, the DCC will generate a compact report for each study participant enrolled in the study on

a nightly basis. This report will be made broadly available and will serve as the basis for in-person monitoring.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, the informed consent document, CRFs, and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study.

11.2 Informed Consent Forms

PIs or designees (research staff) will conduct the informed consent process.

Prior to the baseline appointment, participants will be given a copy of the consent form to review on their own, with ample time. The consent form will provide information regarding the study purpose and research design, procedures, potential risks and benefits, alternatives to participation, voluntary nature of participation, compensation, privacy and confidentiality, research-related injury, and disclosure of new information regarding participation. Contact information for the PIs and study coordinators will also be provided. Research staff will meet one-on-one with the participant in a private space (via HIPAA secure videoconference or in-person) and review each section of the form. Informational materials will be used to facilitate understanding. Participants will be invited to ask questions section by section. Only individuals who demonstrate comprehension will be considered eligible to participate. Persons who are not able to read and write in English or consent for themselves are ineligible.

A signed consent form (e-Consent or written) will be obtained from each participant. All participants will receive a copy of the signed form for their personal records. Original written signed consent forms will be secured in the participant's research file at each of the respective clinical coordinating centers. E-Consent forms will be secured in REDCap. Consent forms for all enrolled participants will also be sent to the DCC electronically via the HIPAA compliant study portal.

Changes to the consent form may be initiated by research staff, investigators, or regulatory oversight boards as needed. Any changes will be approved by the Principal Investigators at each of the Clinical Coordinating Centers and submitted to the IRB of record for approval.

11.3 Participant Confidentiality

Procedures are in place for maintaining the full confidentiality of all information collected. All staff receive HIPAA and data safety training. Participant confidentiality will be safeguarded by the use of password protected databases and locked file cabinets. Research records will be stripped of all identifying information, with keys identifying individual subjects available only to the PIs and selected designees. Further, access to identifiable private information from study participants will only be accessible to study related personnel who have met the training requirements for the responsible conduct of research, HIPAA and data security and have completed study specific training. The HIPAA compliant Zoom videoconferencing software will be used at both CCCs.

Any data, forms, reports, and other records that leave the clinical sites will be identified only by a participant identification number to maintain confidentiality. Data are managed by study number and analyzed anonymously. All published reports will be of summary nature and no individual subjects will

be identified beyond the investigative staff involved. Responses to online surveys are encrypted during transmission to the study center and there is no outbound transmission of identifying information from study servers to study participants.

Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, the NCCIH, the OHRP, or other regulatory oversight agencies.

To further protect participant privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify participants, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

A Certificate of Confidentiality does not prevent participants from voluntarily releasing information about themselves or their involvement in this research. If an insurer, employer, or other person obtains written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

If the investigators learn that a participant or someone with whom they are involved is in serious danger or potential harm, they will need to inform, if required by state law, the appropriate agencies.

11.4 Study Discontinuation

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

12. COMMITTEES

Data Safety and Monitoring Board
Appointed by NCCIH, the DSMB plays a crucial role in ensuring the safety and welfare of patients enrolled in this trial, and operates without undue influence from any interested party, including PACBACK study investigators or NCCIH staff. DSMB responsibilities include protocol approval, interim review of trial enrollment, protocol compliance, and safety data. The protocol review committee is a subset of the DSMB.

PACBACK Steering Committee
The Steering Committee will assume responsibility for the overall direction of this study which includes design and conduct of the study; preparation of essential study documents (e.g., study protocol, protocol amendments, and data collection forms); monitoring recruitment and retention of study participants; changes in study procedures as appropriate; review of study progress in achieving study goals/milestones; review and implementation of recommendations from the DSMB; review and respond to other general advice and/or recommendations (e.g., from the NCCIH program officer and the PIs). The committee will make recommendations via email correspondence. If requested by a majority of members, or by NCCIH or the CCC and DCC PIs, the committee will meet in-person or remotely. This committee includes the following members, and 7 persons constitute a quorum.

Dr. Wendy Weber, Project Scientist, NCCIH

Dr. Gert Bronfort, CCC PI, University of Minnesota
Dr. Roger Chou, Co-Investigator, Oregon Health Sciences University
Dr. Anthony Delitto, CCC Co-PI, University of Pittsburgh
Dr. Roni Evans, CCC Co-Investigator, University of Minnesota
Dr. Steven George, Co-Investigator, Duke University
Dr. Carol Greco, Co-Investigator, University of Pittsburgh
Dr. Patrick Heagerty, DCC PI, University of Washington
Dr. Francis Keefe, PhD, Co-Investigator, Duke University
Dr. John Licciardone, Co-Investigator, University of North Texas
Dr. Michael Schneider, CCC Co-PI, University of Pittsburgh
Dr. Dennis Turk, Co-Investigator, University of Washington
Dr. Peter Murray, Program Officer, (NCCIH ex officio member)

PACBACK Clinical Coordination Committee (Operations)
The clinical coordination committee is responsible for the implementation of the protocol at each of the coordinating sites. This includes the CCC & DCC PIs, CCC Co-Investigators, project coordinators, and the NCCIH project scientist.

PACBACK Coordination Team
The PACBACK Coordination team includes the PIs, Co-Is, Research Coordinators, and other local research staff (e.g., site leads, recruitment coordinators) at each of the UMN and UPITT CCCs. This team is responsible for coordinating study activities between and within the CCCs, and with the DCC, to ensure consistency in protocol implementation; this will include staff training, patient enrollment, intervention delivery and fidelity monitoring, and data collection.

PACBACK Study Monitoring Committee
This committee performs regular onsite and virtual monitoring of individual eligibility determination, assesses adherence to the protocol, ensures the ongoing implementation of appropriate data entry and quality control procedures, and in general assesses adherence to good clinical practices.

PACBACK Advisory Committee
This committee includes patient, provider, health system leadership, and payer stakeholder representation and will provide guidance and advice to the Steering Committee regarding recruitment, communication and dissemination and implementation related efforts.

Publications, Presentations and Ancillary Studies (PPAS) Committee
This committee will facilitate timely dissemination of study findings, maintain high scientific standards for published material, prioritize the order of publication and presentations, and ensure equitable investigator participation and attribution of authorship. The committee will ensure publications are well-aligned with the trial's research agenda and are not redundant. The PPAS committee will review all proposals for data analysis, as well as research abstracts, presentations, and manuscripts before submission. The committee will also review proposals for ancillary studies. The committee will ensure that each publication that meets NIH Open Access criteria is deposited in PubMed Central. See section 13. Publication of Research Findings for additional information.

13. PUBLICATION OF RESEARCH FINDINGS

The DCC is responsible for setting up systems with the PPAS which is a subset of the Steering Committee to develop publication guidelines that include procedures for reviewing and tracking

publications and presentations. The study Publications Guidelines document details processes for defining study publications, for assigning authors in accordance with the guidelines of the International Committee of Medical Journal Editors, and for reviewing publications prior to submission. The study website will include a searchable list of all analysis proposals and will track their status toward publication. The DCC will conduct all multi-site analyses for the primary publications and presentations.

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15. SUPPLEMENTS/APPENDICES

Study Accrual and Retention Plan
Data Safety Monitoring Plan