Integrated Supported Biopsychosocial Self-Management for Back Related Leg Pain (SUPPORT trial)

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Supported by:
The National Center for Complementary and Integrative Health

Grant # R34AT011209

NCT # NCT05022121

V2 October 2021: 11/16/2021

V3 May 2022: 5/24/2022

V4 July 2022: 7/18/2022

Table of Contents:

ABBREVIATIONS

AE	Adverse Event
BCTs	Behavioral Change Techniques
BCW	Behavior Change Wheel
BRLP	Back Related Leg Pain
BPS	Biopsychosocial
CNP	Certified Nurse Practitioner
Co-I	Co-Investigator
Co-PI	Co-Principal Investigator
COM-B	Capability, Opportunity, and Motivation – Behavior system
CRF	Case Report Form
CTSI	Clinical Translational Sciences Institute
CV	Curriculum Vitae
DC	Doctor of Chiropractic
DNP	Doctor of Nursing Practice
DEA	Drug Enforcement Administration
ER	Emergency Room
HEAL	Healing Encounters and Attitudes Lists
HE	Home Exercise
IRB	Institutional Review Board
JD	Juris Doctor
LBP	Low Back Pain
M	Month
MA	Master or Arts
MBA	Master of Business Administration
MBR	Multidisciplinary biopsychosocial rehabilitation
MC	Medical Care
MD	Medical Doctor
MCISc	Master of Clinical Science
MN	Minnesota
MOP	Manual of Operations
MS	Master of Science
NCCIH	National Center for Complementary and Integrative Health
NIH	National Institutes of Health
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OTC	Over-The-Counter
PA	Pennsylvania
PhD	Doctor of Philosophy
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Physical Therapist
QTF	Quebec Task Force
RCT	Randomized Clinical Trial
RMDQ	Roland Morris Disability Questionnaire
RN	Registered Nurse
RNI	Report of New Information

Rx	Prescription
SAE	Serious Adverse Event
SARP	Study Accrual and Retention Plan
SMT	Spinal Manipulation Therapy
SSM	Supported Self-Management
SUPPORT	Biopsychosocial Self-Management for Back Related Leg Pain trial
TIDieR	Template for intervention description and replication
UMN	University of Minnesota
W	Week

STUDY PROTOCOL REVISIONS

Protocol Version Number	Revision Date	Summary of Changes	Protocol Section(s)
V2	October 2021	Updated study personnel; Clarified that the collaborative development between the study provider and participant of an individualized SSM treatment plan is a standard element of the SSM intervention; Removed BRLP knowledge assessment for participants and the Pain Attitudes and Beliefs Scale for study providers.	Study team roster; Study interventions (5.2.1); Study procedures (6.2) and Study outcomes (9.2)
V3	April 2022	Updated study personnel; Added supplemental study aims funded via administrative supplement in addition to methods for completing the supplemental aims; Reduced number of assessments for SSM related measures; updated participating sites.	Study team roster; Study Objectives (1.3); Background and Rationale (2.0); Rationale for Study Design (3.2); Selection and Enrollment of Participants (4.1-4.3); Study procedures (6.1; 6.2.2); Compensation (6.2.5); Known Expected Risks (7.5); Qualitative Data (9.4.3); Study timeline (13.0)
V4	July 2022	Increased the potential number of enrolled participants for the primary study aims	Rationale for Study Design (3.1); Enrollment, Baseline, and/or Randomization (6.2.2); Statistical Considerations (9.1); Study Timeline (13)

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All research activities will be conducted by University of Minnesota researchers and staff. Research activities will occur at the following location through a business use agreement:

The Berman Center for Outcomes & Clinical Research,
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The University of Minnesota will serve as the sole clinical site for this research and will assume the following responsibilities:

- Design and develop the protocol, manual of operations, informed consent and case report forms.
- Collect and maintain critical regulatory documents from affiliated investigators, e.g. resume/CV, medical/clinical license, certification of completion of training, signed COI disclosure forms
- Store and/or manage data, data analysis, and data and monitoring activities
- Ensure informed consent is obtained and documented from each subject in compliance with federal regulations
- Recruitment, screening, and enrollment of participants
- Protection of participants' rights
- Provide study specific training to the research personnel
- Develop and coordinate randomization scheme and process
- Monitor compliance with protocol and track deviations from the study protocol
- Track, report, and maintain documentation of all serious adverse events and unanticipated problems and disseminating the information to appropriate oversight boards
- Provide periodic updates to affiliated investigators on subject enrollment, general study progress, and relevant scientific advances
- Develop and maintain the MOP
- Retention of specific records (e.g., original consent)

- Development of the data flow and data management procedures, including data entry, error identification, and correction
- AE monitoring and reporting
- Quality control procedures
- Generating and disseminating reports (e.g., enrollment, AEs, participant status, site performance, quality control)

1. STUDY OBJECTIVES

Our long-term objective is to shift the current paradigm away from unimodal, symptom-based care, to an individualized, whole person, behavioral targeted approach for BRLP. In response to current evidence gaps, we are conducting a pilot study to assess the feasibility of a future phase II multi-site randomized clinical trial (RCT). Informed by our previous and ongoing research[20] the Integrated **SUPPORT**ed Biopsychosocial Self-Management for Back Related Leg Pain trial will assess the comparative effectiveness of a novel supported self-management (SSM) intervention delivered by PTs or DCs versus Medical Care (MC). Importantly, our team has a unique opportunity to leverage recruitment from our ongoing clinical trial (NCCIH UH3AT008769), which excludes a large number of chronic BRLP patients. The R34 aims are:

1.1. Aim One

To conduct a Planning Phase to develop detailed protocols, train personnel, and secure regulatory approvals. We will place special emphasis on working with DCs and PTs to provide competency-based training in the SSM intervention. SSM focuses on whole person care delivery, and integrates psychosocial strategies (e.g. progressive muscle relaxation, relaxed breathing, guided imagery, pacing, relaxation, problem solving, cognitive restructuring, interpersonal communication) with physically oriented ones (e.g. exercises, SMT) *specifically for chronic BRLP*.

1.2. Aim Two

To assess feasibility of the SUPPORT trial through achievement of pre-specified targets for:

a. Recruiting and enrolling individuals with chronic BRLP by assessing recruitment rates (screens/month; % women and minorities); enrollment rates (participants/month; % women and minorities); and screened participants' views and perspectives (identification of barriers and facilitators for research participation)

b. Delivering experimental and comparison interventions by assessing acceptability and adherence (% never receiving treatment; % receiving prohibited treatments during intervention phase); % attending required sessions; % participating in home practice and taking medications as directed; % satisfied with treatment); provider intervention fidelity rates (% of required activities delivered) and participant and provider views (barriers and facilitators to engaging in/providing interventions; views regarding affordability, practicality, effectiveness, acceptability, and equity)

c. Data collection by assessing follow up rates of future clinical trial outcome measures (% of complete assessments at 12 weeks and six months, in addition to % of completed weekly pain surveys)

1.3. Supplemental Aims

In addition to the primary aims, NCCIH approved the following supplemental aims as part of the parent R34 pilot study. These aims address the original objective of assessing the feasibility of a future phase II RCT, with additional emphasis on engaging individuals often underrepresented in CIH back pain research.

1. To develop procedures and processes that transparently define how researchers and community members will work together on the proposed research.

APPROACH: Based on the literature, preliminary work and collaboration with a Community Advisory Team, we will develop clearly articulated manuals of operations, including a collaborative team charter that describes how researchers, the Community Advisory Team, and community members will work together on the parent trial and beyond.

2. To explore and describe the barriers and facilitators underrepresented populations encounter in relation to participating in CIH back pain research.

APPROACH: We will collect qualitative data from an additional sample of community members (n=20-30) from traditionally underrepresented groups and use deductive analyses using established models and frameworks.

3. To develop community-informed study procedures and materials and assess community members' and participants' views of them.

APPROACH: We will use an iterative design, development, implementation, and evaluation process successfully used by our team, to create recruitment, screening, enrollment, intervention, monitoring, and dissemination processes and materials that are culturally sensitive and meet diverse participant needs in relation to engaging in CIH pain research.

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 chronic pain crisis. Low back pain (LBP) is the most common and disabling chronic pain condition and affects 40 to 80% of adults at some point in their lives.[1,2]

Back related leg pain (BRLP) is one of the most burdensome and complex variations of the very prevalent and costly LBP conditions. It can be defined by a constellation of symptoms characterized by radiating pain originating from the lumbar spine and traveling into the proximal or distal lower extremity with or without neurologic signs.[20,22] Clinically, BRLP is classified in two ways: *without* nerve root involvement (the majority of cases) which is typically referred pain from spinal structures such as a ligament, joint, disc, or

muscle;[4,20,22,23] and *with* nerve root involvement (the most severe cases), often with a suspected pathoanatomic cause (e.g. spondylolisthesis, disc herniation, stenosis, etc.).[4,22,24] However, the cause-effect relationship between pathoanatomical findings and BRLP can rarely be established with certainty, as pathoanatomic findings are very common in asymptomatic individuals.[25] Further, like other chronic pain conditions, central sensitization likely plays a key role in BRLP as well.[26,27]

BRLP affects 30 to 60% of those with LBP,[4,5] and is associated with greater pain severity, back-related disability, depression, anxiety, and social interference than LBP alone.[4-6] Those with BRLP are also more likely to take time off work and be unemployed.[28] BRLP sufferers also use more healthcare including repeat general practitioner visits, physical therapy referrals, and hospitalizations.[28] In the U.S., BRLP with nerve root involvement has been found to have annual costs 2.5 times higher compared to LBP.[29] Further, these more complicated BRLP cases are more likely to be prescribed opioids, undergo diagnostic imaging, visit an ER, become hospitalized, and receive spinal surgery,[29] all of which are associated with increased risks and costs. It is clear that BRLP sufferers require better front-line care than what is currently being offered.

BRLP is a very complex condition comprised of more than a biological or pathoanatomic cause, and is influenced by a web of interrelated physical, psychological, and social factors. Important *biological or physical risk factors* associated with BRLP include severity of physical symptoms such as back pain, leg pain, inability to sit, fatigue, stiffness, sleep difficulty, and strength loss.[7] *Psychological risk factors,* including depression, poor cognitive and emotional coping strategies, and stress have been associated with poorer outcomes for BRLP sufferers,[8] while positive beliefs about recovery have a protective effect.[7] Overall*, social risk factors* have been under-studied, however there is evidence that occupational factors and lack of social support can have a negative impact on BRLP outcomes.[8-10] Drawing from the larger pain field, poor quality relationships and social stressors (e.g. due to isolation, ostracism, injustice, invalidation, etc.) can play a role in impeding adaptive pain behaviors.[38,39]

Medical Care of BRLP

There is a wide range of treatments used in clinical practice for BRLP.[16,29] The majority of cases are not optimally managed, as demonstrated by persistent levels of disability,[4-6] and frequent use of unimodal, pathoanatomic-focused treatments, which have limited scientific backing, and often fail to meet patient

Table 1. Medical Treatments for BRLP

Treatment	Evidence of effectiveness compared to placebo (unless noted)
Non-steroidal anti-inflammatories	Weak evidence for overall improvement, but no improvement in pain or function[12,29,30]
Benzodiazepines	Weak evidence of no effect on function[12,30]
Systemic Corticosteroids	Evidence of no effect on pain and possible small effect on function[12,30]
Spinal injections	Evidence for small short-term treatment effects for pain and function[13,31,32]
Surgery*	Evidence for improvement in pain and function compared non-surgical interventions[14,33]
Evidence is unclear or non-existent for Acetaminophen, Antidepressants, Muscle Relaxants, Opioids, and Anticonvulsant medications [12,302,30]	
*Reserved for severe cases of BRLP unresponsive to conservative therapy and when neurologic signs and pain distribution are accompanied by concordant imaging findings of spinal stenosis, spinal instability or disc herniation[34-36]	

needs.[11-15] The evidence for common medical care treatments for BRLP is summarized in Table 1. An important limitation of these approaches is reliance on the clinician, rather than promoting active self-management.[40,41] Further, most of these interventions are associated with significant risks including gastrointestinal complications with NSAIDs; hyperglycemia and infection with corticosteroids; addiction, abuse, and overdose with benzodiazepines and opioids; hematoma, bleeding, and dural puncture with spinal injections; and hospital-acquired infection, sepsis, or other serious complications with surgery.[11,13,42,43]

Conservative and Complementary Care Treatments for BRLP

There has been very little research investigating conservative and complementary treatments for BRLP (see Table 2). Physical therapists (PTs) and chiropractors (DCs) are the most common providers of conservative and complementary treatments for BRLP in the U.S. Approximately 64% of patients seek care from physical therapists (PT) and 32% from doctors of chiropractic (DC) for BRLP[16] to help manage symptoms and restore movement and functional ability. Historically, treatments by these providers have been primarily biologically or physically oriented, and include a mix of passive and active treatments (e.g. ergonomic advice, exercise, and manual treatments, like spinal manipulation therapy and traction).[46] A recent systematic review of non-invasive treatments for LBP conditions reported limited evidence to support the use of exercise and spinal manipulation for BRLP,[31] which was partially informed by a trial performed by our team and is further described in Preliminary Studies.[20] Serious risks with these treatments are very rare and common side effects are usually self-limiting (e.g. soreness and increased pain).[31]

Table 2. Conservative & Complementary Treatments for BRLP

Treatment	Evidence of effectiveness
Exercise	Weak evidence for small improvements in pain and function compared to usual care or sham exercise[30]
Spinal Manipulation	Weak evidence for small improvements in pain when added to home exercise and advice; unclear evidence compared to other active treatment[30,43]
Traction	Weak evidence of no improvement in pain or function compared to sham or other active treatments[30,44]
Evidence is unclear or non-existent for Pilates, Yoga, Tai Chi, Psychological therapies, Acupuncture, Massage, Ultrasound, TENS, PENS, EMS, Inferential Therapy, Superficial Heat or Cold, Low-level Laser Therapy, Short-wave Diathermy, Lumbar Supports, and Taping[30]	

Self-Management Behaviors and BRLP: Challenges and Solutions

An important and relatively recent observation has been that chronic pain, including BRLP, is much like other chronic health conditions and requires ongoing management.[47,48] Rather than rely on passive and provider-based therapies over the long-term, a preferred solution is to engage pain sufferers in healthy self-management behaviors to successfully address pain themselves.[40,48] While patients recognize the need to take responsibility for their care, they often require assistance from health care providers to initiate and maintain self-management successfully.[49,50] Self-management, like any human behavior, is complex and requires attentiveness to the patient's biopsychosocial needs and risk factors. This includes assessing patients' capabilities (e.g. Do they have the knowledge, skills, and physical capacity?), opportunities (e.g. Do

they have the resources?), and motivations (e.g. Do they have the beliefs and optimism?),[51-53] and providing support based on individual needs.

When coupled with the complexity of chronic pain conditions, like BRLP, designing and studying effective self-management interventions can be challenging. Importantly, advances in behavioral health fields have provided theoretical and evidence-based frameworks and models that can be used to guide the process.[47,51,54] One such model is the Behavior Change Wheel (BCW) which represents a synthesis of 19 behavioral theoretical frameworks (and thus is more comprehensive in addressing the complexity of human behavior versus a single theory driven model). We have used the BCW along with the biopsychosocial model, to develop our conceptual framework and model for the SSM intervention (see Figure 2). This has guided choices regarding: the modifiable factors that should be targeted (e.g self-efficacy beliefs, self-management skills, etc.); the evidence-informed modalities to include (e.g. physical exercises, cognitive strategies, etc.); the most appropriate intervention elements for delivering (e.g. education, training, etc.); and the most salient behavioral change techniques (e.g. instructions and demonstrations, practice and rehearsal, etc.).[55,56]

Biopsychosocial Interventions for LBP and BRLP

Treating pain as a primarily physical phenomenon is inadequate.[40,48] While the biopsychosocial (BPS) model has been promoted for the past several decades,[57,58] most treatment approaches still fail to address the comprehensive range of interwoven factors implicated in BRLP and LBP conditions.[40] While there have been attempts to apply the BPS model to pain management,[57,59] there are still many gaps, particularly for BRLP.

Multidisciplinary approaches: Team based approaches with multiple providers from complementary disciplines has been one way of integrating different therapies to address patients' BPS needs.[40,59] However, these multi-disciplinary approaches have significant challenges including patient inconvenience (multiple appointments with different providers), and the substantial system resources needed to coordinate care across provider types, which often results in disjointed and unsatisfactory care.[40] Further, the research evidence suggests that the benefits of multi-disciplinary interventions may not outweigh the costs. A systematic review of 41 trials examining multi-disciplinary biopsychosocial rehabilitation (MBR) programs for chronic LBP[59] found an advantage compared to usual care or physical treatments for reducing pain and disability and increasing the likelihood of return to work. The authors cautioned that the modest benefits, may not outweigh resources and costs required to deliver care, and suggested MBR be reserved for the most severe cases. Since that review we identified 6 additional trials which generally confirm these findings.[60-65]

Mono-disciplinary approaches: There are pragmatic advantages to having the biopsychosocial elements of care delivered by a single practitioner, including improved accessibility, harmonized care, decreased patient burden, and potentially lower costs.[66] Physical therapists (PTs) and chiropractors (DCs) are the most common providers of non-pharmacologic treatment for back pain conditions in the U.S.[17] This makes them optimally positioned for delivering integrated psychosocial strategies to complement

biological/physical approaches,[46,67] and play a critical role in the frontline non-drug management of BRLP.[18,19] Indeed, there have already been shifts in both the PT and DC fields to integrate more psychosocial aspects into their care models to better support patient self-management.[46,67-69]

Most of the evidence to date regarding mono-disciplinary care for biopsychosocial (BPS) pain management, focuses on PT care for LBP. Two recent systematic reviews have assessed the effectiveness of PT-led BPS interventions compared to education/advice or physical focused care (e.g. exercise, manual treatment).[70,71] Both reviews concluded that PT-led BPS interventions were superior to education/advice. The reviews reached different conclusions regarding effects compared to physical oriented treatment, with one review reporting similar outcomes[71] and the other reporting a small advantage for BPS interventions.[70] This is likely due to limitations of these reviews which resulted in exclusion of several original trials. Overall, trials comparing mono-disciplinary BPS interventions to physical treatments for chronic LBP have reported either similar effects[72-74] or an advantage for biopsychosocial interventions.[75,76]

Of note are two of the larger trials assessing PT-led biopsychosocial interventions, which included large subgroups of BRLP patients and reported more improvement in pain and physical function compared to education[77,78] and usual PT care.[76] While these findings are promising, it is not possible to draw firm conclusions regarding the effectiveness of PT-led BPS interventions for BRLP from these two studies. The effectiveness of DC-led BPS interventions also remains unknown.

Low back pain (LBP) and health inequity. While there have been increased calls to improve the study of LBP by using a more whole person or holistic biopsychosocial approach, change has been slow and investigation of social aspects has been especially under-addressed. In particular, broader knowledge about the social conditions that contribute to health inequity related to LBP, are relatively sparse.[158]

From the limited research that has been done, important disparities are evident. Those with lower education and income are more likely to experience LBP that is chronic, as well as worse outcomes. The strongest evidence for associations are between education and multidimensional aspects of socioeconomic status (e.g. income, employment status, home ownership).[158] While prevalence rates are similar between white and Black Americans, Black Americans are more negatively impacted with higher severity and disability.[159] Disparities in back pain care are also prevalent. A recent, large observational study of older U.S. adults seeking care for back pain noted Blacks and Hispanics used less healthcare and also had less improvement in clinical outcomes relative to whites.[160] The opioid epidemic has hit low-income white communities the hardest, where opioid prescriptions and deaths due to overdose are most prevalent.[161] While Black Americans are less likely to be prescribed opioids for back pain (an advantage in this case),[162,163] they are also more likely to be under-assessed and under-treated in many areas including screening, diagnostic imaging, use of physical therapy, and surgery.[164]

Health equity can be viewed as social justice in health and is related to the bioethical principle of justice; it is achieved when health inequities are eliminated creating equitable opportunities to attain optimal health regardless of social position or socially-determined circumstances.[165] For research in Complementary and Integrative Health (CIH) for LBP, health equity will mean gaining a better understanding about the barriers and facilitators underrepresented groups encounter and the actionable steps that can be taken to address them.

Importantly, it is essential that the full range of biopsychosocial factors be considered. Indeed, understanding and assessing contextual multilevel determinants of health which contribute to health inequity is critical yet underdeveloped across all health fields.[165,166] There is a great need to better understand the dynamic interactions between proximal and distal social contexts (e.g. family, work, community, culture, sociopolitical) that affect underrepresented populations participation in LBP and CIH research.

Research and health inequity. While efforts have been made to address inequity in health research, there is still much to be done. Inclusion of minorities in NIH-funded clinical trials has increased over the past 25 years (from 2.8% to 11.1%), but minorities are still widely underrepresented. Non-Hispanic white Americans represent 60.7% of US population, but account for nearly 90% of clinical trial populations.[167] In the field of musculoskeletal pain research representation of Hispanic and Black patients in orthopedic clinical trials have been 2 to 3.5 times lower relative to census estimates.[168] Enrollment of minorities in rheumatoid arthritis trials is also significantly lower than their representation within the population (16% vs 40%).[169]

Disparities also exist in regards to CIH use in the American population, with lower use among Hispanics (22%) and non-Hispanic Blacks (19.3%) relative to non-Hispanic whites (37.9%). Use of CIH is also lower for the less educated (15.6% in adults w/o high school degree compared to 42.6% in adults with college degree) and the poor (20.6% of poor report CIH use compared to 38.4% of non-poor.)[170]

Systematic efforts to assess participation of traditionally underrepresented groups in CIH studies is also lacking. In the PI's own K01 CIH pain focused research (publication in preparation), participation rates of racial and ethnic groups and those with lower income and education fall well short of representing national estimates of pain sufferers (see Preliminary Studies). Thus, we can surmise that overall, the CIH research for spine pain has yielded findings that are generalizable to only a limited segment of the population, which has important bioethical and translational implications for the field.

Overcoming health inequity in CIH pain research. Enhancing stakeholder engagement has emerged as an important priority for increasing participation of underrepresented populations in research. Community based participatory research and community engaged research practices have become increasingly popular in many health fields[171,172] but have yet to gain significant traction in CIH research for pain.[158] General strategies that are advocated for improving engagement of hard to reach populations include multi-factor approaches for involving community groups and organizations across

all stages of research.[173] It is also essential to gain a better understanding of social contexts, including barriers and facilitators to engagement including mistrust, competing demands, unintended outcomes, misconceptions of research, cultural congruence, and others.[165,174,175] Attention must also be paid to the specific challenges related to the condition and interventions under study.[176]

Limitations & Gaps in Research of Biopsychosocial Self-Management Interventions

Evidence to support mono-disciplinary BPS interventions for BRLP is encouraging. However, existing studies have significant limitations, leaving critical gaps in our scientific understanding.

- Greater attention needs to be paid to intervention design so it aligns with BRLP-specific risk factors, patient needs, and desired outcomes to fully realize the potential of BPS interventions for active self-management (an important goal for overcoming rising costs and disability).[51] This includes approaching self-management as a set of behaviors, and intentionally choosing evidence and theory informed strategies that map to relevant behavioral outcomes, rather than clinical outcomes alone (e.g. pain and disability).
- Methodologically rigorous research of conservative and complementary approaches for BRLP is lacking. Further, the existing literature on BPS and self-management interventions is very heterogenous, with a wide range of goals, rationale, content, training, frequency, intensity, mode of delivery, and attention to intervention fidelity, all which could have a substantial impact on study related outcomes. While better designed BPS studies targeting self-management for LBP are emerging,[54,79] none to our knowledge address the more complicated and burdensome BRLP conditions.
    - Engaging communities in CIH research for chronic pain is inherently complex and is more likely to succeed when grounded in established models and frameworks to guide the work. The proposed supplemental research brings together models used in the parent pilot study to systematically study back-related leg pain for improving pain self-management behaviors with features from the ConNECT Framework to address health equity. We will focus on augmenting the parent study by applying the following features from the ConNECT framework:
        - Paying greater consideration to social contexts (e.g. the situational and interactive influences on health). For CIH and LBP this includes socioecological determinants, as well as biological/physical and psychological influences.
        - Fostering a norm of inclusion (e.g. consistently engaging diverse groups). This means systematically and consistently using community-based research strategies to intentionally reach underrepresented groups in CIH pain research, monitor progress, and making these efforts the norm, not the exception.
        - Doing more, earlier to ensure long-term equitable diffusion of study innovations to facilitate real world benefit for all. For CIH and LBP conditions this means bridging the gap between research and practice, which to date, has been a challenge. While the parent study addresses this in part by engaging clinician stakeholders (who will be tasked with administering the CIH interventions should they prove effective), the administrative supplement proposes to extend

stakeholder engagement to include community members' from traditionally underrepresented populations in CIH and LBP research.

2.2. Preliminary Studies

Collectively, this investigative team has substantial experience conducting comparative effectiveness studies of conservative, complementary, and conventional approaches for LBP conditions.[20,21,81-91]

Table 3.	SMT & HE vs HE	
Outcome	***12 weeks***	***52 weeks***
Leg pain	-10% points (-19 to -2)	-7% points (-15 to 2)
Disability	-11% points (-17 to -5)	-6% points (-12 to 1)
Improvement	-11% points (-16 to -6)	-6% points (-13 to -1)
Satisfaction	-15% points (-20 to -10)	-12% points (-18 to -7
Medication use	56% vs 63%	42% vs 66%
Less med days	OR=1.8 (1.0 to 3.1)	OR=2.6 (1.4 to 4.7)
Self-efficacy*	4% points (1 to 8)	1% point (-2 to 5)
*Not reported in primary manuscript		

A Mixed Methods Study of Spinal Manipulation and Home Exercise for Back Related Leg Pain We conducted one of the few large randomized studies of non-drug therapies for BRLP, which was published in Annals of Internal Medicine.[20] The study included BRLP participants with and without neurological signs (20% had neurological signs), but excluded individuals with potential indications for surgery (e.g. spinal stenosis, spinal instability, progressive neurological deficits). Spinal manipulative therapy (SMT) targeted mobility and symptom relief, and was delivered by chiropractors (up to 20 sessions). Home exercise (HE) was delivered over 4, 60-minute sessions and focused on teaching patients exercises and postural strategies. Clinical outcomes (Table 3): SMT & HE resulted in significantly greater reduction in leg pain, at 12 weeks, but not 52 weeks compared to HE alone. Similar findings were

observed for most secondary outcomes, including medication use. Expected adverse events (e.g. increased pain severity) were mild to moderate, self-limiting, and reported less frequently in the SMT & HE group. Qualitative outcomes: The quality of patient-provider interactions was the most frequently cited theme informing satisfaction.[21] Limitations: It remains unknown how these interventions compare to common types of medical care. Also, the primary focus of both interventions was on the physical aspects of BRLP and did not purposefully address psychological and social factors. This is reflected by fewer improvements in the psychosocial outcomes (e.g. SF-36 mental health domain) compared to those that are 'physically oriented' (e.g. pain, disability).

This study demonstrated DCs could successfully and safely evaluate and treat patients with chronic BRLP. The findings are encouraging in light of the current, very limited BRLP treatment literature, and suggests a need to compare similar non-medical interventions to conventional medical care. Further, in recognizing the complex nature of BRLP, there is an opportunity to better train DCs and PTs to capitalize on patient-provider interactions and intentionally use behavior change techniques to integrate evidence based psychosocial treatments with physically oriented modalities (SMT, HE).

Spinal Manipulation and Patient Self-Management for Preventing Acute to Chronic Back Pain (PACBACK) study (UG3/UH3) Our team recently completed a pilot study of 92 participants with acute low back pain (UG3), which led to an ongoing randomized trial

(n=1180, UH3). Drs. Greco and Evans (Co-Is), designed and developed a DC and PT delivered supported self-management (SSM) intervention (adapted from a Pain Coping Skills program).[66,92,93] SSM was developed in collaboration with a multi-disciplinary group of researchers including DCs, PTs, and psychologists and consists of 4-8, 60-minute sessions, targeting the modifiable physical and psychological risk factors associated with acute LBP. Intervention elements include physical and postural exercises, integrated with cognitive strategies (e.g. relaxed breathing, progressive muscle relaxation, mental imagery), delivered with and without SMT. PTs and DCs are trained to use patient-centered communication and whole person assessment tools to tailor care to meet patient needs.

Select Pilot & Feasibility Outcomes: A total of 5 DCs and 4 PTs were trained by Drs. Greco and Evans (~20 hours). Prior to training, qualitative data suggested providers lacked the tools and training to support patients' psychosocial needs; they also expressed feeling limited in their ability to motivate patients in self-care. Provider confidence in the SSM program improved from pre-training to post-training. Patient adherence to the SSM intervention was high with 41/46 individuals (89%) attending required sessions. Follow up rates were also high (94% for weekly pain severity, 98% for monthly surveys of disability and other outcomes). These findings, along with suggestions from providers, were used to refine the SSM intervention and supporting materials for the ongoing PACBACK trial.

The investigators' current and previous research[20] has led to this R34 pilot study, which will address an important group of patients with chronic BRLP, who are currently ineligible to participate in the PACBACK trial (BRLP is not the condition of interest, and the focus is on acute LBP of <12 weeks duration). We will leverage recruitment from PACBACK to enroll patients in the R34. Similarities in study design will facilitate protocol development, increasing this R34's efficiency, and likelihood of meeting feasibility targets (Table 5). The R34 will provide the opportunity to collaborate with a Clinical Advisory Team to refine and implement a new SSM intervention specific to BRLP, and to sufficiently train DCs and PTs in the additional psychosocial elements and behavior change techniques required to meet the more complicated needs of chronic BRLP patients.[7]

2.3. Study Rationale

There is insufficient high-quality research examining conservative and conventional treatments for BRLP, the most disabling and costly of the LBP conditions. In light of increasing calls for safe and effective treatments that diminish unhealthy pain management behaviors (e.g. inactivity, overuse of medications including opioids), the timing is imminent for PTs and DCs to play a larger role in *initiating and guiding patients' self-management using evidence-based behavioral strategies that educate, motivate, and support patients from a biopsychosocial perspective*.

In response to the current evidence gaps and limitations in the existing research, we propose a pilot study to assess the feasibility of key study methods including recruitment, enrollment, intervention acceptability and credibility, participant adherence, provider fidelity, and data collection in preparation for a multi-site randomized clinical study. The Integrated **SUPPORT**ed Biopsychosocial Self-Management for Back Related Leg Pain

(SUPPORT) trial will assess the comparative effectiveness of a novel supported self-management (SSM) intervention delivered by PTs or DCs, to Medical Care (MC).

This research addresses NCCIH high priority areas of integrated mind body approaches for symptom management of BRLP, one of the most disabling, costly, and understudied LBP conditions, with enhanced efforts for engaging under-represented populations. The R34 pilot study will establish the essential foundation for the first RCT comparing an innovative SSM intervention to medical care for BRLP. In doing so, DCs and PTs can play a more impactful role guiding BRLP patients' healthy pain self-management behaviors, resulting in less BRLP disability, and better overall health and wellbeing.

3. STUDY DESIGN

3.1. Rationale for Study Design

While this team has previously investigated conservative interventions for chronic BRLP, the focus has been on primarily biological/physical interventions. Given the complex web of interrelated physical, psychological, and social factors contributing to chronic BRLP, we have developed a comprehensive evidence and theory informed supported self-management (SSM) intervention. Further, comparisons to medical care (MC) are much needed. Thus, this pilot study provides an opportunity to set a solid foundation for future research efforts, including a multi-site, phase II hybrid effectiveness - implementation randomized clinical trial assessing the effectiveness of 12 weeks of PT or DC delivered SSM compared to MC for chronic BRLP in terms of behavioral and clinical outcomes (see section 6).

For AIM 1, we will focus on critical Planning Phase activities based on the team's previous experience.[20,81-88] This will include:

- Preparation of detailed protocols, procedures and materials, as well as securing necessary regulatory approvals and training study personnel.
- Also, we will work with a clinician advisory panel of PTs and DCs to further refine the SSM intervention and clinician training strategy.

For AIM 2, we will conduct a randomized mixed methods pilot study (n=40-50) using qualitative and quantitative data to assess the feasibility of recruitment, enrollment, intervention acceptability and credibility, participant adherence, provider fidelity, and data collection activities for the future multi-site, phase II randomized clinical trial. Table 5 details feasibility targets and Table 6 describes protocol refinement measures. Figure 1 provides an overview of the pilot study. Section 6 provides additional information about evaluations and outcomes.

Participant involvement will occur from the point of their initial online screening (which is followed by an in-person clinical screen) to the last follow up data collection endpoint (6 months after randomization/enrollment). The total time for subject involvement is approximately 7 months.

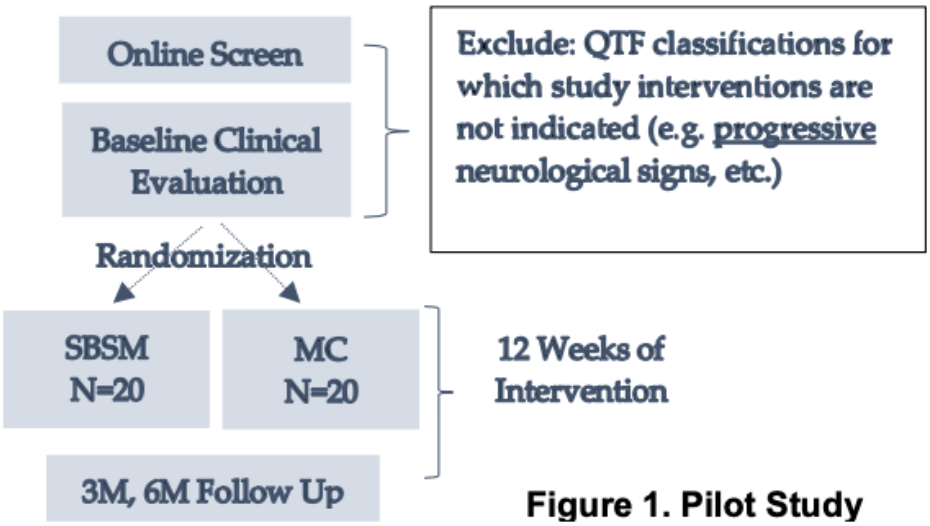


Figure 1. Pilot Study

3.2. Rationale for Supplemental Aims

The nature of the future hybrid effectiveness/implementation RCT design requires participation of multiple levels of stakeholders in addition to those taking part in the randomized pilot study. Through their participation, important partnerships will be formed, and critical contextual information will be gathered which will inform the optimization of the future RCT, and adapt the experimental intervention (SBSM) so that it is suitable for implementation over the long term.

For Supplemental AIM 1, we will assemble a Community Advisory Team (CAT) to develop a clearly articulated CAT manual of operations that includes a collaborative team charter that describes how researchers, the CAT, and community members will work together on the parent pilot study and beyond.

For Supplemental AIM 2, we will collect additional qualitative data from a sample of individuals (n=20-30) from traditionally underrepresented groups. This is an extension of the mixed methods pilot study to assess the feasibility of the future multi-site, phase II randomized clinical trial with an emphasis on exploring intervention acceptability and credibility.

For Supplemental AIM 3, we will use information from Supplemental Aim 2, in consultation with the Community Advisory Team assembled as part of Supplemental Aim 1, to engage in an iterative design, development, implementation, and evaluation process successfully used by our team, to create recruitment, screening, enrollment, intervention, monitoring, and dissemination processes and materials for the future full-scale trial, that are culturally sensitive and meet diverse participant needs in relation to engaging in CIH pain research.

3.2. Sampling, Target Population, & Location

The University of Minnesota (UMN) will serve as the clinical site for the pilot study to first establish feasibility of delivering the SSM and MC interventions. Participants will be offered the option to attend videoconference appointments for visits where in-person activities aren't necessary. Persons who are unable to use Zoom will be seen in-person, and thus will not be excluded if they do not have the means to participate remotely. Zoom is a University of Minnesota supported HIPAA compliant app that allows videotelephony and online chat services through a cloud-based peer-to-peer software platform. This application has been used extensively in research by this study team (UH3AT008769, R33AT009110).

This pilot study (including the supplemental aims) is in anticipation of a larger scale clinical trial that will be performed at clinical research centers affiliated with the UMN in Minneapolis, MN and the University of Pittsburgh in Pittsburgh, PA. The study will draw from the Minneapolis/St. Paul metropolitan area which has a total population of 3.03 million, 25% of which are non-white.[94] See Section 4 and the Study Accrual and Retention Plan (SARP) for additional information related to recruitment and enrollment of participants.

3.3. Covid-19 Impact on Trial Conduct

University of Minnesota policies and guidelines for mitigating the risk of Covid-19 to participants and study staff will be followed. Participants will be provided with standardized information on Covid-19 and research participation during consent. All participants and staff will be screened for signs, symptoms, and potential exposure to Covid-19 prior to all in-person study visits. Study recruitment, screening, enrollment and intervention activities for the project are anticipated to begin in the Fall of 2021. In the event that in-person activities are not possible due to the Covid-19 pandemic, trial procedures will be modified to ensure all visits can be conducted remotely. Our team has designed and implemented remote screening protocols (including assessment of neurological deficits associated with BRLP) for our ongoing NCCIH PACBACK trial. The SMT component of the SSM experimental intervention will be paused until in person visits can safely resume.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. Inclusion Criteria

Participants must meet the following inclusion criteria to participate in the pilot study:

- Back-related leg pain (BRLP) consistent with the Quebec Task Force (QTF) classifications 2-4 (radiating pain into proximal or distal extremity with or without neurological signs).[22,95]
- 18 years of age or older.

- Back-related leg pain severity of 3 or higher at all screening assessments (0 to 10 scale)
- Episode duration of 12 weeks or more
- Ability to read English fluently

4.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria at baseline will not be allowed to participate in the pilot study:

- Spinal stenosis (QTF 7)
- Specific, non-mechanical causes of BRLP (QTF 11; e.g. infection, tumor)
- Contraindications to study interventions (e.g. spinal fracture (QTF 5))
- Inflammatory conditions of the lumbar spine (QTF 11)
- Lumbar fusion
- Progressive neurological deficits
- Cauda equina syndrome
- Pregnancy, nursing
- Ongoing care from another healthcare provider for BRLP
    - Individuals taking prescribed medications for BRLP with the potential for withdrawal symptoms (e.g. opioids, antidepressants, corticosteroids) will be referred to their provider to ensure prescription medications are safely tapered
- Severe unmanaged comorbid conditions (e.g. substance abuse, major depressive disorder, stage 3 hypertension).

Also, as part of the supplemental aims to the pilot study, qualitative interviews will be performed with additional stakeholders to provide important contextual information required as part of the hybrid effectiveness/implementation design. These stakeholders are intended to provide perspectives from individuals with LBP who are often underrepresented in CIH LBP research. Inclusion criteria will be 18 years of age and older, with an episode of LBP (with our without leg pain) and at least one of the following: non-white race; low health services access; lack of health insurance coverage; lower income; higher food insecurity; gender identity of LGBTQ+; and willingness to participate in qualitative data collection.

4.3. Study Enrollment Procedures

<u>Recruitment of Participants</u>

Participants are recruited to participate in this study using the following strategies:

- Leveraging ongoing recruitment efforts of an NIH funded multi-year study (UH3AT008769) of acute and subacute LBP led by Co-PI Bronfort, and Co-I Schneider, which routinely excludes chronic BRLP sufferers during screening (approximately 150 per month).
- Using resources offered through the UMN Clinical and Translational Science Institute (CTSI, NIH UL1TR000114). This includes StudyFinder, which extracts data from UMN

affiliated enrolling studies listed on ClinicalTrials.gov; and ResearchMatch, an electronic volunteer recruitment registry that also provides information about UMN studies.
- Advertising through University affiliated newsletters, websites, Facebook and other social media, and clinics (e.g., Clinics and Surgery Center). Posters will also be distributed publicly throughout the UMN campus and surrounding communities.
- Reaching under-represented populations through collaboration with the UMN Urban Research and Outreach-Engagement Center and the CTSI's Community Engagement Studio. (e.g. through presentations, mentions in organizational newsletters, etc.).
- The SARP details additional plans to recruit participants underrepresented in research (e.g. race, ethnicity, age, education, income, ability, gender and sexual orientation).
- As part of supplemental aim 1, we will work with a Community Advisory Team (CAT) comprised of 6-10 community leaders from organizations including the YMCA of the North's Equity Innovation Center, Social Responsibility Team and ForeverWell Outreach Team; the University of Minnesota's Office of Public Engagement and the Robert J. Jones Urban Research and Outreach Engagement Center (UROC) and others. The Community Advisory Team will meet quarterly to connect researchers to community members; educate and coach researchers in historical issues related to health disparities, cultural agility and competence; review engagement reports; and make recommendations for prioritization of engagement strategies based on community member input.

Participants' private medical and/or employment records will not be accessed for recruitment purposes. Participant's electronic medical records (e.g., EPIC records) will not be accessed by research staff.

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 study team at routine meetings.

Consent Procedures

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

Randomization/Enrollment

Enrolled subjects will be randomized using blocked randomization (with varying block sizes) following stratification for back-related leg pain classification (QTF classification 2, 3, or 4).[95] Computer generated random treatment assignments will be generated by an independent study statistician and conveyed electronically through REDCap (the electronic study database) at the time of enrollment to preserve allocation concealment. Screening clinicians and study staff will be blinded to upcoming treatment assignments.

5. STUDY INTERVENTIONS

The Template for Intervention Description and Replication (TIDieR) checklist has been used to guide the description of the study interventions[80] to facilitate future results interpretation, as well as dissemination and replication. Table 4 illustrates the standard elements **common to both interventions**. Participating clinicians will be trained and certified in study protocols and intervention specific content (see below for additional details).

Table 4. Common Intervention Elements (Experimental & Comparison Groups)

Initial intervention period	12 weeks; # of visits determined collaboratively by provider and patient (once minimum is reached)
Restrictions	No outside care during main 12-week intervention period
Ongoing care	If recurrence or worsening of BRLP after 12 weeks, can receive care in assigned group
Procedures	Appointment reminders, follow up for missed appointments provided
Standardized information	Modified "Back in Action" book covering evidence based BRLP messages
Over the counter medication	As necessary
Location	UMN affiliated outpatient clinic in Minneapolis

The main intervention period is 12 weeks long. All patients will be asked to limit treatment to their assigned intervention for the main 12-week intervention period. Participants in both groups will be monitored during the intervention phase for the development of exclusion criteria impacting participant safety which will result in withdrawal from the study intervention along with a referral for appropriate care (e.g. development of progressive neurological deficits). All patients will receive basic standardized information regarding the etiology, prognosis, and basic self-management of back-related leg pain.

Patients in both groups can take over-the-counter medications, for any reason, as necessary during the entire trial period. Participants may also continue to engage in any self-management practices for BRLP that were used prior to trial enrollment (e.g. exercises, heat application). Following the main 12-week intervention period, participants who experience a recurrence or worsening of back-related leg pain symptoms will be given the option to receive further care in their assigned treatment arm, as is typical in real-world settings. Additional care for back-related leg pain recurrences may occur until week 26. Intervention documentation will include data regarding training and resources required to deliver the interventions. Visit specific information including type or component of treatment, frequency and dose, side effects, etc. will also be measured. These are documented in standardized case report forms.

5.1. Interventions, Administration and Duration

5.1.1. Supported Self-Management (SSM) - Experimental Intervention

Rationale, theory, goals: The program is theory-informed and adapted from previous cognitive behavioral and self-management programs.[20,66,92,93] The primary goal is to enhance patients' ability to manage their BRLP symptoms in both the short and long-term by engaging in healthy physical, psychological, and social self-management behaviors (see Figure 2).[40,51]

Description: The intervention is comprised of an integration of the following core intervention elements and 12-15 behavioral change techniques (BCTs)[55,56] targeting important modifiable biopsychosocial factors for BRLP and which can be successfully delivered by PT or DCs. These include:

- Physical factors of strength, activity, mobility, posture, and pain symptoms;[8,101]
- Psychological factors including beliefs (self-efficacy, fear-avoidance, catastrophizing), thoughts, emotions, and stress;[8-10,41] and
- Social factors including social support and interpersonal relationships.

Providers will use standardized checklists for each session, to ensure they address the required elements (see 5.2.1 below).

Dose/Schedule*:* 6-12 sessions, up to 60 minutes per session, over 12 weeks.

Mode of delivery: One to one, in person or via videoconference when applicable; supplemented with the use of phone, videoconference, and/or email check-ins.

Location: UMN outpatient research facility or via videoconference when applicable

Tailoring and individualization: At the first session, the PT or DC will work with the patient to assess their needs and collaboratively develop an individualized treatment plan. This will include review of BPS baseline measures (see Table 5); a brief physical examination that includes manual palpation and brief postural, strength, and mobility assessments; completion of a Wellbeing Wheel (based on risk factors and the BPS model) and self-evaluation of what it would take to engage in adaptive pain behaviors (COM-B Self-Evaluation Questionnaire V1).[55] These will be re-assessed as needed. In addition, a "Self-Reliance Check In" will be completed at 6 weeks to initiate a conversation regarding release to self-care.

Side Effects/Risks: The risks associated with SSM are considered low for subjects who meet the inclusion/exclusion criteria; to further minimize risks licensed doctors of chiropractic (DC) and physical therapists (PT) will be trained and certified by investigators, and monitored for fidelity to ensure they are implementing SSM in a manner that optimizes patient safety. Experienced investigators and consultants will be readily available as needed to consult with DCs and PTs to clinically manage adverse events as needed. The core elements of SSM include physical and psychosocial strategies.

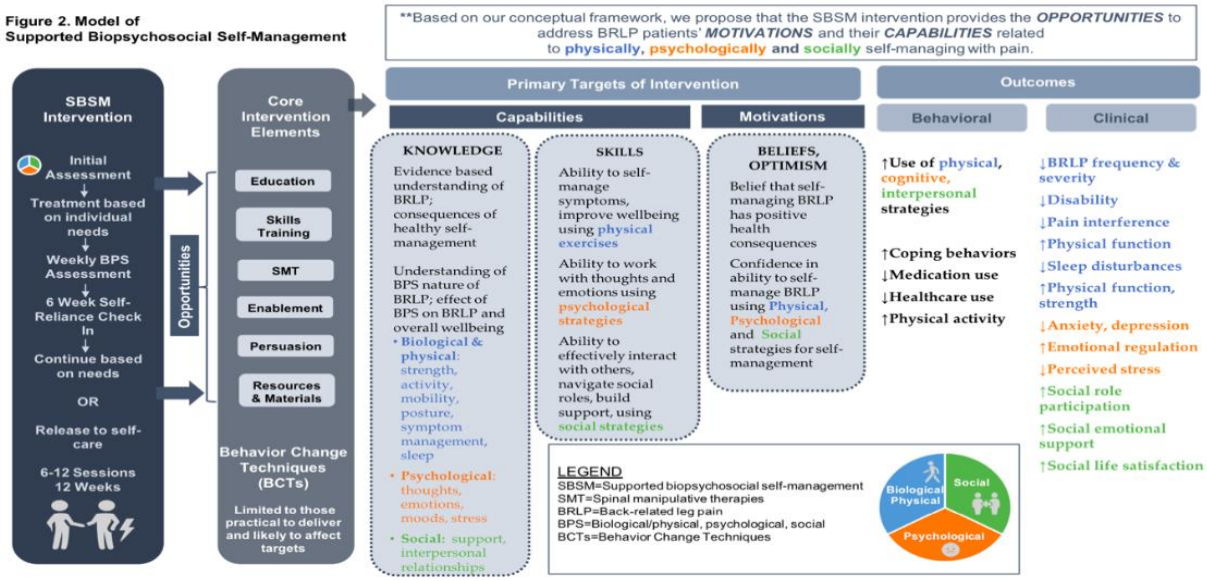
Physical: Side effects associated with manual treatment and exercise are common and benign. Approximately 35% of participants in our previous BRLP trial reported expected self-limiting adverse events that were mild to moderate in severity (e.g. increased pain, soreness).[20] Serious adverse events following manual treatment to the lower back are rare and are estimated to occur once per million to several million visits and include cauda equina syndrome, disc herniation, fracture, hematoma or hemorrhagic cyst.[31, 146]

Psychosocial. Subjects may experience some short-lasting emotional discomfort during and outside the sessions when practicing the psychosocial exercises and strategies

(e.g. of relaxed breathing, guided imagery, pacing, relaxation, pacing, problem solving, cognitive restructuring, interpersonal communication, etc.).

Providers: Licensed PTs and DCs with a minimum of 3 years of clinical experience will be provided an estimated 30 hours of training.

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. We will use methods effectively implemented in the investigators' previous and ongoing studies including video presentations, demonstrations, and simulated patient practice with feedback from investigators responsible for the SSM intervention (CG, RE).
Training content will include the essential information related to the core intervention elements and BCTs, and will emphasize patient-centered communication as a key part of delivery.[15] Clinicians will be assessed for key competencies prior to certification. Competencies will be adapted from ongoing and previous studies with input from The Clinician Advisory Panel comprised of PTs and DCs during the **Aim 1** Planning Phase.



5.1.2. Medical Care (MC) - Comparison Intervention

Rationale, theory, goals: The goal of medical care management for BRLP is to reduce pain and disability associated with the condition. This is achieved through the use of medications targeting pain and inflammation. Medical care is a commonly used standard approach for managing BRLP in the U.S., and thus is appropriate as an active comparison group.

Description: Medical care will be comprised of primarily medication management, which is a standard first-line approach for back-related leg pain in primary care. Choice of medications is informed by the current evidence [12,104] and the American College of Physicians guidelines on noninvasive treatment for LBP.[11]

- Nonsteroidal anti-inflammatory drugs (NSAIDs) will be used as a first-line approach.
- Second-line medications include systemic corticosteroids, skeletal muscle relaxants, acetaminophen, benzodiazepines, antiseizure medications, lidocaine patches, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants and weak opioids (e.g. Tramadol, Tylenol with Codeine) for participants unable to tolerate or unresponsive to first-line medications.
- Strong opioids will not be allowed for the management of chronic BRLP, as the current CDC recommendations prefer non-opioid medications for chronic pain and there is a lack of evidence regarding their use for BRLP.[12,105]

Medication Choice: Decisions regarding medication selection will be made collaboratively between the provider and patient after a discussion of the potential risks, benefits, past experience, and preferences for different medications.

Schedule: Minimum of 2 visits (up to 30 minutes in length) to review clinical presentation, risk/benefit profile and participant preference for first and second-line medications, and response to previous care.

Visit type: The initial visit will be in-person or via videoconference; additional visits will occur in person, by videoconference, or by phone.

Medication Delivery: Medications will be taken orally or applied topically to the skin. Injections will not be allowed. Medications will not be stored at or distributed to participants in the UMN clinic. Prescriptions for medications from the study provider will be sent to the patient's preferred pharmacy. Participants will pick up prescribed medications at their preferred pharmacy. Over the counter (OTC) medications will be picked up by the participant at their retailer of choice.

All medications are paid for by the study. Participants are not required to use their medical insurance benefits to participate, and there are no out of pocket costs for the participants.

Location: UMN outpatient research facility or videoconference

Visit Frequency: Decided collaboratively by the provider and participant, as normally occurs in clinical practice.

Side-Effects: Pharmacological therapies are associated with increased AEs compared to placebo.[7]

Non-steroidal anti-inflammatory drugs (NSAIDs) will be used as a first-line medication. Serious risks include cardiovascular events (heart attack, stroke, heart failure, high blood pressure), gastrointestinal bleeding, allergic reaction (hives, skin irritation, respiratory distress, edema), kidney failure, skin reactions, liver failure, and asthma attacks. Other side effects include stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting and dizziness.

Second-line medications include systemic corticosteroids, skeletal muscle relaxants, acetaminophen, benzodiazepines, antiseizure medications, lidocaine patches, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants for participants unable to tolerate or unresponsive to NSAIDs. Serious risks with these medications include allergic reaction, seizures, infection, hyperglycemia, bone fracture, liver or kidney damage, and addiction or abuse. Other risks include sedation, drowsiness, fatigue, sleep problems, headache, weight gain, muscle weakness, mental/physical impairment, dry mouth, abdominal pain, anorexia, nausea, vomiting, gastritis, occult bleeding, dizziness, vertigo, tremor, syncope, and leukopenia.

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. Participants will be asked about current medications at every treatment visit to assess potential 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.

Study providers will discuss risk/benefit profiles for specific medications with participants before making a shared decision on what medication to prescribe.

Providers: Medical care will be provided by a licensed medical provider with a minimum of 3 years of experience. Providers are required to have a DEA license.

Training: Providers will receive 4 hours of training in protocols for medical visit activities, common intervention elements, medication prescription (first vs second-line), documentation, and adverse events.

5.2. Handling of Study Interventions

5.2.1. Supported Self-Management (SSM) - Experimental Intervention

5.2.1.1. Required Interventions

The following are considered standard elements of the SSM intervention:

- Needs assessment and collaborative development of an individualized treatment plan. Includes review of BPS baseline measures, a brief physical examination that includes manual palpation and brief postural, strength, and mobility assessments; completion of a Wellbeing Wheel (based on risk factors and the BPS model) and self-evaluation of what it would take to engage in adaptive pain behaviors (COM-B Self-Evaluation Questionnaire V1). These will be re-assessed as needed. In addition, a "Self-Reliance Check In" will be completed at 6 weeks to initiate a conversation regarding release to self-care.

- Education will be provided through the communication of key evidence-based *information* about chronic pain, BRLP, BPS factors, and self-management to enhance patients' *knowledge.*[48]

- Skill training will be provided as indicated in strategies and exercises directed towards enhancing *physical, psychological, and social self-management skills.* This includes physical exercises (e.g. postural, strength, stabilization and mobility exercises);[20,31] psychological strategies (e.g. progressive muscle relaxation, relaxed breathing, guided imagery, pacing, relaxation, problem solving, and cognitive restructuring);[66,92,93] and social strategies, including pleasant activity planning with a social focus, and communication techniques for navigating relationships (e.g. work, family, friends) to garner support for self-sufficiency. Specific BCTs used as part of skill training include *instructions, demonstrations, practice and rehearsal, self-monitoring and graded progressions.*[55,56]

- Spinal manipulation therapies (SMT) are manual procedures applied by a practitioner to the lumbar and sacroiliac spinal regions. SMT has been shown to be effective in relieving symptoms and improving mobility.[20,31,102,103] SMT will be applied as a "bridge therapy" as indicated, to support patients' abilities to engage in the skill development described above.

  SMT will include soft-tissue work (e.g. cross-fiber stretch, light friction massage, etc.), mobilization (low velocity, low-high amplitude passive movements) and manipulation (high velocity, low amplitude thrust)

- Enablement (by addressing barriers and facilitators) will also be applied as indicated to improve patients' unhelpful beliefs about their capabilities to self-manage BRLP and overall wellbeing. Specific BCTs used as part of enablement include *emotional support provided by the provider, value-based goal setting, and problem solving.*[55,56]

- Persuasion will be used as needed to influence patients BRLP beliefs, optimism, and motivation which are important for the adaptation of healthy pain coping behaviors. The following BCTs will be integrated into the intervention: *verbal persuasion, focus on past successes, and framing/reframing.*[55,56]

- Resources and materials will be provided to support the patient and include a workbook and digital recordings (e.g. of the physical, psychological and social exercises and strategies described above).

5.2.1.2. Allowed Interventions

The following summarizes optional SSM elements (based on patient needs):
- 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
- Heat may be used to facilitate the delivery of SMT (up to 10 minutes)

5.2.1.3. Prohibited Intervention

SSM providers are prohibited from delivering:

- Education or exercise recommendations beyond the scope of the SSM intervention or what is described under concomitant interventions
- SMT to the neck, upper thoracic spine (above the sixth thoracic vertebrae), or extremity joints (e.g., hip joint)
- Instrument assisted SMT (e.g., activator)
- Passive modalities other than heat for facilitating SMT (e.g., TENS, ice)
- Recommendations to use mind-body practices not described in required or allowable SSM interventions (e.g. yoga, Tai Chi)
- Lumbar belts, strapping, taping, etc.
- Recommendation of bed rest

5.2.2. Medical Care (MC) - Comparison Intervention

5.2.2.1. Required Interventions

First or second-line medications for the management of chronic BRLP. Decisions regarding medication selection will be made collaboratively between the provider and patient after a discussion of risk/benefit profiles and preferences.

- First-line medications include nonsteroidal anti-inflammatory drugs (NSAIDs)
- Second-line medications include systemic corticosteroids, skeletal muscle relaxants, acetaminophen, benzodiazepines, antiseizure medications, lidocaine patches serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and weak opioids (e.g. Tramadol, Tylenol with Codeine) for participants unable to tolerate or unresponsive to first-line medications

5.2.2.2. Allowed Interventions

None

5.2.2.3. Prohibited Interventions

Medical providers are prohibited from recommending the following interventions:

- Medication(s) not listed as first- or second-line under required interventions
- 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)
- Education or exercise recommendations beyond what is described under concomitant interventions

- 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

5.3. Concomitant Interventions

5.3.1. Required Interventions

All participants will receive basic standardized information regarding the generally favorable prognosis of chronic BRLP. We will provide patients with an updated version of the Back in Action book[20] 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 brief summary of the general causes of chronic BRLP and reassurance that the majority of cases do not require specialty care.
- Emphasizes the patient's role in facilitating their own recovery by providing some general recommendations for symptom management (e.g. changing positions frequently).

5.3.2. Allowed Interventions

- Participants will be allowed to use OTC medications as needed during the course of the study.
- Participants will be allowed to continue self-care practices (e.g., heat, ice, stretching) for chronic BRLP they used prior to the study.
- Participants assigned to SSM who experience a significant worsening of chronic BRLP 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.[20]
    - Allowable 'rescue medications' will be identical to first- and second-line medications detailed in the medical care protocol. In addition, weak opioids (e.g. Tramadol) may be used in select cases. Decisions regarding 'rescue medication' selection will be made collaboratively between the provider and patient after a discussion of risk/benefit profiles and preferences.
- Treating clinicians, in consultation with the PIs, may refer for specialty care in the case of AEs or chronic BRLP complications that cannot be adequately managed with the assigned intervention (e.g., progressive neurological deficits).
- Participants will be encouraged to seek any required care for conditions unrelated to the study.

5.3.3. Prohibited Interventions

Participants will be asked to limit treatment to their assigned intervention for the length of the initial 12-week intervention period. However, participants retain the right to discontinue study treatment at any time. Providers will be taught to refrain from delivering interventions that fall outside the scope of the study protocols (see above).

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 6-10 visits being prescribed 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 is defined as:

- Attending 2 or more Medical Care sessions or 6 or more SSM sessions
  And
- Not dropping out of active treatment

5.5. Intervention Fidelity

We will apply robust fidelity activities based on our experience from previous studies to facilitate future intervention replication, internal validity, and accurate interpretation of outcomes.[96-98] This includes training and certification (described in section 5.1); use of standardized intervention checklists to guide clinicians through each session; and monthly group meetings with key investigators to receive ongoing coaching in intervention protocols.[99]

Fidelity assessments. All intervention visits will be video recorded with patient consent; a random selection of 10% will be reviewed for fidelity by study investigators. Standardized fidelity instruments will be used to document required, allowed, and prohibited intervention activities and elements. Individualized feedback will be provided to providers as needed based on fidelity assessments.[99,100] Additionally, standardized treatment clinical report forms will be reviewed for required, allowed, and prohibited interventions.

6. STUDY PROCEDURES

Participation in the pilot study is expected to last approximately 7 months (from initial screening to month 6 follow up assessment). Participants will be sent their final evaluation (a self-report survey) six months after randomization.

6.1. Schedule of Evaluations

(See next page)

Table 5. Pilot Study Data Collection Schedule

Assessment	Initial Screening	Baseline 1	Baseline 2/ Enrollment (Day 0)	Intervention Visits (Month 0-6)	Weekly Follow-Up (Week 1-26)	Monthly Follow-Up (Month 1-6)	Follow-Up (Month 2)	Follow-Up (Month 3)	Follow-Up (Month 6)
Informed Consent	x	x	x						
Demographics	x	x							
Clinical History	x	x							
Physical Exam		x							
Inclusion/Exclusion Criteria	x	x	x						
Quebec Task Force Classification		x							
STarTBack Screening Tool Status		x							
BRLP & LBP frequency & intensity		x	x		x				
Disability, PROMIS-29+2		x	x			x			
Productivity loss, Medication use, Healthcare use			x			x			
Social emotional support, Domain-specific life satisfaction, Perceived stress, Chronic pain acceptance, Chronic pain coping behaviors, Physical activity level, Self-efficacy, Fear-avoidance beliefs, Pain catastrophizing			x					x	x
Treatment expectations			x				x		
Overall satisfaction, Use of key SSM skills, and Global improvement								x	x
Patient-provider connection, healthcare environment							x	x	
Satisfaction with specific components of SBSM								x	
Treatment administered				x					
Adverse events*				x		x			
Qualitative Measures			x					x	
Study close out									x

*Participants can also report adverse events to the PI's or study staff at any point during the trial. **Qualitative data will also be collected from providers regarding their views of barriers and facilitators to care; additionally, as part of supplemental aims, qualitative data will be collected from other stakeholders not taking part in the pilot study to assess their views.

6.2. Description of Evaluations

6.2.1. Pilot Study Screening Evaluations

Consenting Procedures
Potential participants will consent at 4 different time points: a brief initial online screen, a phone screen with study staff, and at two baseline screening appointments.

Initial screening (Online/Phone)

- Interested individuals will be initially screened by a web-based screening portal. An overview of the study will be provided during the web-screen, and electronic consent secured prior to collecting preliminary information on eligibility (e.g. age, English literacy, BRLP severity)
- Following the web-based screening, potential participants will undergo a phone interview with study staff to confirm inclusion criteria (e.g. age, duration and severity of BRLP) and the lack of easily identifiable exclusion criteria (e.g. history of spinal fusion). Verbal consent to collect this information will be collected at the initiation of the phone interview.

Baseline Screening Appointments

- Potential participants will be given a hard or electronic consent form to review on their own that will describe the screening and study procedures at the first baseline screening appointment. See Section 11 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, research coordinator, or designee (i.e., research staff, an investigator) will review the consent form, section by section, one-on-one with each potential participant during the consent interview; participants will be invited to ask questions as they proceed through each section.
- Easy to understand, IRB pre-approved, electronic and print informational materials, including visual media, will be used to facilitate understanding.
- A signed and dated consent form will be obtained from each study candidate. All participants will be given a copy of the signed consent form for their personal records.
- Original signed paper consent forms will be secured in the respective participants research file at the UMN. Signed e-consent forms will be maintained in REDCap.
- 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.
- At the second baseline appointment, participants will confirm continued consent for the study prior to randomization.

Consent & Human Subjects 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 for additional information about the consent form. In addition,

staff will complete human subjects training in accordance with the UMN's human subjects and HIPAA 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 Rights 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 Procedures

Initial Screening (Online/Phone)

- Following consent, potential participants will be asked a series of self-report questions through an online portal to screen basic eligibility. Persons who meet basic inclusion criteria (e.g., age, BRLP 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).
- Baseline screening visits (In-person) will occur as soon as possible, but the first baseline screening visit must occur within 30 days of completing the phone screen; otherwise, the phone screen will be redone.

Baseline Screening Visit 1

- Written or electronic consent will be collected from participants prior to any screening procedures at this visit.
- Participants will complete study surveys to collect basic demographic information along with health history information to inform the detailed clinical evaluation and confirm eligibility. The surveys will include:
  - Demographics
  - Limited set of key patient-reported outcomes (see Table 5)
  - Past and ongoing BRLP treatment
  - Comorbid health conditions
    - Participants reporting current or past history of mental health disorders and related treatment will undergo additional screening if unmanaged major depression is suspected or reported. Scores of 3 or higher on the Patient Health Questionnaire-2 (PHQ-2)[147] will lead to additional screening for suicidality. A score of 2 or higher on question 12 from the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)[148] for suicidal ideation will warrant

exclusion and referral. Mental health resources will be provided to these participants (e.g. suicide hotlines, emergency services)
    - Participants reporting potential substance abuse (having 6 or more drinks on a weekly basis, using illegal drugs, or prescription medication for non-medical reasons) will undergo additional screening for potential substance abuse. Scores ≥ 20 on the 10-item Alcohol Use Disorders Identification Test (AUDIT) for alcohol149or ≥ 6 on the 10-item Drug Abuse Screening Test (DAST)150-152 are exclusionary and warrant referral. The AUDIT and DAST will be available to administer at any time if the clinician suspects a problem.
- A licensed healthcare provider (e.g., DC, PT, advanced practice nurse) will conduct a clinical history and a focused low back and lower extremity physical exam that will include posture assessment, orthopaedic and neurological tests (e.g. straight leg raise, lower extremity muscle strength, sensation, and reflexes), palpation, and vascular assessments. Current medications and vitals will also be collected.
- Women with reproductive potential will take a pregnancy test.
- Suspicion of declining cognitive function during medical history/clinical exam will lead to administration of the Mini-mental state examination. A score of 23 or below is exclusionary.[153]
- Eligible participants will complete baseline measures of self-reported study outcomes (see Table 5).

Baseline Screening Visit 2 (within 21 days of Baseline Screening Visit 1)

- Prior to the second baseline screening visit, investigators and study clinicians will review each case at weekly case review meetings for clinical eligibility determination. A review of inclusion and exclusion criteria based on the medical history, physical exam, and patient reported measures collected at the first baseline screening visit will be conducted for each participant. The review committee reaches consensus on every case and recommends exclusion, inclusion, or further evaluation to determine eligibility (e.g. diagnostic imaging).
- Potential participants who present with signs and symptoms suggestive of a specific cause of BRLP (e.g., nephrolithiasis, cauda equina), contraindication to study treatments, (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.
- Eligible participants will complete repeat assessments of key patient reported outcomes to confirm eligibility (i.e. BRLP intensity) and account for potential regression to the mean (See Table 5). Baseline measures of other self-reported study outcomes (clinical, behavioral, and mediating outcomes) will also be completed.
- In addition, participants will provide feedback on key study recruitment and screening procedures using open-ended survey questions.
- Confirmation of consent and randomization of eligible participants will occur at the second baseline screening visit.

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. 40-50 participants will be enrolled.

Baseline Assessments

Baseline measures will include demographic, occupational, clinical and behavioral characteristics, and mediating outcomes including the NIH Research Task Force's minimum dataset for chronic LBP.[111] The following will be collected at baseline:

- Demographics including PhenX ToolkKit's core measures for Social Determinants of Health[155]
- Quebec Task Force Classification for spinal disorders[95] and Pain Detect Questionnaire to identify neuropathic presentations of BRLP[156]
- STarT Back Screening tool[112]

Clinical Outcome Measures

- BRLP and LBP frequency over the past week (number of days with BRLP symptoms).
- BRLP and LBP intensity (0-10 pain scale) over the past week using the ordinal 11-box NRS (0=no BRLP/LBP, 10=the worst BRLP/LBP possible).
- Disability will be measured with the 23-item Roland Morris Disability Questionnaire which was adapted and validated for BRLP.[115]
- PROMIS-29 +2 includes measures of pain interference with normal activities, physical function, fatigue, sleep disturbance, anxiety, depression, and participation in social roles and activities.[116-118] The PROMIS-29+2 also provides a preference-based summary of health-related quality of life.[119] Other PROMIS/NIH Toolbox instruments will include social emotional support;[116,117] domain-specific life satisfaction (e.g. work, family, housing);[120] and perceived stress.[122]
- Productivity loss related to BRLP (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.[123]

Behavioral Outcomes

The following behavioral outcomes are chosen because they're most likely to affect the experimental intervention:

- Chronic pain coping behaviors will be measured using the Chronic Pain Coping Inventory - 2-item version.[128]
- Over-the-counter and prescription medication use[20] for BRLP, including class of medication and frequency of use.

- Healthcare use for BRLP including MRIs, injections, hospitalizations, surgeries, and provider-based visits.[20]
- Physical activity levels (e.g. amount of sedentary activity) measured with the International Physical Activity Questionnaire.[129]

Mediating Outcomes

Mediating outcomes and targets of the intervention theorized to affect the clinical and behavioral outcomes will also be collected to inform protocol refinement. These include:

- BRLP related capabilities (e.g. knowledge, skills, physical capacity), opportunities (e.g. available resources), motivations (e.g. optimism)[51-53] for participants enrolled into supported self-management.
- Beliefs related to self-efficacy as measured by confidence in ability to manage daily activities, symptoms, emotions, and social interactions (PROMIS self-efficacy for managing chronic conditions);[130] the chronic pain acceptance questionnaire will also be administered.[157]
- Fear-avoidance beliefs using the Fear-avoidance Beliefs Questionnaire [131]
- Catastrophizing measured using the 13-item Pain Catastrophizing Scale;[132] it uses a 5-item point scale (0=not at all, 4 all the time) and has internal consistency and validity.
- Expectations about back pain treatments (HEAL items).[135]

Qualitative measures

Qualitative measures will be collected from enrolled subjects, as well as providers regarding their views of barriers, facilitators, affordability, practicality, effectiveness, acceptability, and equity.

As part of the supplemental aims, qualitative information will be collected from other stakeholders with pain who are underrepresented in CIH LBP/BRLP research to explore their views of barriers and facilitators to care for LBP/BRLP.

Randomization

In the pilot study, randomization precedes intervention administration. Randomization will occur within 21 days of completing the first baseline screening visit. Participants who are not randomized within this time frame will repeat the in-person screening. Interventions will be initiated within 14 days of randomization/enrollment.

6.2.3. Blinding

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

- Study personnel involved in screening and enrollment will be masked to upcoming randomization assignments
- The statistician will be blinded to treatment group until the analysis is complete.

- Participants will be queried in self-report questionnaires as to whether or not anybody attempted to influence their responses.

Blinded Personnel: Select investigators and the study statistician will be blinded until the database is locked and the analysis is complete. The study's statistician will assign a member of his staff to create the random allocation tables according to the allocation plan, which will be administered using the randomization module in REDCap.

Unblinded Personnel: The study coordinator, clinicians, data manager, and investigators participating in fidelity assessment will not be blinded to study interventions.

Individuals authorized to break the blind: The PIs and their investigator designees are authorized to break the blind.

Circumstances for breaking the blind: This will occur when it is in the participants' safety-related interest. The primary example is a reportable adverse event.

6.2.4 Follow-up Visits

Intervention Visits (M0-M6)

The following information will be collected at each intervention visit in the pilot study, which will occur as needed throughout the six months, as there is no set schedule of treatments:

- Treatment administered – study providers will record treatment administered at each visit including required, allowed, and prohibited treatments.

- 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 (∓ 3 DAYS)

Weekly outcomes will be collected electronically via direct patient self-report for six months; 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.

Clinical Outcome Measures

- BRLP and LBP frequency and intensity

Monthly Follow-up (∓ 14 DAYS)

Monthly follow-up data (Months 1-6) 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 6 months (± 14 days):

Clinical Outcome Measures

- Disability, PROMIS-29+2 measures, and productivity loss
- Adverse Events - participants will be asked if they experienced any potential adverse events associated with study interventions (e.g. increased pain, neurological symptoms, nausea)

Behavioral Outcome Measures

- BRLP-related medication and healthcare use

Month 2 Follow-up (∓ 14 DAYS)

Mediating Outcome Measures

- Satisfaction related to the patient-provider connection and healthcare environment (HEAL items).[135] Treatment expectations for the assigned intervention will also be assessed.

Month 3 Follow-up (∓ 14 DAYS)

Clinical Outcome Measures

- PROMIS/NIH Toolbox measures for social emotional support, domain-specific life satisfaction, and perceived stress.
- Global improvement will be measured using a 9-point scale ranging from completely recovered to vastly worse.[154]

Behavioral Outcome Measures

- Chronic pain coping behaviors, physical activity levels

Mediating Outcome Measures

- BRLP related capabilities (e.g. knowledge, skills, physical capacity), opportunities (e.g. available resources), motivations (e.g. optimism) for participants enrolled in SSM [51-53]
- Beliefs regarding self-efficacy, fear avoidance, and treatment.
- Satisfaction related to the patient-provider connection, healthcare environment (HEAL items),[135] specific components of the SBSM intervention, and overall treatment[20]

Qualitative Measures

For the pilot study, qualitative data will be collected via open-ended questions in REDCap surveys, as well as semi-structured, audio-recorded interviews.[106] Patient and provider views of barriers, facilitators, affordability, practicality, effectiveness, acceptability, equity will be collected.

Month 6 Follow-Up & Final Close Out/Final Evaluation (-14 to +28 DAYS)

Clinical Outcome Measures

- PROMIS/NIH Toolbox measures for social emotional support, domain-specific life satisfaction, and perceived stress
- Global improvement

Behavioral Outcome Measures

- Chronic pain coping behaviors, physical activity levels

Mediating Outcome Measures

- Beliefs regarding self-efficacy and fear avoidance.
- Satisfaction related to the patient-provider connection, healthcare environment (HEAL items),[135] specific components of study interventions, and overall treatment[20]

Participant Close-out

- Final participation will be used to record participant status. Participants will receive notice of their participation being complete (via email or mail).

6.2.5. Compensation

There is no cost for participation in the study. Participants and their insurers will not be billed for study screening and treatment visits. Participants in the pilot study will be compensated a total of $150.00 for time associated with participating in the study, in the form of a UMN ClinCard. Participants are not compensated for attending screening and/or intervention study visits. ClinCards will be administered at an in-person study visit or via mail following enrollment in the study. The following compensation scheduled will be used:

80% of weekly surveys completed	$40.00
Month 1 follow-up completion	$10.00
Month 2 follow-up completion	$10.00
Month 3 follow-up completion	$40.00
Month 4 follow-up completion	$10.00

Month 5 follow-up completion	$10.00
Month 6 follow-up completion	$30.00

In addition, prescription and over-the-counter medications recommended for participants in the MC group will be paid for by the study. Study staff will load cards with funds for participants to pay for their study medications. ClinCards will be administered at an in-person study visit or via mail following enrollment in the study.

For the supplemental aims qualitative interviews, participants will be compensated $50.00 per interview.

7. SAFETY ASSESSMENTS

7.1. AEs and SAEs, Expectedness, and Relatedness- Definitions

The Co-PIs are responsible for adjudicating AEs/SAEs.

Adverse Event

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 two 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 intervention visits. Each unique occurrence will receive a separate ID in order to avoid duplication in documentation.

Serious Adverse Event

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 BRLP-specific serious events: death; severe or permanent disabilities; life-threatening conditions; hospitalizations; other important medical events; progressive neurological deficits, or cauda equina syndrome.

Expectedness:

AEs and SAEs will be classified as expected if

- They have been documented as a known adverse reaction (disclosed in the consent form) or are part of an existing comorbid disease process. The PI or designee is responsible for making this determination.

Relatedness to Research Participation:

AEs and SAEs will be classified as either unrelated, unlikely related, possibly related, probably related, or definitely related to participation in the research project. The PI or designee is responsible for making this determination. To assess relationship of an event to study intervention, the following guidelines are used:

Related (Possible, Probable, Definite)

- The event is known to occur with the study intervention.
- There is a temporal relationship between the intervention and event onset.
- The event abates when the intervention is discontinued.
- The event reappears upon a re-challenge with the intervention.

Not Related (Unlikely, Unrelated)

- There is no temporal relationship between the intervention and event onset.
- An alternate etiology has been established.

7.2 Adverse Event Identification

Adverse events will be identified in the following ways:

- Following enrollment, participants will be asked about the occurrence of AE/SAEs by their treatment provider at every visit.
- Participants will be informed to report AE/SAEs directly to study staff throughout the study period
- Participants will be asked if they experienced any AE/SAEs during their monthly self-report questionnaires.

7.3 Follow-up for Adverse Events

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.

AEs During the Intervention Phase

If an AE/SAE occurs during the intervention phase, the study clinician or designee will obtain information about the event, which will be used by the PI to assess the severity, expectedness and relatedness to the study. 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. Participants who cannot continue with the study intervention due to safety concerns will be removed from the intervention and/or study when warranted. See Study Discontinuation.

The rescue medication protocol may apply. See Rescue Medication.

AEs During the Monthly Follow-Up (M1-M6)

If an AE/SAE occurs during the follow-up phase, study staff (clinician, coordinator, PI or designee) will contact the participant (or their emergency contact with the participant's permission), to obtain information about the event, including but not limited to what happened, when the event occurred, and treatment rendered. This information will be used by the PI to assess the severity, expectedness and relatedness to the study.

Events will be followed for outcome information until resolution or stabilization. Resolution and stabilization will be determined by a PI with input from the study clinician when appropriate.

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.

7.4 Reporting Procedures

AEs/SAEs/Unanticipated problems will be reported to NCCIH and the UMN IRB. "Awareness" or "Aware" is defined as the date on which the research team is able to discuss the event with the participant (or their designee) to gather additional information about the event for adjudication. See AEs and SAEs, Expectedness, and Relatedness-Definitions for information related to how decisions will be made regarding determining relatedness and severity.

NCCIH

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 3 days of the investigator becoming aware of the event.

Other serious, unexpected AEs related to the intervention will be reported within 7 business days.

UPIRTSOs will be reported within 7 business days.

All other AEs documented during the course of the trial will be summarized and reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH.

UMN IRB
The UMN IRB will be notified via a Report of New Information (RNI) of *any harm* (e.g. AE or SAE) experienced by a participant or other individual that, in the opinion of the PI or designee, is *unexpected and at least probably related* to the research procedures within 5 business days of the study team becoming aware of the event.

Unexpected death: Unexpected death of a locally enrolled participant whether considered related to the research or not will be reported to the UMN IRB via a RNI within 5 business days of the study team being made aware of the event. Death is considered unexpected if the risk of death is not listed in the consent form.

If new information becomes available to the research team that suggests a new or increased risk to study participants, a safety issue or a reduction in benefit, this information will be reported to the UMN IRB via a RNI within 5 business days of the study team being made aware of the new information.

Effective March 27, 2017, submitting logs of events at continuing review is not required.

See Protocol Deviations for reporting information related to deviations and participant harm.

7.5. Known Expected Risks

Supported Biopsychosocial Self-Management
The risks associated with SSM are considered low for subjects who meet the inclusion/exclusion criteria. To further minimize risks, licensed doctors of chiropractic (DC) and physical therapists (PT) will be trained and certified by investigators, and monitored for fidelity to ensure they are implementing SSM in a manner that optimizes patient safety. Experienced investigators and consultants will be available as needed to assist DCs and PTs in managing adverse events if needed. The core elements of SSM include physical, psychological and social strategies.

Physical: Side effects associated with manual treatment and exercise are common and benign. Approximately 35% of participants in our previous BRLP trial reported expected self-limiting adverse events that were mild to moderate in severity (e.g. increased pain, soreness).[20]

Serious adverse events following manual treatment to the lower back are rare and are estimated to occur once per million to several million visits.

Psychological and social: Subjects may experience some short-lasting emotional discomfort during and outside the sessions when practicing the psychological and social exercises and strategies (e.g. of relaxed breathing, guided imagery, pacing, relaxation, pacing, problem solving, cognitive restructuring, interpersonal communication, etc.).

Expected risks include

- Cauda equina syndrome
- Disc herniation
- Emotional discomfort
- Exacerbation of low back pain/back related leg pain, soreness or stiffness in the region treated
- Fracture
- Hematomas or hemorrhagic cysts.[31, 146]

Medical Care

The risks associated vary depending on the medications prescribed. Choice of first and second-line medications for the study protocol was informed by the current evidence and the American College of Physicians guidelines on noninvasive treatment for LBP which balances evidence for risks and benefits when making recommendations. Licensed medical providers will care for participants randomized to medical care. Pharmacological therapies are associated with increased adverse events compared to placebo.[31] Study providers will discuss risk/benefit profiles for specific medications with participants before making a shared decision on what medication to prescribe.

Expected risks include:

- Non-steroidal anti-inflammatory drugs (First-Line Medications)
  - Serious risks include cardiovascular events (heart attack, stroke, heart failure, high blood pressure), gastrointestinal bleeding, allergic reaction (hives, skin irritation, respiratory distress, edema), kidney failure, skin reactions, liver failure, and asthma attacks.
  - Other side effects include stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting and dizziness.

- Second-line medications
  - Serious risks with these medications include allergic reaction, seizures, infection, hyperglycemia, bone fracture, liver or kidney damage, and addiction or abuse.
  - Other risks include sedation, drowsiness, fatigue, sleep problems, headache, weight gain, muscle weakness, mental/physical impairment, dry mouth, abdominal pain, anorexia, nausea, vomiting, gastritis, occult bleeding, dizziness, vertigo, tremor, syncope, and leukopenia.

Pilot study and supplemental aims qualitative data collection: there are few risks associated with this data collection. Risks include feeling uncomfortable answering certain questions; to minimize this, participants can decline responding to questions

7.6. Safety Monitoring

The Independent Monitoring Committee (IMC) for this study will review accruing data on a semi-annual basis to ensure:

1. The study is adequately enrolling to meet targeted goals
2. Data collection and protocol adherence rates are acceptable
3. There are no serious safety concerns

7.7. Potential Benefits

There may be no direct benefit to participants. Some participants may experience an improvement or resolution of their BRLP or associated signs and symptoms. Some participants may learn new ways to manage their BRLP on their own.

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 BRLP and was erroneously diagnosed during screening.
- New evidence emerges and suggests it is unsafe for the participant to proceed with the intervention.

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 BRLP 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 questionnaires and monthly questionnaires, if possible. Efforts will be made to accommodate participant compliance.

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 during the active intervention phase of the study.

Withdrawal Procedures
Participants will be asked to submit a letter or email in writing to the PI (signed and dated when possible) if they want to withdraw from the study. For reporting purposes, research staff will inquire about reasons for their withdrawal. Participants may also be asked if they're willing to complete self-report questionnaires as a means of collecting primary and secondary outcomes. If they refuse, participants will not be contacted by the study team. A formal letter will be sent by the PI, or designee, indicating receipt of their request for withdrawal and additional provisions around data collection, if applicable. The letter will reiterate our appreciation for their participation to date and remind participants that their withdrawal will not affect their relationship with the university. Further, regulatory bodies will be provided summary information related to attrition (e.g., losses to follow-up, withdrawals etc.). Individual participants will not be named.

Termination Procedures
This research may be discontinued at any time by the UMN IRB, the NIH, OHRP, UMN, or other government agencies as part of their duties to ensure research participants are protected.

9. STATISTICAL CONSIDERATIONS

9.1. General Design Issues

We will conduct a parallel, two-group randomized pilot study in preparation for a future phase II multi-site randomized clinical trial. A total of 40-50 participants with chronic back-related leg pain (BRLP) will be randomly assigned to either 12 weeks of: 1) Supported Self-Management (SSM) or 2) Medical Care. The pilot study will assess the feasibility of key methods and procedures to be used in the larger randomized trial. The aims of the pilot study are to:

1. To conduct a Planning Phase to develop detailed protocols and procedures, train project personnel, and secure necessary oversight approvals.
2. To assess future trial feasibility through achievement of pre-specified targets for:

a. Recruiting and enrolling individuals with chronic BRLP by assessing recruitment rates; enrollment rates; and screened participants' views and perspectives
b. Delivering experimental and comparison interventions by assessing acceptability and adherence; provider intervention fidelity rates; and participant and provider views
c. Data collection by assessing follow up rates of future clinical trial outcome measures

9.2. Sample Size

The sample size for this pilot study has been informed by previous pilot studies by the investigators, who have found approximately 15-20 participants per group sufficient for informing the feasibility of larger, randomized clinical trials. The feasibility of recruitment, enrollment, intervention acceptability and credibility, participant adherence, provider fidelity, and data collection activities will be assessed using designated feasibility measures and targets. Protocol refinement measures will be collected using qualitative and quantitative methods to identify areas for modification in the future trial. Because of the relatively small number of providers needed for a pilot study, and budget restrictions, we will also engage our consultants and The Clinician Advisory Panel to provide input to the development and subsequent revisions of the intervention and training protocols.

9.3. Treatment Assignment Procedures

Enrolled subjects will be randomized using blocked randomization (with varying block sizes) following stratification for back-related leg pain classification (QTF classification 2, 3, or 4).[95] Computer generated random treatment assignments will be generated by an independent study statistician and conveyed electronically through REDCap (the electronic study database) at the time of enrollment to preserve allocation concealment. Screening clinicians and study staff will be blinded to upcoming treatment assignments.

9.4. Outcomes

9.4.1. Primary Outcomes

Primary outcomes for the pilot study are feasibility measures for the larger randomized trial including:

- Recruitment feasibility - Number of participants screened per month; percentage of screened participants who are female; percentage of screened participants who are minorities; participant views and perspectives on research participation
- Enrollment feasibility - Number of participants enrolled per month; percentage of enrolled participants who are female; percentage of enrolled participants who are minorities; participant views and perspectives on research participation
- Intervention acceptability and credibility feasibility - Percentage of enrollees not receiving any treatment; percentage of enrollees receiving prohibited treatments during the 12-week intervention phase (contamination); percentage of enrollees satisfied with treatment

- Participant treatment adherence feasibility - Percentage of enrollees attending required sessions; percentage of enrollees in the supported biopsychosocial self-management group reporting participation in home practice; percentage of enrollees in medical care group reporting taking medications as prescribed
- Provider fidelity feasibility - Percentage of provider visits where 100% of required intervention activities were delivered
- Data collection feasibility - Percentage of enrollees completing the month 3 assessment; percentage of enrollees completing the month 6 assessment; percentage of weekly pain severity and frequency assessments completed

Table 6. Feasibility Measures & Targets	
Recruitment	≥40 screened/month (50% women, 25% minorities)
Enrollment	≥8 enrolled/month (50% women, 25% minorities)
Intervention acceptability, credibility	≤10% never receive any treatment; ≤10% receive prohibited treatments during 12-week intervention phase (contamination) ≥80% satisfied with treatment
Participant adherence	≥80% participants attend required sessions (SSM=4; MC=2) ≥70% of SSM participants report participation in home practices ≥70% of MC participants report taking medications as prescribed
Provider fidelity	Providers deliver 100% of required intervention activities on ≥70% of visits
Data collection	≥85% of participants complete 12 weeks follow up ≥80% of participants complete 25-week follow up ≥80% of weekly pain severity and frequency surveys completed

9.4.2. Secondary Outcomes

Secondary outcomes for the pilot study are protocol refinement measures for the larger randomized trial including:

- Recruitment protocol refinement - Percentage of participants screened per month by recruitment method; percentage of screened participants who are female by recruitment method; percentage of screened participants who are minorities by recruitment method
- Enrollment protocol refinement - Percentage of participants excluded by eligibility criterion; percentage of participants declining participation; main reasons for declined participation; average time to enrollment from initial screening
- Intervention protocol refinement - Percentage of enrollees withdrawing from treatment; reasons for withdrawal from treatment; Enrollee and provider views of intervention including affordability, practicality, effectiveness, acceptability, and equity; percentage of required intervention activities not performed by provider; frequency of required intervention activities not performed by provider with reasons; provider beliefs

regarding back-related leg pain (also assessed pre and post-training in intervention protocols)
- Data collection protocol refinement - Percentage of missing variables by data collection instrument; reasons for missed assessments; average duration of assessments

9.4.3. Qualitative Data

Qualitative information will provide important context and understanding to facilitate refinement for the future trial. These include: enrollee and provider views of intervention including affordability, practicality, effectiveness, acceptability, and equity; percentage of required intervention activities not performed by provider; frequency of required intervention activities not performed by provider with reasons; provider beliefs regarding back-related leg pain (also assessed pre and post-training in intervention protocols).

As part of the supplemental aims we will also seek qualitative information from other stakeholders who are traditionally underrepresented in CIH LBP/BRLP research, regarding their views.

Table 7 Protocol Refinement Measures (Examples)	
Recruitment	-% screened/month per recruitment method; -% women and minorities screened/month per recruitment method
Enrollment	-% excluded by criterion -% declining participation, reasons -average time to enroll
Intervention acceptability, credibility	-% dropouts from intervention, reasons -Patient and provider views of barriers, facilitators, affordability, practicality, effectiveness, acceptability, equity*
Provider fidelity	-% of required intervention activities per session not performed, reasons - provider BRLP beliefs (pre-/post training)**
Data collection	- % of missing variables -reasons for missed assessments -average duration of assessments
***Collected via qualitative data collection (open-ended survey questions, interviews and focus groups) ****Collected via survey pre-/post-training**	

9.5. Data Analyses

Feasibility outcomes (Aims 2a-2c) will be assessed using a combination of descriptive statistics and qualitative analyses (described under Protocol refinement measures). For AIM 2a, we will determine the mean number of participants screened/month and enrolled/month in addition to the percentage of women and minorities screened and enrolled. For AIM 2b, we will report the percentage of enrolled participants compliant with treatment protocols by group (visit attendance, home practice, contamination) and

percentage of treatment visits delivered according to protocol (provider fidelity). For AIM 2c, percentage of outcome assessments completed at 12 weeks and 6 months will be described, in addition to the percentage of weekly pain severity and frequency assessments completed.

Protocol refinement measures will be analyzed and presented descriptively in a similar fashion as described above. Qualitative data (collected via open-ended questions in REDCap surveys, and transcribed interviews), will be analyzed using template style qualitative content analysis informed by the conceptual framework for the study (see Figure 2).[89,106,137-139] by study team members with qualitative research experience.[21,89,90,136] Representative quotations will be identified during the coding process, and coded themes will be quantified by categorizing them as present or absent for each case, and presented as frequencies.[139]

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. Phone-based screening data, in-person, and virtual video/teleconference screening data will be entered directly into the study REDCap database by research staff to confirm study eligibility. A procedure/visit case report form will be filled out by research staff for every study-related visit and electronically entered directly into the study REDCap database. Electronic web-based surveys will be sent to study participants as indicated in section 6, with computer-assisted telephone interviewing or mailed surveys used as a back-up in cases where follow-up may be challenging.

10.2. Data Management

The Principal Investigators, Data Manager and Project Director are responsible for ensuring the accuracy, completeness and timeliness of study data. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

10.2.1. Data security and storage

CRFs for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported

systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password. Electronic communication with outside collaborators will involve only non-identifiable information and investigators will be blinded to group assignment until after the analysis by the study statistician is complete.

Electronic source documents will be stored on password protected computers issued by the University of Minnesota. University-issued computers are supported and maintained by the UMN Academic Health Center-Information system. Participant ID numbers will be used to protect participants' confidentiality. All paper source documents (e.g. combined signed consent forms & HIPAA forms) will be stored in a locked file cabinet, in a locked office at the University of Minnesota maintained by the Project Director and her designees.

10.3. Quality Assurance and Control

10.3.1. Quality Assurance

The primary method of data collection for participant self-reported outcomes will be direct electronic entry through a survey interface with REDCap. Logic rules specifying the type and range of acceptable responses will be programmed into REDCap. Participants will receive an error message if they enter an invalid response.

10.3.2. Training

Training for study staff responsible for data collection will be conducted prior to study recruitment. Certification by the principal investigator (or designee) requires adherence to standard operating procedures for data collection outlined in the study protocol. Staff will be required to demonstrate proficiency in key data management steps (screening, randomization, data entry, documentation of AEs, data management protocol compliance, etc.).

10.3.3. Quality Control Committee

The Study Steering Committee will review reports on data capture and quality on a monthly basis. Missing data reporting and other customized reports will be developed in order to facilitate efficient workflow and high-quality data capture. CRF-specific follow-up rates will be tabulated on a nightly basis and reviewed during the weekly check-in meetings between the PIs and study staff.

10.3.4. Metrics

For each 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. Survey completion rates will be primarily based upon the completion of pain and functional outcome measures, but we will additionally tabulate follow-up by each instrument to monitor and evaluate survey burden. Data on other key feasibility measures and targets will also be reviewed weekly

by the PIs and monthly by the Study Steering Committee (e.g. recruitment rates, enrollment rates, intervention acceptability, credibility, and adherence, provider fidelity, adverse event reporting).

Loss to Follow-Up: Participants are considered loss to follow-up if any of the criteria below are met:

1. Participant dies
2. Participant formally withdraws from the study
3. Participant misses 3 consecutive monthly and 8 consecutive weekly surveys without responding to reminders by email (at least 3) or phone (at least 3).

Participant's meeting criteria 3 can have their loss to follow up status removed if they contact the study and request continuation of data collection activities.

10.3.5. Protocol Deviations

A protocol deviation occurs when activities on this study diverge from the UMN IRB approved protocol. Examples include divergence(s), that

- Reduce the quality or completeness of the data,
- Make the Informed Consent Form inaccurate, or
- Impacts a subject's safety, rights, or welfare.

Protocol deviations include, but are not limited to the following:

- Failure to keep IRB approval up to date
- Outcome assessment and/or measurement not performed
- Implementing protocol modifications without obtaining prospective IRB approval;
- Conducting research during a lapse in IRB approval;
- Enrolling more subjects than what's approved in the protocol;
- Performing research procedures outside the protocol specified window;
- Failure on the part of any individual involved in research review or oversight to abide by applicable laws or regulations, or the University of Minnesota IRB policies.
- Randomization of an ineligible participant; not-adhering to inclusion/exclusion criteria;
- Failure to obtain Informed Consent or altering from the informed consent process as described in the IRB approved protocol;
- Obtaining consent using an outdated consent form;
- Performing non-exempt human subject research without obtaining prospective University IRB approval;
- Failure to report an SAE
- Wrong intervention administered to a participant

Protocol deviations will be logged by research staff in REDCap. Details regarding the protocol deviation including whether it resulted in an adverse event will be included in the log. Reports on protocol deviations will be reviewed by the PIs and study team on a regular basis. Corrective action plans will be implemented when relevant. Study operating

procedures will be modified as necessary based on review of protocol deviation summaries.

Protocol deviations that result in harm to a research participant will be reported to the UMN IRB via a RNI within 5 business days of the study team being made aware of the harm and/or deviation.

10.3.6. Monitoring

Automated queries will be used to assess protocol deviations (e.g. missing evaluations or evaluations performed outside of allowed timeframe, non- compliance with assigned interventions). In addition, 100% of enrolled participants' records will be reviewed to ensure proper recording of screening data, informed consent documentation, and treatment fidelity. The PIs and the Study Steering Committee will review findings from the monitoring reports and other measures of trial progress and quality on a monthly basis.

Table 8: Monitoring Schedule

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Steering Committee
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Steering Committee
	Semi-annually	Independent Monitor(s)
Findings from ongoing quality assurance and quality control procedures	Monthly	PI, Steering Committee
	Semi-annually	Independent Monitor(s)
Adherence data regarding study visits and intervention	Monthly	PI, Steering Committee
	Semi-annually	Independent Monitor(s)
AEs and rates	Monthly	PI, Steering Committee
	Semi-annually	Independent Monitor(s)
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor (s) NIH/NCCIH, IRB
SAEs (expected or unrelated)	Per Occurrence	PI, Steering Committee
	Per Policy	Independent Monitor (s), NIH/NCCIH, IRB
Unanticipated Problems	Per occurrence	PI, Steering Committee
	Per Policy	Independent Monitor (s), NIH/NCCIH, IRB

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1. Institutional Review Board (IRB) Review

This protocol, informed consent document, participant facing CRFs and any subsequent modifications will be reviewed and approved by the UMN IRB

11.2 Informed Consent Forms

This study will use the combined HIPAA Authorization / Consent document (UMN HRP-593).

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

Participants will be given an electronic or hard 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, privacy and confidentiality, research-related injury, and disclosure of new information regarding participation. Contact information for the PIs and study coordinator will also be provided.

Research staff will meet one-on-one with the participant in a private space 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. Persons under 18 years old are not eligible.

A signed consent form will be obtained from each participant. All participants will receive a copy of the signed form for their personal records. Original signed consent forms will be secured in the participant's research file. E-consent forms will be secured in the participant's research file in REDCap.

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 co-Principal Investigators and submitted to the IRB of record for approval.

11.3 Participant Confidentiality

Procedures are in place for maintaining the confidentiality of all information collected. All staff receive HIPAA and data safety training as well as intensive orientation on the confidentiality of the research record and maintaining the security of clinical information. Data are managed by study number and analyzed anonymously. Electronic data will be housed on password protected, HIPAA compliant databases stored on secure servers also operated by the UMN Academic Health Center-Information System (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the

backups stored in accordance with the AHC-IS. All hard copy study files will be stored in locked filing cabinets located in secured, access restricted offices. Identifiable information will be accessible to study related personnel who have met the UMN's training requirements for the Responsible Conduct of Research, HIPAA and data security.

All published reports will be summary in nature and no individual participants will be identified.

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.

11.4. Study Discontinuation

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

12. COMMITTEES

Leadership team: Dr. Brent Leininger will serve as the contact PI and Dr. Gert Bronfort will serve as a Co-PI; together they will provide oversight to the entire project and development and implementation of all policies, procedures, and processes. Additional details can be found in the Multiple PI Leadership Plan. The PIs will meet weekly to collaborate on the overall planning, administration, implementation, management, and oversight of the study.

Study steering committee: The steering committee is comprised of the PIs, the Co-Is, and the Project Coordinator. They will convene to review and monitor study activities (see Project Timeline) including regulatory approvals, protocol and operations development, recruitment, enrollment, intervention implementation and fidelity, data collection, and reporting. Other study staff will be invited as needed to participate.

Clinic team: The clinic team is comprised of one of the PIs (Leininger), the Project Coordinator, and the Co-I Evans and Greco; they will coordinate training, clinic resources and staff, and fidelity monitoring. The Clinic Team will also convene meetings between study clinicians and Co-Is Greco and Evans to review and discuss the SSM intervention implementation.

Data Team: The data team is comprised of at least one of the PIs, the Statistician, and Co-I Schulz; they will coordinate data management and collection activities, including required reports.

Clinician Advisory Team: In the Planning Phase, we will assemble a group of physical therapists and chiropractors to take part on a Clinician Advisory Team. The role of this group will be to provide review of study protocols, procedures, and materials, particularly related to the Biopsychosocial Supported Self-Management Intervention.

13. STUDY TIMELINE

Planning phase. This project has a 6 month planning phase during which time the study team will develop and obtain the necessary regulatory approvals for the protocol, the Study Accrual and Retention Plan (SARP), Data Safety and Monitoring Plan (DSMP) if required, and case report forms (CRFs). Qualitative data collection will also be conducted with physical therapists (PT) and doctors of chiropractic (DCs) to inform development and refinement of the supported self-management (SSM) intervention. Qualitative data will also be collected from community members to provide feedback on patient-facing materials. Training of providers will also take place prior to commencing the pilot study clinical phase.

Clinical phase. This pilot study will take place over the course of one year (last 6 months of year 1, and first 6 months of year 2). We project enrolling 40-50 participants over a 6 month period.

Data collection & analyses. Data collection will begin from the first screening, through the 6 month follow up (quarter 3 of year 2). Data preparation and analyses will take place in the final 2 quarters of year 2.

Table 9. Project Timeline

	Year One				Year Two			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Planning								
IRB Approval	X							
Protocol, SARP, DSMP, CRF Approval	X	X						
MOP Development		X	X					
Training		X	X					
Qualitative data collection and analyses (Providers, patient representatives, other stakeholders)	X	X	X	X	X	X	X	
Clinical								
Recruitment			X	X	X			
Screening & Enrollment				X	X			
Intervention Application				X	X	X		
Fidelity Monitoring				X	X	X		
Data Collection & Analysis (Pilot Study & Supplemental Aims)								
Data Collection			X	X	X	X	X	
Data Preparation & Analysis							X	X
Dissemination								X
Preparation of proposal for phase II trial								X

Enrollment of First Subject

First enrolled subject anticipated in the last quarter of Year 1.

14. PUBLICATION OF RESEARCH FINDINGS & FUTURE RESEARCH

Individual participant results (e.g, pre and post results) will not be shared with participants.

Future Research. After establishing feasibility (Table 6), we will use refinement data (Table 7) to further optimize study methods. This work will lead to a phase II multi-site randomized trial with team members from the University of Pittsburgh, to determine the short and long-term relative effectiveness of supported biopsychosocial self-management compared to medical care for BRLP.

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