Strategies To Assist with Management of Pain (STAMP) Study

FINAL PROTOCOL

Final (funding agency-approved) protocol changes: April 12, 2023
Final institutional review board approval: October 31, 2023

ClinicalTrials.gov ID: NCT03115359

MAIN TITLE: STRATEGIES TO ASSIST WITH MANAGEMENT OF PAIN (STAMP)

PCORI-APPROVED PROTOCOL TITLE: A COMPARATIVE EFFECTIVENESS RANDOMIZED CONTROLLED TRIAL OF MINDFULNESS MEDITATION VERSUS COGNITIVE BEHAVIORAL THERAPY FOR OPIOID-TREATED CHRONIC LOW BACK PAIN

Dual Principal Investigators: Aleksandra Zgierska, MD, PhD and Bruce Barrett, MD, PhD

PROTOCOL VERSION and AMENDMENTS

Protocol Version	Date	Change Initiated (Initials)	Brief description of protocol modification/actions requested, if any
Template V6	9/6/16	TNK	Input from IRB, OCT, MARCH, IND/IDE services, PIs
CLBPprotocol_V1-1	12/9/16	CAB	Initial protocol draft
CLBPprotocol_V1-2	2/9/17	TNK	First review of protocol draft
CLBPprotocol_V1-3	2/15/17	CAB	Initial protocol revision
CLBPprotocol_V1-4	2/20/17	AZ	Initial protocol revision
CLBPprotocol_V1-5	2/24/17	CAB	Initial protocol revision
CLBPprotocol_V1-6	2/26/17	AZ	Initial protocol revision
CLBPprotocol_V1-7	3/1/17	CAB	Initial protocol revision
CLBPprotocol_V1-8	3/3/17	TNK	Initial protocol revision
CLBPprotocol_V1-9	3/3/17	CAB	Initial protocol revision
CLBPprotocol_V1-10	3/5/17	AZ	Initial protocol revision
CLBPprotocol_V1-10	3/5/17	RRE	Initial protocol revision
CLBPprotocol_V1-10	3/5/17	EG	Initial protocol revision
CLBPprotocol_V1-11	3/9/17	CAB	Initial protocol revision
CLBPprotocol_V1-12	3/9/17	AZ	Initial protocol revision
CLBPprotocol_V1-13	3/10/17	CAB	Initial protocol revision
CLBPprotocol_V1-14	3/10/17	AZ	Initial protocol revision
CLBPprotocol_V1-15	3/15/17	CAB	Initial protocol revision
CLBPprotocol_V1-16	3/15/17	AZ	Initial protocol revision
CLBPprotocol_V1-17	3/16/17	CAB	Initial protocol revision
CLBPprotocol_V1-17	3/17/17	AZ	Initial protocol revision
CLBPprotocol_V1-18	4/28/17	CAB, AZ	Initial protocol revision based on the IRB pre-review comments
CLBPprotocol_V2-00	5/31/17	CAB, AZ	Initial protocol revision based on the IRB comments
CLBPprotocol_V3-00	6/17/17	CAB	Change of protocol revision, including adding recruitment sites
CLBPprotocol_V4-00	7/13/17	CAB, AZ	Change of protocol revision, including change to SLC additional optional testing
CLBPprotocol_V5-00	7/28/17	CAB	Change of protocol revision, relating to EHR data
CLBPprotocol_V6-00	11/16/17	CAB	Change of protocol revision, related to recruitment emails
CLBPprotocol_V7-00	11/28/17	CAB	Change of protocol revision, related to allowing flexibility for contact attempts for data collection
CLBPprotocol_V8-00	2/16/18	CAB	Change of protocol revision, related to the $100 for perfect intervention attendance; updated recruitment strategy.

CLBPprotocol_V9-00	4/20/18	CAB	Change of protocol revision, related to elimination of the data collection portion of the monthly check-in; and clarification of exclusion criteria.
CLBPprotocol_V10-00	5/10/18	CAB	Clarification of change V9-00 per IRB Reviewer request
CLBPprotocol_V11-00	5/18/18	CAB	Expansion of recruitment/enrollment window; page 31.
CLBPprotocol_V12-00	6/28/18	CAB	Expanding screening options to include in-person screening.
CLBPprotocol_V13-00	9/21/18	CAB	Change to eligibility criteria re: morphine-equivalent dose (MED), Elizabeth Jacobs was removed as a key personnel (she is now a consultant), and other minor changes for clarification.
CLBPprotocol_V14-00	12/7/18	CAB	Update to allow viewing of patient lists at clinics regarding upcoming medical appointments, to aid in study recruitment; and to allow additional participant check-ins as needed for engagement purposes.
CLBPprotocol_V15-00	6/11/19	CAB	Update to allow up to 4 additional mailings of recruitment materials to potential participants; addition of a reminder letter; other minor changes for clarification.
CLBPprotocol_V16-00	5/7/20	CAB	Update to allow tele-health delivery of our group study interventions when in-person delivery is not a feasible option; added Hershey site key personnel.
CLBPprotocol_V17-00	5/27/20	CAB	Update to minimization of risk section per IRB request.
CLBPprotocol_V18-00	10/1/20	CAB	Update to expand “in-person” to “virtual or in-person” study options.
CLBPprotocol_V18-01	10/9/20	CAB	Update to describe virtual consent process for virtual participants, per IRB recommendation.
CLBPprotocol_V19-00	1/29/21	CAB	Update to recruitment methods.
CLBPprotocol_V19-01	2/19/21	CAB	Clarification of update to recruitment methods.
CLBPprotocol_V20-00	3/7/22	CAB	Clarification of withdrawal reasons.
CLBPprotocol_V21-00	7/26/23	CAB	Update to statistical methods section 8.2, submitted to PCORI on March 20, approved in April 2023.

PROTOCOL SIGNATURE PAGE

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drug or device and the conduct of the study.

I will use the informed consent form approved by the SPONSOR and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 7 of this protocol.

I further agree that the SPONSOR has access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including study drug or device) provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol guidelines, as well as local regulations; and to accept respective revisions conducted by authorized personnel of SPONSOR and by regulatory authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Aleksandra Zgierska, MD, PhD Study-wide and Hershey Site Principal Investigator		3-6-17
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Robert Edwards, PhD Boston Site's Principal Investigator		3-8-17
Eric Garland, PhD, LCSW Salt Lake City Site's Principal Investigator		3-8-17

STATEMENT OF COMPLIANCE

The research will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the PCORI Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

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Study-wide and Madison Site Principal Investigator Robert Edwards, PhD		3-8-17
Boston Site's Principal Investigator Eric Garland, PhD, LCSW		3-8-17
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Study Product:	Mindfulness Meditation group intervention; Cognitive Behavioral Therapy group intervention
PCORI Protocol Number:	OPD-1601-33860
UW Project ID Number:	AAB7469
UW IRB Number:	TBD

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List of Abbreviations

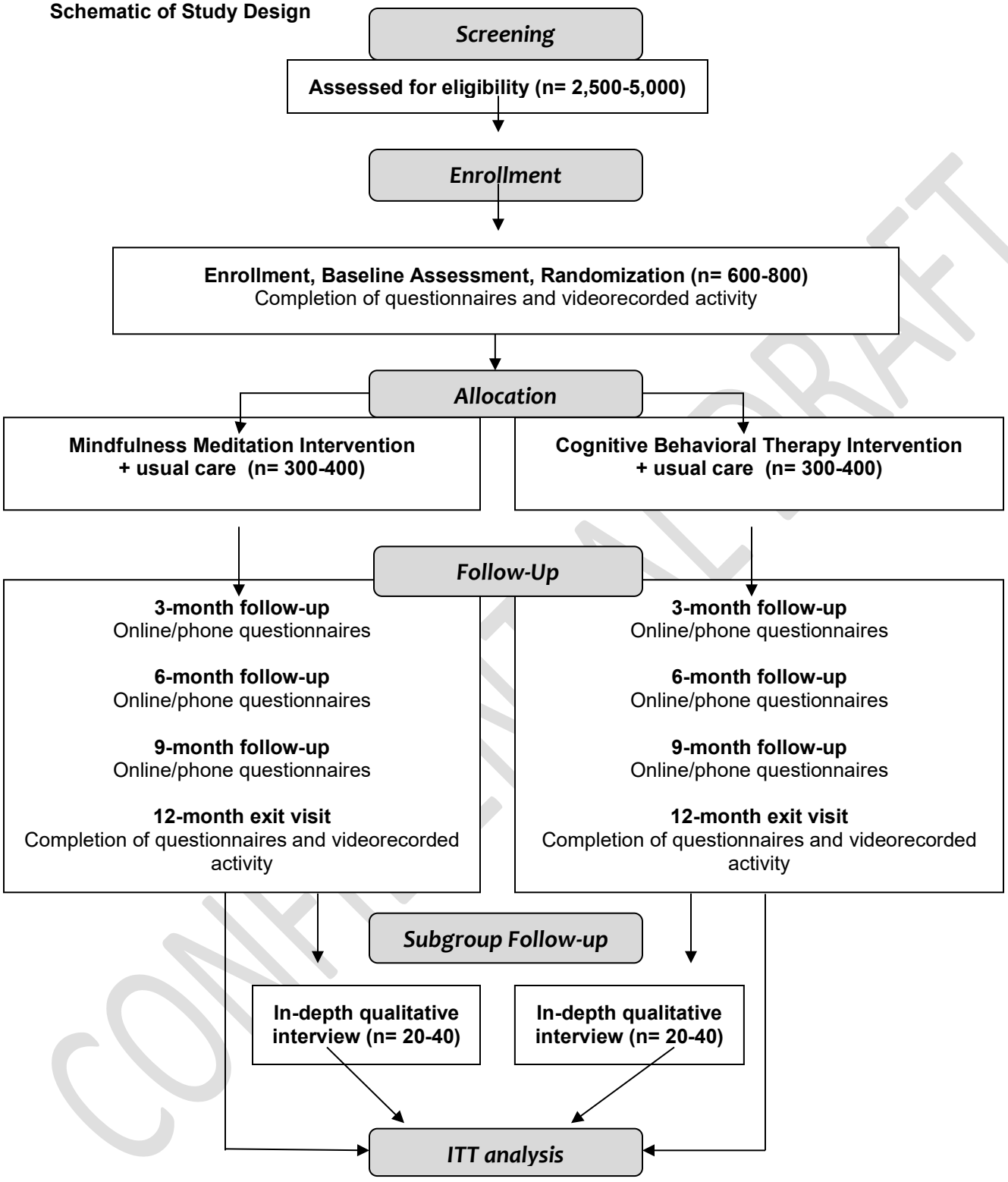
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BPI	Brief Pain Inventory
CARDS	Community Advisors on Research Design and Strategies
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal regulations
CLBP	Chronic Low Back Pain
COMMS	Current Opioid Misuse Measure
CPAQ	Chronic Pain Assessment Questionnaire
CRF	Case Report Form
DCC	Data Coordinating Center
DFMCH	Department of Family Medicine and Community Health
DHHS	Department of Health and Human Services
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration
GIC	Global Impression of Change
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
ICTR	Institute of Clinical and Translational Research
IOM	Institute of Medicine
IRB	Investigational Review Board
ITT	Intention To Treat
MAAS	Mindful Attention Awareness Scale
MBSR	Mindfulness-Based Stress Reduction
MD	Mean Difference
MIC	Minimal Important Change
MM	Mindfulness Meditation
MOO	Manual of Operations
MOP	Manual of Procedures
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NIH	National Institute of Health
NRS	Numerical Rating Scale
OCC	Opioid Compliance Checklist
ODI	Oswestry Disability Index
OHRP	Office for Human Research Protections
PCORI	Patient-Centered Outcomes Research Institute
PCS	Pain Catastrophizing Scale
PFA	Patient/Family Advisor
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcomes
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life

RCT	Randomized Controlled Trial
SAC	Stakeholder Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Side Effects
SF-12	Medical Outcomes Study 12-Item Short Form
SOWS	Short Opioid Withdrawal Scale
SSH	Secure Shell
TLFB	Timeline Followback
TUG	Timed Up and Go
UP	Unanticipated Problems
UW	University of Wisconsin
VAS	Visual Analog Scale
WINRS	Wisconsin Network for Research Support

Study Summary

Official (Research Protocol) Title	A comparative effectiveness randomized controlled trial of mindfulness meditation versus cognitive behavioral therapy for opioid-treated chronic low back pain.
Short Title and Précis	Mind-Body Therapies for Back Pain. This study will compare the effectiveness of two interventions: Mindfulness Meditation and Cognitive Behavioral Therapy for improving outcomes (pain, function, quality of life, daily opioid dose) in adults with opioid-treated chronic low back pain over a 12 month follow-up period.
Protocol Number	PCORI# OPD-1601-33860 UW Project ID# AAB7469 UW IRB# TBD
ClinicalTrials.gov number and link	TBD; TBD
Methodology	Randomized controlled trial
Study Duration	5 years
Study Center(s)	The study will include the following sites: Madison, WI (led by University of Wisconsin-Madison): UW Health, Access Community Health Centers, UnityPoint Health - Meriter, SSM Health, Group Health Cooperative; Boston, MA (led by Harvard University, Brigham and Women's Hospital): Partners Healthcare; Salt Lake City, UT (led by University of Utah): University of Utah Healthcare Primary Care Clinics
Objectives	Main goal: To compare the effectiveness of Mindfulness Meditation (MM) and standard-of-care Cognitive Behavioral Therapy (CBT) for improving outcomes in adults with opioid-treated chronic low back pain. Aim 1: To compare the effectiveness of MM to CBT for reducing pain and increasing function over a 12 month follow-up period. Aim 2: To compare the effectiveness of MM to CBT for improving quality of life and reducing daily opioid dose over a 12 month follow-up period. Aim 3: To examine if participant baseline characteristics impact treatment response to MM or CBT.
Number of Participants	Up to 800 participants
Diagnosis	Opioid-treated chronic low back pain
Main Inclusion Criteria	Moderate to severe chronic low back pain treated with ≥ 15 mg/day of morphine-equivalent opioid dose for ≥ 3 months; age 21+
Main Exclusion Criteria	Prior formal MM or CBT training; inability to safely or reliably participate; current pregnancy; pre-existing borderline personality, delusional or bipolar (manic) disorders ("active" in the prior 12 months). Competent adults, meeting eligibility criteria, will be able to participate regardless of gender, race, ethnicity, religion or socioeconomic status. Prisoners, pregnant women and mentally impaired persons will not be included. Children, per eligibility criteria, are not eligible.
Study Interventions	Two behavioral therapies: Mindfulness Meditation and Cognitive Behavioral Therapy, delivered in addition to "usual care"
Intervention Duration	Both MM and CBT interventions will consist of 8 weekly two-hour therapist-led group-therapy sessions (total 16 hours); in addition, participants will be asked to engage in home practice of either MM or CBT techniques for at least 30 minutes/day, 6 days/week during the 12-month study.
Statistical Methodology	Primary outcome analysis: Intention-to-treat analysis in the framework of linear mixed effects to examine the comparative effectiveness of treatment on the change in pain severity, function (Aim 1) and quality of life scores and opioid dose (Aim 2) over 12-months between the two groups. Qualitative analysis for qualitative data.

Schematic of Study Design



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2 Background and Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with Department of Health and Human Services (DHHS) regulations, 45 CFR 46, the PCORI Terms of Award, applicable government regulations, and Institutional policies and procedures.

2.1 Background and Rationale

Opioid-treated chronic low back pain (CLBP) has a substantial impact on US society
Chronic non-cancer pain is a leading cause of disability and reduced quality of life in the US, affecting over 100 million Americans and costing nearly $600 billion annually.[1] Existing therapies for chronic pain are suboptimal.[1,2] As a result, 5-8 million patients with chronic pain are treated with opioids and CLBP is the top chronic non-cancer condition for which opioids are prescribed.[3] There are very limited data on the long-term efficacy of opioids, and much concern about their harms, which are *dose-dependent* and include worsened mental health, addiction and overdose death.[4,5] Many opioid-treated patients continue to have inadequate pain relief, and impaired function and quality of life; comorbidities include depression, anxiety and opioid misuse, the severity of which has been linked to worse treatment response in chronic pain.[3,4,6,7] With this complex interplay between CLBP, opioids, co-existing mental health problems, and their effects on outcomes, treatment strategies must address each of these factors. However, there is little research on how to effectively improve outcomes and reduce opioid use; the Institute of Medicine (IOM),[1] the NIH[8] and the PCORI[9] call for studies to identify effective safe strategies for chronic pain care and opioid use reduction.

Mindfulness Meditation (MM) is a popular mind-body modality that is widely used for improving health and well-being[10] and may be an effective alternative treatment for CLBP.[11,12] Some studies suggest that MM-induced gains can be sustained over time.[13,14] MM offers unique skills for acceptance-based pain coping that are different from those taught by cognitive behavioral therapy (CBT), which is the current "gold standard" of traditional psychological approaches for chronic pain.

As supported by the existing evidence, including data from our pilot RCT, MM has the potential to address both chronic pain and its comorbidities, depression, anxiety, and opioid misuse, and to help patients reduce their reliance on opioids.[10,15-17] Even modest dose reduction would be beneficial to patients, decreasing the harms associated with opioid therapy.[5] Research is needed to evaluate the effectiveness of MM for pain severity, function and quality of life, and opioid use, as compared to a suitable alternative treatment such as CBT. We have chosen these outcomes because they are endorsed by our stakeholders and are very patient-centered. We have designed this study to help inform decision-making by patients with opioid-treated CLBP and their clinicians as they consider choosing between MM and CBT; the proposed work will also provide data on the effectiveness of each approach for those with comorbid anxiety, depression and opioid misuse. The proposed mixed methods, pragmatic RCT will compare the effectiveness of MM and CBT over 12 months in up to 800 adults with opioid-treated CLBP. We hypothesize that MM, relative to CBT, will improve patient-centered outcomes: pain and function (Aim 1), quality of life and opioid use (Aim 2), especially in those with anxiety, depression or opioid misuse, factors that can impact treatment response (Aim 3).

2.2 Hypotheses

Our objective is to compare the effectiveness of MM to standard-of-care CBT, adjunctive to "usual care," for improving outcomes in patients with opioid-treated CLBP. We will follow participants over 12 months and compare quantitative (survey, opioid dose, functional test data) and qualitative outcomes that matter to patients and their families in up to 800 adults randomized (1:1 ratio) to the MM or CBT group, controlling for relevant factors.

Hypothesis 1: Participants in the MM group will report a greater reduction in pain severity and a greater increase in function at 6 and 12 months compared to participants in the CBT group.

Hypothesis 2: Participants in the MM group will report a greater improvement in Quality of Life (QoL) and a greater decrease in daily opioid dose at 6 and 12 months compared to participants in the CBT group.

Hypothesis 3: Among those with increased baseline symptom severity of negative affect (depression, anxiety) and opioid misuse behaviors, MM will be more beneficial than CBT for reducing pain, increasing function, improving quality of life, and reducing daily opioid dose.

2.3 Study Interventions

CBT, a traditional, standard-of-care behavioral therapy for chronic pain, attempts to teach patients to change unhealthy illness-related thoughts, emotions and behaviors so that they can develop more adaptive skills for coping with pain and related issues (Fig. 1).[18-23] It draws upon a range of strategies and is typically tailored to the specific condition; as such, it is usually delivered in separate specialty settings, e.g., pain medicine, mental health or substance abuse programs, in the group or individual therapy format.[18-23] This study intervention will be delivered in a group format.

MM training encourages *enhanced awareness* of present-moment experiences (bodily sensations, thoughts, emotions).[24] An intentional non-judgmental awareness and acceptance of one's state of body and mind, without becoming preoccupied by it, promotes *change in the relationship to this experience,*[24] without trying to change the experience itself (Fig. 1). MM fosters an ability to disentangle a given experience (e.g., pain) from associated bodily sensations, emotions and thoughts;[25] this, in turn, is thought to improve emotion regulation, adaptive response to stressors, and a decrease in suffering.[26] MM practice can be a foundation for engagement in life from a place of *"being with," rather than changing*, one's experiences, an important distinction from traditional CBT that may make MM a more effective pain-coping strategy for patients with CLBP.[27] This study intervention will be delivered in a group format.

Fig.1. MM and CBT offer different skills for the management of chronic pain.

2.4 Summary of Relevant Clinical Data

The results from our pilot RCT (N=35) suggest that MM is acceptable, feasible and can improve outcomes in patients with high-impact opioid-treated CLBP,[17] documenting the need for a large pragmatic study of MM in this population. At baseline, participants (80% female; 51.8 ± 9.7 years old) reported substantial daily pain (5.8±1.4 points on a 0-10 scale), disability (66.7±11.4 on a 0-100 scale) and treatment with a high daily opioid dose (148.3±129.2 morphine-equivalent mg/day), confirming subpar results of usual care. By 26 weeks, using *intention-to-treat* repeated measures analysis, the MM group (N=21) lowered pain severity ratings by 1.0 point ([95%CI: 0.2, 1.9]; p=0.045; large effect size, d=0.86; *Fig.3*) and decreased pain sensitivity to thermal stimuli (p=0.008), compared to a wait-list control (N=14). The largest gains (p<0.05) were in MM participants who engaged in "higher-dose" practice, suggesting a dose-response relationship. The MM group participants, relative to controls, also improved function by 6.5 points ([95%CI: -1.0, 14.0]; p=0.21, medium effect size, d=0.68), achieving the minimal important change (MIC) for both pain[28,29] and function.[28-30] The MM group reported reduction in opioid dose by an average of 10 morphine-equivalent mg/day relative to controls (p=0.82). Patients and clinicians enthusiastically received this study, completing enrollment within 10 weeks. During the study, the MM group reported, on average, 164±122 min/week of formal and 104±112 min/week of brief informal MM practice.[16,17] Seventeen MM participants evaluated the intervention, indicating satisfaction, and rating it, using a 0-10 scale, as "important" (8.0±1.8) and "useful" for pain coping (7.2±2.4), and stating they were likely to continue formal (8.1±2.8) and informal (9.4±1.0) practices; the themes identified by qualitative evaluations noted MM as useful for improving pain care and opioid use reduction.[16]

Evidence on MM's efficacy in CLBP, especially in opioid-treated patients, is promising yet limited and inconclusive, presenting a critical knowledge gap, as noted by the Agency for Healthcare Research and Quality (AHRQ),[10] NIH,[31] PCORI's Stakeholders[32] and systematic reviews.[11,12,33] Assessment of MM for pain has been prioritized by the IOM in the 2nd quartile of its "top 100" comparative effectiveness research topics.[34] The AHRQ's meta-analysis[10] supports MM's efficacy for pain in general (*medium effect* size, Cohen's d=0.33 [95% Confidence Interval, CI: 0.03, 0.62]), while noting the limitations of existing studies, such as inadequate longer-term follow-up and an absence of studies in opioid-treated pain. Two more recent trials by our team assessed MM for *opioid-treated* chronic pain.[15,17] Garland et al. (N=115)[15] found that MM, compared to an educational intervention, reduced pain severity (*medium effect size*, d=0.5; p=0.038) by 1 point on a 0-10 scale, and decreased pain interference (*medium effect size*, d=0.78; p=0.003)

and the desire for opioids (*medium effect size*, d= 0.5; p=0.027) at 3 months; however, opioid dose was not assessed. **The PI's pilot RCT (N=35)[17] suggested efficacy of MM in opioid-treated CLBP** for reducing pain ratings (*large effect size*, d=0.86; p=0.045) and hyperalgesia (p=0.008) at 6 months, as compared to a wait-list control. Although function appeared to improve as well, this change was not statistically significant (*medium effect size*, d=0.68; p=0.21) in this small trial. The change in opioid dose was also non-significant yet encouraging, with participants in the MM group reducing dose by an average of 300 morphine-equivalent mg/month relative to controls (p=0.84).[17] The pilot study participants were satisfied with MM and its effects, viewing it as useful for pain care and opioid use reduction.

Although CBT is considered standard-of-care for chronic pain, evidence supports only modest benefit of CBT for CLBP and its long-term effects have not been well studied, especially in opioid-treated groups.[18-20,35,36] A systematic review of behavioral therapies for CLBP[18] noted low quality evidence favoring CBT over no-treatment for short-term pain relief (*small effect size*; pooled weighted mean difference, MD from -7.0 [95%CI: -12.3,-1.7] to -12.7 [95%CI: -20.3,-5.1]) and, to an even lesser extent, for function (MD -2.9 [95%CI:-7.2, 1.4]). The Cochrane Collaboration's meta-analysis[19] found CBT to be better than usual care for short-term pain relief (*small effect size*; MD -5.2 [95%CI: -9.8,-0.6] on a 0-100 visual analog scale), but **not** for longer-term pain relief or function, which was consistent with a second systematic review.[20] The impact of CBT on opioid use in chronic pain is unclear due to a lack of high-quality research on this topic.[18-20,35]

MM and CBT may produce different gains depending on patient's individual characteristics. An RCT[37] of 143 patients with rheumatoid arthritis showed that both MM and CBT improved pain, function and negative affect outcomes. However, those with a history of depression benefitted more from MM than CBT in terms of improved pain coping, and reduced pain catastrophizing and negative affect (p<0.05).[38] The authors hypothesized that MM training, focused on observing and accepting the experience, helped meditators become more adept at detecting subtle early cues, allowing them to start regulating responses to pain or stress *before* emotions become too intense.[37,39] CBT on the other hand involves a cognitive reappraisal, which is usually deployed *after* the emotions have intensified; the usefulness of this cognitive strategy is often compromised when the intensity of negative emotions is high.[40,41] It is possible that individuals with chronic pain and co-occurring anxiety, depression and/or opioid misuse, all conditions common in chronic pain and characterized by high-level of negative affect and emotion dysregulation, may respond better to MM than CBT. Evaluation of treatment response in relation to these factors is essential because chronic pain patients with comorbid anxiety, depression or opioid misuse are the very patients who have been found to be less responsive to existing therapies.[42-44] Determining the individual patient phenotype most responsive to particular therapy would help guide clinical decision-making about optimal treatment choice.

New evidence-based therapies are urgently needed for opioid-treated CLBP, and stakeholders are interested in MM. In preparation for this study, we solicited input from the vital stakeholders – patients with opioid-treated CLBP. Seventeen patient-participants in our pilot study[16,17] expressed strong dissatisfaction with existing therapy options and were very interested in MM as a therapy for managing their pain, improving function and quality of life, and helping reduce opioid needs. The high patient interest in MM was also reflected in rapid recruitment into our pilot.[16,17] Other important local stakeholders, including clinicians and health system leaders, have also seen the need and importance of MM as a treatment option. Since our pilot RCT, clinicians have continued to inquire about referring patients for MM, and leaders of local health systems have shown enthusiasm for MM as a therapy for opioid-treated patients.

This research has the potential to improve healthcare and outcomes in patients with opioid-treated CLBP. The proposed RCT will be the first to directly address the effectiveness of MM compared to CBT in opioid-treated CLBP, delivered in addition to "usual care". The study goals and the chosen interventions are very relevant to the affected patients, their clinicians and health systems. Outcomes favoring MM would help establish it as standard-of-care and provide the rationale to increase its availability to patients, thus, improving outcomes in opioid-treated CLBP. Offering clinicians effective, safe options for CLBP, such as MM, would help reduce clinician burden related to the management of opioid therapy, as described by Co-Investigator Jamison[45] and noted by clinician-partners advising on this project. The mission of health systems is to deliver evidence-based care and improve health of their patients; this mission could be advanced by offering MM, if proven effective.

2.5 Potential Risks and Benefits to Participants

2.5.1 Known Potential Risks

The proposed interventions are not anticipated to lead to serious side effects or adverse events, as based on the existing literature[10,19,20] and our prior studies.[17,46-48]

Minor, immediate risks associated with this study may include:

- Mild, usually short-lived psychological distress associated with difficult emotions or thoughts that may come up during the behavioral interventions.
- Physical distress while staying in one position for a longer period of time.
- Discomfort while answering sensitive survey questions about medications, mental health, pain or disability.
- Risk of loss of confidentiality including legal, insurance, and/or employment issues.

There are no anticipated long-range risks or reproductive risks.

While the risks associated with this study's interventions are minimal, our study team realizes that opioid-treated CLBP patients are generally at increased risk for pain worsening, mental health problems, and substance use disorders; while these issues may occur independently of study participation, we are aware that participants may experience these issues during the study, and we are committed to helping participants minimize these issues as detailed in 2.5.2.

The value of the information to be gained from this research far outweighs the minimal possible risks associated with study participation. The proposed research may be beneficial to the community and society-at-large if mindfulness meditation proves an effective therapy for CLBP, a common, debilitating and expensive condition with a high local, national, and global burden, and for which existing strategies are unsatisfactory. Information gained could potentially lead to the acceptance of MM as a 'standard of care,' thus increasing access to these interventions for patients, benefitting patient, community, and society.

Site-specific, Optional, Additional Tests

Madison Site: Mindful Attention (Breath Counting) Test (Madison, WI)

There are no known risks specifically associated with the breath counting test.

Boston Site: Pain Sensitivity and Modulation (QST) Test

There is a slight chance of mild transient bruising and discomfort associated with use of the probes or algometer. In our experience, this is quite rare (< 5 % of cases). There are no known risks associated with hand immersion in cold water, with the participant explicitly instructed to remove the hand and stop the task when it becomes painful.

Salt Lake City Site: Emotion Regulation and Cue-Reactivity (ERCR) Test

There is a slight chance that the ER and CR tasks may result in mild distress. In our experience, this is quite rare (< 5% of cases). It is very unlikely that such distress will exceed that which would occur on an everyday basis, given that the images used in the proposed study are similar to scenes present in participants' natural environments.

2.5.2 Protection Against Risks

The investigators have taken multiple steps, tested in prior trials, to protect participants against potential risks of participation in a clinical trial of behavioral interventions.

In order to reduce the risk of psychological, emotional, and physical distress due to the study participation, we will make every effort to make our participants comfortable during all study procedures. Participants will be informed that they can choose not to perform any tasks or answer any question at any time, in the event that certain questions or assessment tasks cause emotional, psychological, or physical discomfort. Participants will also be encouraged to discuss any potential concerns with the research team members.

In order to minimize the risk of psychological and/or physical risks that patients with opioid-treated CLBP are more likely to experience, this study will utilize a robust safety protocol. All study personnel will be trained in this protocol.

All In-person study assessment and intervention sessions will be held at a clinical or research facility, where access to the phone will be readily available. The study interventions will be delivered in a clinical or research facility by a trained therapist with at least one other research staff member or clinician present or readily available and access to the phone readily available. When remote participation in the study activities (e.g., intervention sessions, assessment visits) is needed, the virtual delivery will take place via an approved, secure, HIPAA-compliant platform (e.g., WebEx, HIPAA-compliant Zoom, etc.) or by phone. During the in-person videorecorded activity (at baseline and exit), a researcher will walk alongside the participant for assistance; this will minimize the risk of falls. As pain flares are common in this population, participants will be encouraged to implement the study-taught techniques for pain coping and consult their regular physician, if needed, for additional pain care.

Drs. Bruce Barrett, Nalini Sehgal (Madison, WI); Edgar Ross, Edward Michna (Boston, MA); Aleksandra Zgierska, Robert Lennon (Hershey, PA) are physicians; Dr. Linda Oakley (Madison, WI) is a Nurse Practitioner; Drs. Robert Edwards, Robert Jamison, (Boston, MA), and Eric Garland (Salt Lake City, UT) are clinicians practicing in the fields of mental health. All the above Investigators are experienced in the management of issues related to the treatment of CLBP and mental health problems including acute suicidality. In addition, Dr. Julie Fritz (Salt Lake City, UT) and Evan Nelson (Madison, WI) have expertise in physiotherapy for CLBP. Together, the above Investigators as well as the study therapists and other designated study clinicians will be able to address any medical or mental health issues that may arise. A designated 'on call' study physician will always be readily available via cell phone or pager for study-related questions or problems; a designated ‘on call’ mental health specialist will be able to address mental health related issues, including acute suicidality. A study clinician will always be consulted if the Safety Protocol is initiated (see Appendix). The Safety Protocol has been successfully utilized in the PI's prior studies. The data safety monitoring committee (DSMC) and the IRB will be timely notified in the case of a serious adverse event.

The therapists delivering the study interventions will have a background in psychology, counseling or social work, thus well-equipped to address any potential psychological discomfort in relation to the interventions. In case of worrisome symptoms observed during the intervention sessions or assessment sessions, regardless of their mode of delivery (ie, in person, by phone, or via online platforms), the therapist or a research staff will discuss the concerns individually with the symptomatic participant, follow the Safety Protocol procedures, and contact the designated study clinician for consultation as needed if concerns persist for further assessment and directions (see Section 2.5.2 for details). Depending on clinical assessment, participants will be cleared to stay home or go home (by themselves, with family members/friends or via study-provided cab) or referred to the appropriate Emergency Department (ED). Participants who are sent home will be encouraged to contact their regular providers for evaluation, if needed, and receive a follow-up phone call the following day. Information on the resources available for counseling or other services to help with anxiety, distress, or feelings of sadness will be provided as a part of the Safety Protocol; these referred services will be paid for by the participant/participant’s health plan. In case of emergency, the therapist or research staff will call 911, and the participant’s emergency contact person will be notified (this procedure will be outlined in the consent/HIPAA form). Study staff will have emergency contact information available for all participants participating in a meeting.

The additional, optional, site-specific tests will be completed for in-person study visits only. Although they are considered overall safe, should unforeseen problems occur, the main study’s Safety Protocol procedures will be implemented, and the study’s on-call clinician will be contacted to assess the participant. In addition, in the Salt Lake City study site, where Emotion Regulation and Cue-Reactivity (ERCR) test will be implemented, to monitor for potential risk of emotional distress, participants will be asked to rate their negative mood on a 5-point numeric rating scale (1= none, 5= extreme) before and after the ER and CR tasks, and then again at the end of the assessment session. In the unlikely event that participants report distress resulting from the task as determined by an elevation in negative mood by 2 points from baseline levels at the end of the assessment, the research staff performing the test will be trained by the PI (a licensed clinical social worker and clinician with over 12 years of experience) to debrief participants, assess risk, and provide 15 minutes of progressive muscle relaxation to ensure subjects have experienced a reduction in negative mood to a level of within 2 points of their baseline level. In three RCTs with opioid-treated chronic pain patients, Dr. Garland used the risk management strategy, and no participants remained distressed after this procedure. Should the distress level persist though, or unforeseen problems occur, the main study’s Safety Protocol procedures will be implemented, and the Utah PI (a licensed clinical social worker with 12 years of clinical experience) or the study’s on-call clinician will be contacted to assess the participant.

All efforts will be made to protect participant privacy and confidentiality:

- The initial screening, informed consent process and all in-person data collection will be conducted in private settings.
- During the intervention sessions, participants will be able to use their first names or nicknames, and be asked to keep the information shared by others confidential.
- During virtual study sessions, participants will be recommended to engage in the session in a private location, with headphones/earbuds if possible, and to turn off other devices as to protect confidentiality.
- During virtual study sessions, the study staff present for the sessions will engage in the session in a private location, with headphones/earbuds, and will turn off other devices as to protect confidentiality.
- During virtual study sessions, the videorecorded activity will be recorded using the institutionally-approved HIPAA-compliant virtual platform; after the session, it will be transferred to and stored at the secure UW servers.
- During the intervention sessions, the therapist and the research staff will moderate the session to ensure that only study participants are present for both virtual and in-person sessions.
- Collection of sensitive information about participants is limited to the amount necessary to achieve the aims of the research.
- All of the data related to study participation will be kept confidential; data will be coded with a unique code for each participant and stripped of identifiers prior to being viewed by Investigators.
- Electronic outcome data will be managed using the secure REDCap database.
- Experienced EHR data analyst will help link the EHR data on prescribed opioids to other outcome data in a way that does not compromise participant confidentiality, using a study ID number for all data linkages.
- A master list with identifiers will be kept in a separate secure database/separate locked filing cabinet, by the Site PI or Site Manager at the site's research office.
- Identifying information will not be recorded on any outcome measures/data.
- All patient identifying data will be destroyed after the trial is completed, per IRB guidance.
- All computerized data will be password-protected and personnel will be restricted to viewing only data appropriate to their role in the project; all study personnel will receive the training required by the IRB.
- Outcome data will NOT become a part of the participant medical record; all data will be collected for research purposes only.

2.5.3 Potential Benefits to Participants

Participants may experience added benefit should a given study intervention have a positive effect on their CLBP-related outcomes. All study participants can benefit from the additional safety and support net provided by the study, which may facilitate stepped-up care, if needed, more quickly than 'usual care' alone.

3 Study Objectives and Purpose

Our objective is to compare the effectiveness of MM to standard-of-care CBT for improving outcomes over a 12-month follow-up period in patients with opioid-treated CLBP.

- **Primary Objective**: To compare the effectiveness of MM to CBT, delivered in addition to "usual care," for reducing pain and increasing function (primary outcomes) in adults with opioid-treated CLBP.

- **Secondary Objective**: To compare the effectiveness of MM to CBT, delivered in addition to "usual care," for improving quality of life (QoL) and reducing daily opioid dose (secondary outcomes) in adults with opioid-treated CLBP.

- **Tertiary Objective**: To examine if participant baseline characteristics impact treatment response to MM or CBT.

4 Study Design and Endpoints

4.1 General Design

We will conduct a 5-year multi-center RCT (up to 800 participants), comparing the effectiveness of MM and CBT, delivered in addition to "usual care," for improving patient-centered outcomes in adults with opioid-treated CLBP.

Participants will be recruited by three main study sites: University of Wisconsin-Madison, Harvard University, Brigham and Women's Hospital, and University of Utah. Each participant will be followed-up for a period of 12 months. They will be randomly (1:1 ratio) assigned to MM or CBT arms; participants will receive an 8-week MM or CBT intervention, and asked to practice MM or CBT, respectively, at home daily during the entire study.

Outcome data will be collected twice virtually or in person at baseline and at exit assessment visits, and three times "remotely" (online or by phone) at 3, 6, and 9 months post-intervention start date. A subset of participants will be invited to a by-phone in-depth qualitative interview at the end of the study.

Table 1: Timeline of Study Activities, Contact and Data Collected for Individual Participants During the 12-month Study

Recruitment & screening	Enrollment, Baseline Assessment, Randomization	Study Intervention	Follow-up Assessments at 3, 6 and 9 months	Exit Assessment at 12 months post-entry
▪Recruitment, eligibility screen (by phone or in person)	▪Informed consent; ▪All survey-based data (virtually or in person) ▪Brief videorecorded activity (virtually or in person) ▪Randomization ▪EHR (selected participatnts): prescribed opioids (researcher collected)	▪MM/CBT course (virtually or in person; 8 weeks, 2 hours/week); ▪MM/CBT practice (at home; entire study, 30 min/day, 6 days/week)	▪Survey-based data (online/phone): outcome, adherence, safety data at 3, 6, and 9 months other survey data at 6 months only	▪All survey-based data (virtually or in person); ▪Brief videorecorded activity (virtually or in person); ▪EHR (selected participants): prescribed opioids (researcher collected) ▪**Subgroup**: in-depth interview (by phone)

4.1.1 Primary Study Endpoints

Outcome measures are described in Section 9.2.2

- **Pain intensity** will be assessed using the 0-10 point *Numerical Rating Scale* (NRS) from the Brief Pain Inventory (BPI).[49,50]

- **Physical function** will be measured using the validated *Oswestry Disability Index* (ODI);[51,52] in addition, we will use 7 pain interference items from the BPI.[49,50,53]

4.1.2 Secondary Study Endpoints

- **Quality of life** will be assessed using the validated *Medical Outcomes Study Short Form Health Survey* (SF-12 v.2),[54,55] a common measure of health and QoL in CLBP.[56]

- **Daily dose of prescription opioids** for "the past 14 days" will be collected with the *Timeline Followback* (TLFB) method,[57-59] and verified against a participant's EHR data on prescribed opioids. This will enable longitudinal evaluation of opioid dose change during the proposed 52 week follow-up. To calculate a "daily opioid dose," doses of all reported opioids will be converted to a morphine-equivalent dose by multiplying daily dose of a given opioid by the published conversion factors, as we pilot-tested.[60]

5 Study Participants – Enrollment and Withdrawal

We will enroll English-speaking adults with opioid-treated CLBP who are diverse in terms of gender, race, ethnicity, and mental and physical health conditions. Our sample will include participants enrolled by three sites: Madison, WI, Boston, MA, and Salt Lake City, UT.

We conservatively estimate the need to screen approximately 4,000 individuals to enroll up to 800 participants within the first 4 years, assuming the attrition rate not to exceed 20%.

5.1 Participant Population

Our sample will include participants who are patients with opioid-treated chronic low back pain, and enrolled by one of the three study sites: Madison, Wisconsin, Boston, Massachusetts, and Salt Lake City, Utah. Eligible participants will be English-speaking adults ≥ 21 years old with opioid-treated CLBP who are diverse in terms of gender, race, ethnicity, and mental and physical health conditions.

5.2 Inclusion Criteria

Inclusion Criteria (based on self-report)
1. English-speaking
2. ≥ 21 years old
3. Diagnosis of chronic low back pain (defined as a pain in lumbosacral region or sciatica for ≥3 months) as the main pain source
4. Average daily pain score ≥3 on a 0-10 numerical rating scale (question from the Brief Pain Inventory)
5. Treatment with ≥15 mg/day of morphine-equivalent dose for ≥3 months
6. Report at least moderate CLBP-related disability (≥21 score on the Oswestry Disability Index) [52]
7. Capable of giving informed consent
8. Willing to complete all study activities

Rationale: CLBP is the leading chronic non-cancer pain for which opioids are prescribed. Age 21 years old defines an adult per the NIH guidelines, and treatment with long-term opioids for CLBP is uncommon in those younger than 21 years.[61] Because pain severity and function are the main outcomes, we will enroll those reporting at least moderate pain/disability. We will enroll patients treated with ≥15 mg/day of morphine-equivalent dose because: a) This dose range will enable evaluation of dose change (including any potential increases) across the spectrum of daily opioid dose categories. This is important, as the risk associated with opioid therapy is dose dependent. Even those in a lower daily dose category of 20-49 mg/day have a 44% increase in the risk of overdose compared to those treated with a daily opioid dose of less than 20 mg/day (Hazard Ratio 1.44; 95% CI: 0.57–3.62).[62] In addition, the group of patients treated with lower daily opioid doses may have the best chance for tapering off opioids completely, should other treatments (e.g., MM) prove effective. The enrollment of patients treated with a broad spectrum of daily opioid doses will facilitate evaluation of the study intervention effects on opioid use/dose over time, especially in the proposed subgroups of participants as those treated with a lower daily opioid dose are more likely to have lower negative affect and opioid misuse scores compared to those treated with higher daily opioid doses.

5.3 Exclusion Criteria

We will exclude those with specific mental health disorders, described in the exclusion criteria, and other conditions or circumstances that may pose concerns for safety or reliable participation. We will not exclude on the basis of common mental health (anxiety, depression) or substance use disorders, because they are prevalent in this population and can affect outcomes (Aim 3 hypothesis). We will not exclude based on anxiety, depression or substance use disorders, as these conditions are common and can impact treatment success in opioid-treated CLBP,[4] or based on a socio-economic status, gender, race or ethnicity.

Additional Exclusion Criteria for Optional, Additional Tests

Madison Site: Mindful Attention (Breath Counting) Test (Madison, WI): None

Boston Site: Pain Sensitivity and Modulation (QST) Test (Boston, MA)

1) Raynaud's syndrome in the hands
2) Hemophilia or other clotting disorders (may increase the risk of bruising)

Salt Lake City Site: Emotion Regulation and Cue-Reactivity (ERCR) Test: None

Exclusion Criteria (based on self-report)
1. Prior formal Mindfulness Meditation or Cognitive Behavioral Therapy training
2. Current pregnancy

3. Diagnosed with borderline personality, delusional, or bipolar (mania) disorders ("active" in the prior 12 months)
4. Inability to safely or reliably participate in the study

5.4 Participant Screening for Recruitment

5.4.1 Participant Identification

Participants will be identified using several mechanisms tested in previous studies[26,40,65,66]:

Recruitment activities in Madison will include Access Community Health Centers (ACHC), SSM Health, Group Health Cooperative (GHC) of South Central Wisconsin, UnityPoint Health - Meriter, and UW Health; in Boston, they will include Brigham and Women's Hospital/Harvard Medical School health system; and in Salt Lake City, they will include University of Utah health system. The recruitment plan includes (1.) direct referral by clinicians, involving for example clinicians identifying potential subjects and providing them with contact information for the study team, securely sharing of the referred patient's name and contact information with the research team after the patient signs a permission form, which will then be securely faxed to the study team; (2.) self-referral by patients (including contacting the study team's via study-designated phone number or email) via study information posted in clinics, community centers, and other locations, via media including television, radio, the web, online streaming services, and others; and through the "word of mouth"; (3.) research coordinators working with participating clinics' clinical staff to identify study-eligible patients among those receiving care at the clinic and scheduled for an appointment. Once a potentially eligible patient is identified, they will be provided study information (such as the study brochure) by the clinic staff and encouraged to contact research coordinator to find out more about the study; should the patient indicate interest during the appointment and not object to it, the research coordinator will then contact the patient after their appointment (e.g., in person at the clinic; by phone) to assess interest in study participation, and if the patient is interested and agreeable, to proceed with the screening process; (4.) identification of potential participants through referral from other studies. Once a potentially eligible participant is referred, they will be contacted and, if interested, provided the study information, and offered an opportunity to be screened for eligibility; and (5.) identification of potential participants through electronic health record (EHR) data extraction. The EHR database search will be conducted using a protocolized data search algorithm, which will search for adult patients with chronic low back pain, treated with chronic opioids. This data search will generate a list of potential participants including the patient's name, gender, age, address, phone number, and primary care provider (if possible), information. No individual health record will be reviewed. Recruitment letters and response cards will be sent to those who are identified, and follow-up calls made to those who didn't opt-out by the study team. For those unreachable by phone after the initial mailing of recruitment materials, recruitment materials will be re-sent a second time via mail and/or by email, with follow-up by phone and/or email. For those unreachable after the second mailing, the recruitment materials will be re-sent up to 3 additional times, as needed, with follow-up by phone and/or email. Clinicians and clinic staff will not receive any incentives for participant recruitment. When sending invitation letters to potential participants, we will include: the invitation letter signed by the site PI; and the invitation letter signed by both the site PI and the given health system's leadership representative at the University of Utah, Brigham and Women's Hospital/Harvard Medical School, UW Health, ACHC, UnityPoint Meriter GHC and SSM Health health systems. For all involved research sites, UW IRB will serve as the IRB of record. These sites will be engaged in research, including the extraction of data from patient medical records for recruitment purposes, and will provide the study team with contact information of potential participants to allow for recruitment letters to be mailed and/or emailed and follow-up calls and/or emails to be made, as appropriate, by the study team

5.4.2 Recruitment and Retention Strategies

Our patient, family and community advisors, including the CARDS group; staff from the Wisconsin Network for Research Support; and Investigators with expertise in engaging patients have advised on the recruitment strategies and materials.

Potential participants identified via health record-based data search or by their clinicians will be mailed letters with an opt-out/response card (see section 5.4.1. for details). Those who do not return these cards within the pre-specified time period will be contacted by the study coordinator by phone. Potential participants will also be able to call the research coordinator directly using the contact information found in the study brochure, website or other advertising.

During the initial screening conversation by phone or in person, study coordinators will read an informational statement about the study and about the risks and rights as a participant, in particular the right to cease participation at any time without any repercussion or loss of benefits. The coordinator will also ask if the potential participant has any questions about the study and will answer questions they may have before seeking a verbal consent to proceed with eligibility screening. Those ineligible or uninterested will be offered information about MM and CBT therapy options. Interested eligible persons will be invited to a virtual or in-person meeting with the study coordinator to go over the details of study participation, review an informed consent and authorization for the use of health information form (one combined form) and provide oral (or written, for in-person meetings) consent. The participant will receive a copy of the consent form for their records. When a participant provides written consent, a copy will also be kept as part of the study records; for oral consent, the provision of consent will be indicated in the study records. All participants will be informed that their participation is voluntary, of their right to withdraw at any time for any reason, and will be encouraged to ask questions at any time.

We conservatively estimate the need to screen 4,000 individuals to enroll up to 800 participants within the first 4 years of the study, with the assumption that the attrition rate will not exceed 20%. These assumptions and estimates were based on previous research conducted by the PI and Co-Is, and the results of sample size calculation (see Appendix).

Retention

Every effort will be made to retain participants through the 12-month study period, encourage completion of all study activities and measures, and minimize missing data. We will utilize several methods to retain participants that have been successfully used in our prior RCTs[17,46-48]

- We will have study-designated phone numbers for ease of contact.
- We will collect information on different ways for contacting participants (home / email addresses, phone numbers, emergency contact) and update it at each follow-up contact.
- Participants will receive reminder messages prior to scheduled meetings.
- Study personnel will inquire about participant experience, and solicit comments, questions, and potential problems during each contact so that issues can be identified and resolved quickly.
- We will use brief assessment tools and limit the number of assessments and in-person or virtual meetings.
- We will allow breaks during study activities.
- We will reimburse participants for their time/effort. They will be compensated: $30 for each baseline and exit survey completion and $20 for each remote follow-up survey completion; $20 for the completion of each videorecorded activity; $50 for an in-depth interview (a subgroup of participants); and a $10 for each attended intervention session.
- We will additionally incentivize adherence by implementing a $100 bonus for those who were adherent to the study intervention sessions during a given MM or CBT intervention cycle.
- We will provide light snacks during each of the 2-hour intervention sessions when conducted in person.
- We will offer transportation assistance to study activities if needed; we estimate ~6% of study visits will require transportation assistance, usually a cab ride.[30,41,68]
- In-person interventions and study assessments will be conducted at medical or research facilities that are easily accessible by bus and/or have convenient parking.
- In addition, for those who enroll in the optional additional in-person testing, we will provide the reimbursement of $10 per additional test, totaling up to $20 during the study.

Furthermore, this study utilizes several stakeholder groups, including the PFA, the SAC, the WINRS and the CARDS®, that have actively guided study planning and implementation, and will engage in problem solving efforts as needed. These groups will provide ongoing support for successful participant engagement throughout this study.[63]

5.5 Vulnerable Populations

Competent adults, meeting eligibility criteria, will be able to participate regardless of gender, race, ethnicity, religion or socioeconomic status. Prisoners, pregnant women and mentally impaired persons will not be included. Children, per eligibility criteria, are not eligible.

TABLE 1: Vulnerable populations included and excluded from this study:

Include	Exclude	Vulnerable Population Type
	x	Adults unable to consent

	x	Individuals who are not yet adults (e.g. infants, children, teenagers), age <21 years old
	x	Wards of the State (e.g. foster children)
	x	Pregnant women
	x	Prisoners

5.5.1 Participant Capacity

N/A

5.5.2 Participant/Representative Comprehension

N/A

5.6 Informed Consent

The PI will be responsible for ensuring that valid consent is obtained and documented for all participants. Informed consent will be obtained as a two part process. This multi-step screening/consent process will allow each potential participant to have an ample time to consider and decide about their study participation.

1. Potential participants will discuss the study by phone or in person with the study coordinator and complete the initial eligibility screen. During this conversation, the coordinator will read an informational statement about the study and about the risks and rights as a participant, in particular the right to cease participation at any time without any repercussion or loss of benefits. The coordinator will then obtain oral consent to proceed with the eligibility screening process.

2. Persons who pass the initial eligibility screening will be invited to a virtual or in-person meeting with a study coordinator to review details of study participation, review an informed consent and HIPAA authorization for the use of health information form, provide oral or written for in-person meetings) consent, and receive a study information sheet. The participant will also receive a copy of the consent form for their records. When a participant provides written consent, a copy will also be kept as part of the study records; for oral consent, the providing of consent will be indicated in the study records.

5.6.1 Process of Consent

Prospective participants will discuss the study with a research coordinator. During this conversation, the research coordinator will read an informational statement describing the study and informing the participant of the risks and his/her rights as a participant, in particular the right to cease participation at any time without any repercussion or loss of benefits. The study coordinator will then seek to obtain participant's verbal consent to proceed with eligibility screening. Those not eligible or interested in study participation will be referred back to their usual providers and offered information about MM and CBT therapy options. Eligible and interested individuals will be invited to a virtual or in person meeting (enrollment meeting) with a study coordinator where informed consent procedures will take place. At both the in-person and virtual meetings, the research coordinator will explain the study details and answer questions the participant may have about participation. Participants will then have time to privately review (with the study coordinator available) the informed consent and authorization for use of health information form, have questions answered and then provide oral or written, for in-person meetings consent, if interested in participating in the study.

<u>In-Person Consent</u>

At the in-person version of the initial meeting, The participant will review the consent form in person with the research coordinator present, have an opportunity to ask questions, then decide if they would like to participate in the study. For those interested in participating, they will sign a written consent form and receive a copy for their records. A copy will also be kept as part of the study records. Participants will also be given a one page info sheet, which briefly explains the study and who to contact with questions or concerns. Participants will also be provided explanation and opportunity to discuss the site-specific additional, optional testing (see Appendix), which would take place at the end of the in-person study visits. They will need to complete an additional consent form for the additional, optional testing. Their agreeing to, or declining, the additional, optional testing will not impact their participation in the main study. Participants will be informed of their right to withdraw from participation at any time, for any reason, and will be encouraged to ask any questions at any time. The study coordinator will be trained in confidentiality, informed consent procedures, and other aspects of human subject protection.

Virtual Consent

After the participant is screened as eligible through the phone screening process, they will be emailed/mailed the consent form and one page info sheet, which briefly explains the study and who to contact with questions or concerns, in advance of the virtual initial meeting and asked to review it prior to the meeting. At the virtual initial meeting, the research coordinator will confirm that the participant reviewed the consent form, and if not, provide time for the participant to read through it. After it's confirmed that the participant has read the consent form, the participant will have an opportunity to ask questions, then decide if they would like to participate in the study. For those interested in participating, the research coordinator will read a script (see Virtual Enrollment Script) to obtain participant oral consent/HIPAA authorization, and will indicate the obtaining of oral consent in the study records. Participants will be informed of their right to withdraw from participation at any time, for any reason, and will be encouraged to ask any questions at any time. The study coordinator will be trained in confidentiality, informed consent procedures, and other aspects of human subject protection.

5.6.2 Combined Consent and HIPAA Form

Attached in Appendix.

5.6.3 HIPAA

We will collect the following protected health information (PHI) from each participant:

- Name, date of birth, contact information, emergency contact information, and the name of the participant's primary medical provider.
- Information collected from participants as part of research procedures, including self-reported information about participant's symptoms, health, study experience and health care and medication utilization; objectively-measured physical function during a videorecorded task; and data from the EHR on prescribed opioids.

In addition, in a subgroup of participants, we will collect the following:

- Interview-based qualitative data on the study-related experiences in selected subgroup of participants who completed the study follow-up.
- Site-specific optional, additional data during in-person visits only on the following: ability to focus attention (breath counting test, performed on a computer) in Madison Site; pain sensitivity and modulation testing (quantitative sensory testing method) in Boston Site; and emotion regulation testing (heart rate variability, respiration, facial activity-based measures) in Salt Lake Site. The study participants, once enrolled into the main study, will be able to decide, by signing an additional consent, if they wish to participate in these optional additional tests.

The research information collected from participants during this study will be used by researchers at UW-Madison, Pennsylvania State University, Harvard University, and University of Utah for research purposes only. Regulatory and research oversight boards and offices, accounting and billing personnel, and research support staff at each of these institutions may also need to use participants' health information over the course of this research, e.g., for tracking or payment purposes.

Other parties outside these institutions who may need to receive participants' health information in the course of this research include:

- Federal oversight and regulatory groups, such as the U.S. Food and Drug Administration (FDA) and the study's funding agency - Patient-Centered Outcomes Research Institute (PCORI).
- Healthcare providers, in the event that worrisome symptoms that warrant concern about a participant's health or safety during the study require a referral to the Emergency Department.

Participants' protected health information will be kept confidential. We will protect participants' confidentiality by identifying each participant with a code, and keeping records in secure databases and filing locations. A key to connect the codes to identified information about the participants will remain with the researchers who have been granted this permission by the PI and have appropriate training. Participant identifiable information will not appear in any publication of the results of the study. We may publish selected videorecorded segments for the purpose of result dissemination but this will happen only with the explicit written permission from those participants.

Unless a participant withdraws their permission in writing to stop the use of their research data or PHI, there is no end date for its use in this research study.

5.6.4 Revoking Consent

Withdrawal of permission to use health information can be made at any time in writing to the study or site PIs (Zgierska, Barrett, Edwards, Garland). Beginning on the date a participant's permission ends, no new health information will be used. Any health information that was shared before the participant withdrew permission will continue to be used. If a participant withdraws their permission, they can no longer actively take part in the research study.

5.6.5 Costs to the Participant

Participants will not be responsible for any costs related to study materials, procedures or intervention delivery.

5.6.6 Payment for Participation

Participants in both intervention groups will be compensated for time and travel, to a total of up to $240 for the main study. Compensation will be prorated based on the number of study assessments and intervention sessions completed. All participants will receive a total of up to $160 for the completion of the assessments ($30 for each baseline and exit assessment and $20 for each of two videorecorded activities [baseline, exit interview]; $20 for each of three remote follow-up assessments [3, 6, 9 month follow-ups]). In addition, all participants will also receive up to $80 reimbursement for completing the intervention sessions ($10 for each attended intervention session). A subset of up to 80 participants will be selected to complete a single in-depth qualitative interview after they complete the study, for which they will receive $50. We will additionally incentivize adherence by implementing a $100 bonus for those who were adherent to the intervention sessions during a given MM or CBT intervention course. Participants will receive the study interventions, along with handouts, and other materials to facilitate daily home practice, free of charge. Bus passes or cab rides for study-related transportation will be provided, if needed. Study participants who agree to the optional, additional testing (conducted at baseline and exit) will be reimbursed $10 per each additional testing (total up to $20).

5.7 Early Withdrawal of Participants

5.7.1 Premature termination of study

This study is considered a "minimal risk". Therefore, we do not plan to implement formal interim safety/efficacy analyses with pre-defined stopping rules. However, we will monitor the study and participant progress and safety. If there are safety concerns, we will bring them to the DSMC, the IRB and the PCORI and address them appropriately.

5.7.2 When and How to Withdraw Participants

It is possible that participants may need to be withdrawn from the study or the additional testing (if they signed up for it) prior to their expected completion date. Participants may be withdrawn if:

- S/he is determined by the Study or Site PI and the DSMC to be unable to continue participation due to safety, physical or mental health concerns.
- Submits written notification of consent withdrawal to the Study or Site PI.

5.7.3 Data Collection and Follow-up for Withdrawn Participants

If a participant chooses to stop attending the intervention sessions, but does not withdraw from the study, outcome data will be collected per usual data collection protocol. If a participant is withdrawn from the study for reasons as described in 5.7.2, no further data will be collected.

6 Description of Study Interventions

This study evaluates a comparative effectiveness of two behavioral interventions, MM and CBT, delivered in addition to "usual care," which will be provided to the study participants for their opioid-treated CLBP by their regular providers.

The choice of CBT as a comparator intervention to MM is appropriate because CBT is standard-of-care for CLBP,[1,18-20,35] and, similarly to MM, is a psychological therapy that can be delivered in a group format.[21,22]

Both MM and CBT interventions have been patterned after existing programs[21,22,24,64,65] and adapted to meet the needs of patients with opioid-treated CLBP, with input from content experts and patient advisors who were participants in the PI's pilot RCT.[36] These interventions will be matched in terms of duration, setting and contact time to limit *intervention bias*. Each intervention will follow a written manual and be delivered by a trained therapist with at least one other research staff member or clinician present or easily accessible by phone over 8 weeks (weekly two-hour group sessions). In-person delivery will take place in a clinical, research- or community-based facility. When remote participation in the study activities (e.g., intervention sessions, assessment visits) is needed, the telehealth delivery will take place via an approved, secure, HIPAA-compliant platform (e.g., WebEx, HIPAA-compliant Zoom, etc.) or by phone. In addition, participants will be asked to practice MM or CBT strategies at home for at least 30 minutes/day, 6 days/week during the 12-month study and log their practice minutes. The session format will be comparable between the interventions. Each session will start with the review of home practice, experiences, concerns and questions, followed by a MM or CBT exercise, then introduction to the session-specific core concepts and 2-3 MM or CBT exercises (concept application), each followed by discussion of participant experiences and MM skills for coping with challenges related to opioid-treated CLBP. This interactive format will enable monitoring and enhancement of participant treatment receipt and enactment, essential elements of *treatment fidelity*. Each session will end with a review of the home practice for the following week. These methods and targets are feasible.[16,17,47,66] The outline of the MM and CBT interventions is attached in Appendix.

6.1 Usual Care

All participants will be asked to continue their usual treatment, including opioid therapy management and other treatments for CLBP, through their regular providers. Usual treatment for CLBP includes: physical therapy, surgery, acupuncture, chiropractic care, hydrotherapy, medication therapy (including but not limited to: tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, NSAIDs and other over the counter pain medication), and vitamins and herbal remedies.

In addition to study-specific outcome measures, which include self-reports on the daily opioid dose, we will also obtain data from the participant's EHR on opioids prescribed in the course of usual care; study participants will consent to the release of this medical information as a part of their consent form.

6.2 Randomization and Blinding of Study Intervention

N/A Participants will be randomized equally between MM and CBT arms (1:1 ratio), using a permuted blocks of random size strategy, stratified by site and prepared by the study statistician. Sealed envelopes with group assignment will be distributed consecutively; participants will break the seal after completing the baseline assessments.

Although participants, therapists and outcome assessors cannot be blinded to the study intervention, investigators and analysts will be blinded to the group status until the first stages of analysis and reporting are completed.

7 Study Procedures

The initial eligibility screening will take place by phone or in person (see Section 5.4.2 for details). Those eligible and interested in participation will meet in person with the study coordinator.

<u>In-Person Consent/Enrollment/Baseline/Randomization</u>

During the in-person meeting at baseline, eligibility will be confirmed. Eligible, interested individuals will complete the written informed consent procedures and be assigned a study ID number (approximately 20 minutes to complete, on average). Then they will complete the baseline questionnaires (approximately 55 minutes to complete, on average), followed by a brief videorecorded activity focused on the assessment of physical function (approximately 10 minutes to complete). This videorecorded activity will involve the participant performing the standardized Timed Up and Go (TUG) test, evaluating a participant ability to stand up from a chair, walk 3 meters, before walking back to the chair and sitting down,[110,111] and a brief interview about the impact of back pain and opioid therapy, and expectations/impact of the study. Then participants will be randomized (1:1 block scheme prepared by the study statistician) to the MM or CBT groups, and receive information about details and scheduling of their respective interventions. All baseline questionnaires can be completed verbally, electronically, or on paper if the participant requests it.

<u>Virtual Consent/Enrollment/Baseline/Randomization</u>

During the virtual meeting at baseline, eligibility will be confirmed. Eligible, interested individuals will complete the verbal informed consent procedures and be assigned a study ID number (approximately 20 minutes to complete, on average). Then they will complete verbally or electronically the baseline questionnaires (approximately 55 minutes to complete, on average), followed by a brief videorecorded activity (approximately 9 minutes to complete), which will only involve a brief interview about the impact of back pain and opioid therapy, and expectations/impact of the study. Then participants will be randomized (1:1 block scheme prepared by the study statistician) to the MM or CBT groups, and receive information about details and scheduling of their respective interventions. All baseline questionnaires will be completed verbally, electronically, or on paper if the participant requests it.

Intervention Sessions

Participants in each intervention group will be asked to attend eight weekly 2-hour sessions of their respective intervention, practice the intervention-taught techniques at home (at least 30 minutes/day; 6 days/week during the 12-month study), and log/report their home practice. The standardized form for collecting the home practice data is attached in Appendix. Intervention sessions will be audio-recorded and monitored/audited for fidelity. In each course's final session, participants will fill out a survey (see Appendix) reflecting on their intervention- and study-related experiences. The content for both the in-person and virtual versions of the interventions is the same. They are both delivered in group format, both include a break halfway through, and both encourage active participant engagement and discussion.

In-person sessions

In-person intervention sessions will occur in a group format in a clinical, research, or community-based location. Participants will receive hard copies of the intervention materials in the first class they attend. Home practice and intervention session specific materials will be collected during the in person sessions when possible.

Virtual sessions

Virtual intervention sessions will occur in a group format using a given site's institutionally-approved HIPAA-compliant virtual video platform. Participants that do not have video capabilities will be able to call in to the sessions. Participants will receive electronic copies of the intervention materials, along with hard copies of worksheets/logs which are expected to be filled out by the participants during each session. These materials will be collected using a unique, secure link from REDCap, verbally, by phone, or per participant preference.

Follow Up Assessment Sessions (all participants regardless of study participation method)

The follow-up assessments will take place at 3, 6, 9 and 12 months after the start of a given participant's intervention. The follow-up assessments will "remotely" (online or by phone; or by participant preference) gather self-reported data at 3, 6 and 9 months (30-60 minutes to complete, on average). These assessments will also include collection of home practice minutes for the past 14 days, and side effects diaries (used to assess for any potential interval SAEs/AEs/UPs).

The final "exit" assessment at 12 months will be conducted in person or virtually. For in-person exit assessments, a participant will meet with a researcher to complete the final set of questionnaires (55 minutes to complete, on average) and the brief videorecorded activity (10 minutes to complete, on average). The virtual exit assessments will be similar to the in-person assessments, except the walking portion of the videorecorded activity will not be conducted (only the interview portion will be completed). Please see Section 9.2.3 for a summary, and Appendix for details of outcome measures.

In-depth exit interviews

In-depth exit interviews (30-45 min to complete, on average) with a subset of up to 40 participants from each arm will allow for in-depth exploration of the experience of those who reduced their daily opioid dose the most. They will be conducted by phone after the participant – in a Boston, Salt Lake or Madison site - exited the study by the qualitative methods specialists from the UW Survey Center.

Participant "check-ins"

In addition to the study contact for the intervention sessions and outcome data collection, participants will be contacted approximately every 2-4 weeks (and additionally as needed for engagement purposes) to "check in", to inquire about how the study is going for them and if they have any questions, and answer questions they may have.

Optional, Additional Testing (in-person participants only)

Participants who are eligible for it will be given the choice to consent to participate in optional, additional testing, when offered in person. The testing will be site-specific, conducted at the end of the two in-person study assessment visits (at baseline and exit). Each test will take on average approximately 15 minutes. For Madison participants, this test will involve a breath counting test using a laptop to measure mindful attention; for Boston participants, it will involve application of mechanical pressure to several body sites (pressure similar to the sensation of pressing a fingertip with steadily increasing pressure against the skin) and submerging hand in cold water at the temperature of 4 degrees centigrade (approximately the temperature of ice water) for no more than 2 minutes, to measure pain sensitivity and modulation; for Salt Lake City participants, it will involve engaging in computer-based emotional regulation and cue reactivity tasks using images from the International Affective Picture System (IAPS) and photos taken from media libraries on the internet. IAPS Images will include negative (angry faces, violent scenes), pain-related (accident scenes, injuries, medical conditions), and neutral images; opioid-related images (pills, pill bottles) will be taken from media libraries. The photographs will not be any more explicit than those seen in an R-rated movie. It is very unlikely that distress from the photos would exceed a distress which would occur on an everyday basis, given that the images we use are similar to images seen in our usual environments. Psychophysiological assessment (heart rate variability, respiration, facial activity) will be measured during these tasks.

The study manager, site managers, the PI, site-PIs and Co-Is will be responsible for monitoring and coordination of all study activities.

7.1 LABS

N/A- No labs will be obtained as part of the study.

7.2 Study Visits

7.2.1 Screening/Baseline:

Potential participants will be identified through the methods described in Section 5.4.1. Potential participants, meeting pre-specified eligibility criteria, will be sent invitation letters with opt-out/response card; those not opting out will be contacted by phone by the study coordinator. Potential participants will also be able to obtain the information about the study through their clinicians, study brochures, and media advertisement, and contact the study coordinator directly to inquire about the study.

A study coordinator will call potential subjects to introduce the study and answer any questions. During this conversation, the researcher will read an informational statement describing the study and informing the participant of the risks and his/her rights as a participant, in particular the right to cease participation at any time without any repercussion or loss of benefits. The researcher will then seek to obtain the participant's verbal consent to proceed with eligibility screening. Screening will be based on self-report and take 10-15 minutes to complete (see Appendix for the scripted text). Those not eligible for or interested in study participation will be referred back to their usual providers.

Those who are eligible and interested will be invited to schedule a virtual or in-person meeting with the study coordinator to complete the screening, enrollment and consent procedures. This meeting will be held virtually or at a clinical or research facility in person. The study participant will be assigned a unique, study-specific ID number, and complete baseline assessments (questionnaires, followed by the videorecorded activity). Enrolled participants will also be given the option to sign an additional consent for optional additional testing, when in person visits are offered (see Section 7, Study Procedures).

Finally, the participant will be randomized to one of the study arms and scheduled for the MM or CBT intervention. A reminder letter, emphasizing the importance of research participation, will be sent to the enrolled participants prior to the intervention start date and/or handed out at the beginning of the intervention course.

For those screened but not enrolled in the study, all identifiable information will be destroyed. We will retain non-identifiable information collected during the screening process to help determine main reasons for ineligibility or declining participation and inform future research. All potential subjects will provide verbal consent for obtaining these data at the beginning of their screening process.

7.2.2 Follow up:

Table 4. Acceptable Window for Study Visits (including weekends)

Visit	Window	Activities
Initial Visit (Screening, Enrollment, Baseline Assessment, Randomization)	+ up to 12 weeks from the last contact / screening	Virtual or in-person visit. Confirm eligibility; consent/HIPAA authorization form; enrollment; completion of baseline questionnaires and videorecorded activity; randomization; scheduling for the intervention; compensation.
3-month follow-up	+ up to 8 weeks from due date	Online/phone/mail (if necessary) questionnaires, compensation mailed
6-month follow-up	+ up to 8 weeks from due date	Online/phone/mail (if necessary) questionnaires, compensation mailed
9-month follow-up	+ up to 8 weeks from due date	Online/phone/mail (if necessary) questionnaires, compensation mailed
12- month follow-up (exit)	+ up to 16 weeks from due date	Virtual or in-person visit. Completion of exit questionnaires and videorecorded activity, compensation. Completion by phone or mail if necessary.
In-depth qualitative interview (subset of 80 participants)	+ up to 16 weeks from due date	Qualitative interview by phone; compensation mailed.

The final study visit, the "Exit Visit", will occur approximately 12 months from the intervention start date for a given participant (Table 4). A subset of participants who completed the final study visit will be invited to undergo an in-depth qualitative interview by phone about their experience with the study intervention and its effects (Table 4).

7.2.3 Additional contact

In addition to the contact with study team members during the scheduled intervention and follow-up assessment sessions, participants will be contacted approximately every 2-4 weeks (and additionally as needed for engagement purposes) to "check in", to inquire about how the study is going for them and if they have any questions, and answer questions they may have. Participants who had undergone the videorecorded activity and are interested in receiving this material will be mailed a DVD with his/her own video recordings after their study completion.

8 Study Analysis

8.1 Sample Size Determination

We conservatively estimate the need to screen approximately 4,000 individuals to enroll up to 800 participants. In our pilot RCT of MM for opioid-treated CLBP, 304 potential participants were identified through the EHR data and clinician and self-referrals; 87 were screened, 48 were eligible and 35 were enrolled.[17] During the 26-week pilot study, no participant withdrew, and two (5.7%) missed the final assessment. In the PI's other trial of MM, 92% of 123 alcohol dependent adults completed a 1-year follow-up.[47] Our other studies have also had excellent recruitment and retention. Two RCTs of MM led by Bruce Barrett had an overall 95% (540/567) retention rate over a 9 month follow-up. For these studies, 2,080 adults were screened, 183 were found eligible but declined and 567 (27.3%) were enrolled.[46,48]

Using estimates from systematic reviews and meta-analyses, comparing MM and CBT to a wait-list controls,[10,18-20,35] and from two previous trials of MM in opioid-treated chronic pain,[15,17] as outlined in the Background, we assume an effect size d=0.25 of MM vs CBT for pain severity and function, and a dropout rate of not more than 20%. We adjust for multiplicity of the co-primary outcomes by using a significance level of 0.025 for each Aim 1 outcome, for an overall significance level of at most 0.05. With 383 participants randomized to each of the treatment arms (766 total), a two-sample test with a significance level 0.025 and at most a 20% dropout rate is powered to detect an effect size of 0.25 of MM versus CBT for primary outcomes with power of 0.80.

To assess power to detect treatment differences between the proposed subgroups, we used the sample size of N=383 per group and a significance level α=0.05 (i.e., not adjusting for multiplicity). Based on the existing literature and prior studies by Co-Investigators, we anticipate that approximately 35% of the study participants will show an elevated level of negative affect and approximately 45% of the sample will have an elevated level of opioid-related aberrant drug use

behaviors. For the power to assess Aim 3, we wish to be able to detect a difference of 0.5 (moderate effect size) between the subgroups, assuming no effect for the subgroup with less pathology (lower HADS [score ≤11][42,67] or COMM [score <9][68] scores) and an effect size of 0.5 for the intervention effects in the subgroup with elevated negative affect and/or opioid misuse scores. The proposed subgroup analyses are based on the assumptions for the prevalence of elevated scores of negative affect (score > 11 on the HADS) and opioid misuse behaviors (score ≥ 9 on the COMM) that indicate a person's increased risk for anxiety, depression or opioid use disorders.[42,43,68] We chose the effect size of 0.5 for the proposed subgroup analyses per existing recommendations; this doubles the proposed main effect size of the study, assumed to be 0.25, for the subgroup hypothesized to benefit most from the intervention. [69] Based on the statistical simulations of size 10,000 (so that the margin of error is approximately 0.01) we conducted, we will have at least 80% power (84% for negative affect subgroup and 86% opioid misuse subgroup) to detect a significant (subgroup x treatment) interaction effect for each of these two main subgroups.

8.2 Statistical Methods

There are no planned interim analyses for this minimum-risk study. Primary, secondary, and exploratory analyses will be tested in the framework of linear mixed effects to examine the comparative effectiveness of treatment on the change in pain severity, function (Aim 1) and QoL scores and opioid dose (Aim 2) over 12-months between the two groups. Tests will be performed at a two-tailed significance level of 0.025 for each co-primary outcome (Aim 1) and a 0.05 significance level for the secondary outcomes (Aim 2). Contrasts will be used to test for an overall treatment effect at 6 and 12 months. Detailed Statistical Analysis Plan is located in Appendix.

If and only if, the planned superiority analysis does not find statistically significant differences between the two groups, we will employ a formal non-inferiority analysis as a pre-specified secondary analysis. This analysis would employ mixed effects models to determine 95% confidence intervals for the difference between the mean scores of the primary outcomes of pain (BPI) and function (ODI) between the two groups, with the purpose of assessing whether MBT is non-inferior to CBT for treatment of people with opioid-treated chronic low back pain, using acceptable difference delta values of 0.8 for the BPI pain scale and 8.0 for the ODI function scale.

8.3 Planned Interim Analysis

There are no planned interim analyses for this minimum-risk study.

9 Data Collection, Handling and Record Keeping

9.1 Data Confidentiality

All efforts will be made to protect subject confidentiality. The initial interview, informed consent process, in-person and virtual data collection, and in-person and virtual intervention conduct will be conducted in private settings (when conducted virtually, all parties will be encouraged to use headphones/earbuds for added privacy and asked to turn off any 'smart devices'). During the intervention sessions, participants will be able to use their first names or nicknames, and be asked to keep the information shared by others confidential.

All data related to study participation will be kept confidential. Participant identity, medical record number, health information, and answers to questions will be kept confidential. Identifiable subject information will be linkable to a given subject outcome data via the unique identifier, and will be stored in a locked filing cabinet and a secure electronic tracking database. Only Investigators and Investigator-approved staff will be able to access these data. Outcome data will be coded with a unique code for each subject and stripped of identifiers, and will be stored and managed using the secure electronic REDCap database, housed at the UW Department of Family Medicine and Community Health (DFMCH). The servers storing the REDCap database are in a physically secure location and backed up nightly, with the backups stored in accordance with the DFMCH-ITS 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 DFMCH servers provide a stable, secure, well-maintained, and high-capacity data storage environment. Access to study data in REDCap will be restricted to the IRB approved members of the study research team who will be able to log into this database using person-specific username and password.

In-person baseline and exit surveys will be completed by participants in a clinical or research-based location, on a study-designated secure laptop, provided and administered by the DFMCH IT specialists. For virtual assessments, if

the participant is not able or willing to provide data via online system, s/he will have an option to complete these surveys "on paper" or online or by phone with the assistance from the researcher. Follow-up surveys (at 3, 6, and 9-months) will be completed online and by phone, and check-ins (approximately every 2-4 weeks) will be conducted per participant communication preference. For surveys completed online, each participant will follow a unique web link (emailed to each participant at the time of follow-up) that will allow answering survey questions online. The online responses will be entered by the participant directly into the DFMCH-housed secure REDCap database using a participant-specific web link. At follow-up, those who prefer to provide data by phone will be called by the study coordinator who will mark the participant responses "on paper" or enter directly into the electronic database. Data collected "on paper" (e.g. because of participant preference; as a result of a phone interview; due to computer malfunction; data on prescribed opioids extracted from participant electronic health record) will be labeled with participant ID only, entered into the REDCap database by a research staff member and stored in a separate locked filing cabinet. Only participant ID will be linked to the participant outcome data stored in the REDCap database.

Participant videorecorded data will be uploaded to the UW DFMCH secure storage system via a web-based interface. During virtual study sessions, the videorecorded activity (interview portion) will be recorded using the institutionally-approved HIPAA-compliant virtual platform; after the session, it will be transferred to the UW DFMCH secure storage system. Security will be provided by utilizing Secure Shell (SSH) with shared/private-key encryption on all connections to and from the DFMCH storage system. Additionally, security and identify verification will be provided utilizing individual usernames and passwords (adhering to DFMCH/UW Health password complexity policy) as well as an added two-factor authentication system. This will provide an extra layer of security for access into the system. The storage system will be housed in the DFMCH server facility, which is secured 24x7 and has limited access, and will provide full-disk encryption (at rest encryption) for all files.

Participant name and/or video/photos will not appear in any publications or other materials stemming from the study and designed for dissemination, or in any electronic/print media without participant's explicit written consent.

All study-essential documents and records (including participant paper data and electronic data records) will be retained for a period of time specified by the IRB after the close of the study, and destroyed after that time. Before the shredding of participant's study documents, records with participant's identifying number only, not name, may be evaluated by study monitors, auditors, or members of the UW Ethics Committee (Institutional Review Board). The Universities' Research Subject Advocates, the Data and Safety Monitoring members, the US Food and Drug Administration and the funding agency (PCORI) may review study records and information to ensure that the research methods comply with all ethics rules. Computer data will be protected by a password and electronic "firewall" and will be kept for 7 years as required by the University of Wisconsin policy.

For those screened but not enrolled in the study, all identifiable information will be destroyed. We will retain the non-identifiable information obtained during the screening process to help us determine main reasons for and/or correlates of ineligibility or declining participation and inform future research. All potential participants will provide verbal consent for obtaining this data at the beginning of their screening.

After all identifiers have been removed and shredded, the screening data will be entered and stored in the UW DFMCH-housed subject tracking REDCap database. Access to the database will be password protected; the study team will have full control over which users can see what parts of the data, giving us the ability to provide de-identified views of the data where required. The development of the subject tracking database is NOT the purpose of the study.

Certificate of Confidentiality (CoC)

A Certificate of Confidentiality was provided by the National Institutes of Health; language indicating the receipt of the CoC will be incorporated into the revised consent form, and those already enrolled will be informed about the receipt of the CoC per approved study protocol.

Data Sharing

Registration*:* We will register our trial on www.clinicaltrials.gov in order to ensure transparency of our research and comply with ethical standards of the field.

Study protocol and materials*:* We will provide PCORI a final protocol of the study when all study activities are complete that includes all changes made throughout the process. All versions of the protocol will be saved with track changes and will include reasons for changes throughout the study.

Data organization and management*:* Data will be organized following the PCORnet Common Data Model to standardize data labeling, entry and enable sharing.[70] To further promote data and information sharing, we will collect the "minimum data set" data, in addition to other outcome measures, as recommended by the NIH Task Force describing the best research practices for clinical trials on CLBP.[71]

All data dictionaries, programming codes, qualitative codebooks, and other study materials developed will be provided to PCORI within 3 months of funding completion in order to promote replication of our research process. PCORI may share any and all of our materials with requested researchers after consultation with the PI, Dr. Zgierska.

A final clean dataset will be available for data sharing after the project and analysis completion. All de-identified quantitative data will be exported from our database and available as csv file. Qualitative data will be made available including the coding taxonomy and coded themes. The coding taxonomy will include definitions and rich description in order to promote transparency of our coding structure. We will set up an online sharing tool for interested researchers in order to accommodate data sharing requests.

9.1.1 Confidentiality of Participant Records

By signing the protocol, the Investigator agrees that *the PCORI, DSMC, IRB, or Regulatory Agency* representative may consult and/or copy study documents in order to verify CRF data. By signing or orally consenting to (when unable to sign) the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Investigators will ensure that the identity of subjects is protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. The Coordinating Center will maintain, in a secure database, participant enrollment documentation that includes subject identifying information and links subjects to their study-specific identification number. This database (identifiable information) will be separate from the outcome measures database (de-identified data).

9.2 Data Capture

9.2.1 Source Documents

- EHR data on prospective participants, identified through an EHR database search for appropriate patients meeting the study criteria. See Appendix for data extraction protocol.
- EHR data on prescribed opioids (past 3 months) for selected participants at baseline and exit assessments. See Appendix for data extraction protocol.
- Self-report survey data at baseline, 3-month, 6-month, 9-month, and exit (12-month) assessments (see section 9.2.2 and Appendix for details).
- Videorecorded data, collected at baseline and exit assessments (see section 9.2.2 and Appendix).
- Qualitative in-depth interview data on participant experiences (subset of participants) that facilitated, and were related to, opioid dose reduction (see section 9.2.2 and Appendix).
- Madison site-specific optional, additional data (collected during in-person visits only): ability to focus attention (breath counting test, performed on a computer). The study participants, once enrolled into the main study, will be able to decide, by signing an additional consent, if they wish to participate in this optional additional testing.
- Boston site-specific optional, additional data (collected during in-person visits only): pain sensitivity and modulation testing (quantitative sensory testing method). The study participants, once enrolled into the main study, will be able to decide, by signing an additional consent, if they wish to participate in this optional additional testing.
- Salt Lake City site-specific optional, additional data (collected during in-person visits only): emotion regulation testing (heart rate variability, respiration, facial activity-based measures) The study participants, once enrolled into the main study, will be able to decide, by signing an additional consent, if they wish to participate in this optional additional testing.

9.2.2 Missing Data

To minimize the extent of missing data, all surveys conducted electronically will be built to require a response for each question before proceeding. All non-electronic surveys will be double-checked for completeness by study personnel prior to conclusion of the assessment session. If missing data is discovered in a given participant's record after they have left the assessment session, the research coordinator will contact them by phone and attempt to collect the data within 14 days of the participant's assessment session.

The majority data at 3, 6 and 9 month follow-up visits is expected to be collected remotely, online or by phone. In cases where internet or phone access is not available, data may be collected by mail. The exit follow-up will be conducted in person when feasible. Data on main outcomes is planned to be collected at all assessments. Other survey-based data is planned to be collected at selected follow-up assessments and other contact times as outlined in Appendix. To minimize recall bias, subjects will be asked to keep a log of MM and CBT home practice, adverse effects, and opioid medication use with standardized data collection forms (see Appendix) and submit it by internet, phone or mail. We will design the study's RedCap database to send participants reminders about keeping track of the above data. We will call those unable or unwilling to use the online reporting and/or reminders.

We will implement statistical methods to assess for and minimize the impact of missing data (see Appendix).

9.2.3 Data Collection Tools (see Appendix for all data collection tools)

Outcome measures will assess pain intensity, physical function, quality of life, opioid dose, depression, anxiety, opioid misuse, pain acceptance, pain catastrophizing, mindfulness level, sleep problems, neuropathic pain, change in pain and function, health care utilization, loss of productivity, PTSD, loneliness, feeling loved, sites of pain, NIH minimum data set, treatment expectations/satisfaction, non-protocol treatment, MM/CBT practice, adverse events, demographics, well-being, and experiences of those who reduced their opioid dose the most.

Primary Outcomes

Pain intensity will be assessed using the 0-10 point *Numerical Rating Scale* (NRS) from the Brief Pain Inventory (BPI).[49,50] The NRS is reliable and valid in CLBP (α=0.85).[53] A 1-point between-group difference is considered a minimal important change (MIC).[28,29]

Physical function will be measured using the validated *Oswestry Disability Index* (ODI),[51,52] which has good internal consistency (0.76-0.90), is reliable (0.83-0.99) and responsive to change.[56,72] Its total score (0-100) reflects the percent of disability. A reduction of 4-10 points constitutes the MIC.[28-30] In addition, functional status will also be assessed with 7 pain interference items from the BPI.[49,50,53]

Secondary Outcomes

Quality of life (QoL) will be assessed using the validated *Medical Outcomes Study Short Form Health Survey* (SF-12 v.2),[54,55] a common measure of health and QoL in CLBP.[56] The SF-12 has good reliability in CLBP (α=0.76-0.89), and yields one composite and two component (mental and physical) scores measuring general health and QoL.[54,55]

Daily dose of prescription opioids for "the past 14 days" will be collected with the *Timeline Followback* (TLFB) method, a validated tool for daily substance use evaluation, with good test-retest reliability (0.79-0.97),[57-59] and verified, when possible, against a participant's EHR data on prescribed opioids. This will enable longitudinal evaluation of opioid dose change during the proposed 52 week follow-up. We will work with the collaborating health systems to leverage the EHR data and collect information on the prescribed opioids at baseline and exit ("past 3 months"). When possible, data on prescribed opioids will be obtained in one of the 2 ways depending on each health system's preference and method feasibility: 1) Extraction of data on prescribed opioids directly from the EHR by the health system's EHR database analyst or research team member with appropriate clearance provided by a given health care system; the UW Health data analyst will ensure process integrity across the health systems and appropriate data linkage. 2) If needed, we will obtain prescription data through medical records with participant's written permission, if a request to medical archives is sent for the medical records pertaining to medication data. Because a health system's prescription record may not accurately reflect the actual use of opioids, we will rely on participant self-report as the primary measure of opioid use. To calculate a "daily opioid dose," doses of all reported opioids will be converted to a morphine-equivalent dose by multiplying daily dose of a given opioid by the published conversion factors, as we pilot-tested.[60]

Tertiary Outcomes (hypothesized main prognosticators)
The proposed subgroup analyses are based on the assumptions for the prevalence of elevated scores of negative affect (score > 11 on the Hospital Anxiety and Depression Scale) and opioid misuse behaviors (score ≥ 9 on the Current Opioid Misuse Measure) that indicate a person's increased risk for anxiety, depression or opioid use disorders.[42,43,68]

Negative affect (anxiety, depression) will be assessed by the *Hospital Anxiety and Depression Scale*,[67,73] the increased score of which has been associated with worse treatment outcomes in opioid-treated patients.[1,4,6]

Opioid misuse behaviors will be assessed with the validated *Current Opioid Misuse Measure*[74] and *Opioid Compliance Checklist*,[75,76] both developed by Co-Investigator Jamison. We will also evaluate the potential impact of other factors that might influence treatment effects.

Other Measures

Survey-based Other Measures:
Pain catastrophizing, pain acceptance and mindfulness level can impact outcomes in chronic pain;[77,78] and neuropathic pain and sleep problems have been linked to worse outcomes.[79,80] Pain catastrophizing will be assessed with the *Pain Catastrophizing Scale.*[81] Pain acceptance will be assessed with the *Chronic Pain Acceptance Questionnaire*.[82] Mindfulness level will be assessed with the *Mindful Attention Awareness Scale*.[83] Neuropathic pain will be evaluated with the painDETECT.[84] Sleep problems will be assessed with the "minimum data set" sleep questions.[71]

Change in pain, function and opioid use: Because it is not well-established what level of improvement (or worsening) constitutes a clinically meaningful change in individuals with chronic pain, we will ask the study participants to both rate their pain and function as well as the importance of change at each assessment by asking them if they are "better," "about the same," or "worse," compared with the beginning of the trial.[29] This approach will enable us to classify each trial participant as "improved," "stable" or "worse" and conduct a secondary responder analysis.

Health Care Utilization (number of clinic visits, emergency department visits; number of nights hospitalized) and Loss of Productivity (days missed of work and leisure), will be assessed using a survey developed for prior studies.[17,47]

PTSD symptom severity will be assessed with the 4-item Primary Care PTSD Screen (PC-PTSD).[85,86]

Loneliness will be assessed with the validated 3-item scale[87] and Feeling Loved with the 4-item Feeling Loved instrument.[88]

The number of location of the Sites of Pain will be assessed using the NIH-recommended instruments.[71,89]

The Minimum Data Set will be collected using the NIH-recommended survey for back pain studies.[71]

Treatment expectation/satisfaction will be assessed with the Global Impression of Change survey[90] and the Looking Back Survey.

Adherence to the intervention protocol will be assessed through participant session attendance of their assigned intervention (researcher-recorded); participant logs of home MM/CBT practice; and survey on non-protocol treatments.

Adverse events (AEs), Unanticipated Problems (UPs), Serious Adverse Events (SAEs), and side effects (SEs) will be evaluated at each study contact, with a *standardized UW Institute of Clinical and Translational Research's Adverse Events Tracking Log*. We will also collect data at the baseline and follow-up scheduled assessments on potential adverse effects in relation to opioid dose reduction with the 10-item brief validated instrument, the *Short Opiate Withdrawal Scale*, which assesses the presence and severity of opioid withdrawal symptoms.[91,92]

Demographics will be collected using the NIH "minimum data set" form[71] and additional questions developed by the research team and implemented in prior studies.

Qualitative measure of pain, function, and well-being will be assessed using a brief videorecorded activity of all participants at baseline and exit. It will complement quantitative measures of pain, function and QoL, and provide context

to our quantitative measurement of outcomes.[93,94] Selected recordings will bring patient voices and experiences into view and help promote dissemination.[95] The use of a brief videorecorded activity for outcome evaluation is novel and patient-driven; it was recommended by Penney Cowan, a patient advocate, and endorsed by our Patient Advisors. The premise is to enable a comparison of participant's qualitative presentation of pain, physical function and well-being (as a proxy for QoL) over time and across the two study arms, and to contrast it with the results from the validated patient-reported outcomes (PROs).

For this activity, we will use a standardized simple functional task (for in-person meetings only) and semi-structured interview (see Appendix). The functional assessment task will be carried out by a trained researcher and utilize the Timed Up and Go (TUG) test,[96,97] which is standardized and routinely used in clinical settings, including UW Health. TUG takes 1-3 minutes to complete and includes getting up from the chair, walking 3 meters, then coming back to sit down. The task performance will be scored, using the standardized scoring protocol developed by the research team to measure the perceived level of pain, ease of physical function, and general well-being. Following the TUG test, participants will be asked several open-ended questions about their thoughts and experience with the test, the study and the disease impact on their lives. The test administration and scoring protocol will be fine-tuned in an iterative manner, derived from the qualitative research methodological approach, based on the information from initial videorecorded activity data.

Qualitative measure of experience of those who reduced daily opioid dose the most will be assessed with in-depth exit interviews (30-45 min) with a subset of up to 40 participants from each arm (total: up to 80 participants) will allow for in-depth exploration of the experience of those who reduced their daily opioid dose the most. They will be conducted by phone after the participant exited the study by the qualitative methods specialists from the UW Survey Center. The UW Survey Center's team will help develop the protocols, conduct the interviews, and assist with data transcription, analysis and result summary. They will work with our research and stakeholder team to optimize and then continue fine-tuning the protocols in an iterative manner, derived from the qualitative research methodological approach, based on the information from initial interviews.

Optional, additional tests
These additional tests will be site-specific and only offered for in-person meetings, when in-person meetings are available. The enrolled study participants will have the choice to agree to or decline this optional testing. A separate consent will be obtained for this additional, optional testing. The additional tests (one per site) are non-invasive, and will take, on average, approximately 15 minutes to complete (see Appendix for details).

Madison Site: Madison Site Participants will be offered the breath counting test, developed by Dr. Richard Davidson's team.[98] This test will provide an objective evaluation of participant ability to sustain attention and complement the self-reported measures of mindfulness (Mindfulness Attention Awareness Scale survey) and logs of at-home practice. We hypothesize that participants in mindfulness meditation group will achieve greater improvements in their ability to sustain attention (better accuracy of breath counting) compared to those in the CBT group; this may mediate potential differences in treatment effects. For this test, participants will be instructed to "be aware of the movement of breath" and count their breaths in cycles from one to nine. They will be asked to press one of two different keys on the laptop/computer indicating which breath they are on, and a third key if they miss a breath. During the test, a set of 3 probes will appear on the screen inquiring about attention and breath count. This test will be administered by a trained research staff.

Boston, MA (Site PI: Rob Edwards):
Boston Site Participants will be offered the standardized Quantitative Sensory Testing (QST) to non-invasively measure pain sensitivity and pain modulation.[17,99] This brief "bedside" QST testing paradigm will conveniently measure mechanical pain sensitivity (pain threshold), temporal summation of pain (reflecting pain-promoting processes), and conditioned pain modulation (reflecting endogenous pain inhibition). We hypothesize that participants in mindfulness meditation group will achieve greater improvements in pain sensitivity and modulation parameters than those in the CBT group, which may mediate potential differences in treatment effects. For this test, participants will receive pain pressure stimulation from a Somedic pressure algometer, which will be measured using a standard set of weighted probes. Pain threshold and tolerance will be measured on the following sites on both the left and right sides of the body: low back, trapezius, and thumb. Participants will also immerse their hand in a cold water bath twice and rate intensity of the code pain on a numeric rating scale. This test will be administered by a trained research staff.

Salt Lake City, UT (Site PI: Eric Garland):
Salt Lake City Site Participants will be offered a test of the biological effects of mindfulness meditation and CBT interventions on the ability to regulate emotional responses to negative emotional cues and opioid-related cues using brief, non-invasive objective tasks[100,101] and physiological measures (e.g., heart rate variability, respiration, facial activity).The proposed testing will enable us to examine to what extent the study interventions can impact the ability to regulate negative emotions and unhealthy responses to opioid cues. We hypothesize that participants in mindfulness meditation group will increase regulation ability in response to negative cues and opioid cues to a larger extent than those in the CBT group, which may mediate potential differences in treatment effects, especially on the daily opioid dose. For this test, there will be three parts: participants will 1) view negative emotional images and regulate their emotional response to the images based on an instructed strategy; 2) view neutral and pain-related photos; their cue-reactivity will be assessed using a dot-probe task; 3) have heart rate, respiration, and facial activity assessed using ECG leads, respiration belt, and EMG sensors, respectively, while engaging in part 1 and 2 above. This test will be administered by a trained research staff on the study.

9.3 Data Management

Study-collected data will be stored "centrally" on a secure UW DFMCH server. These data will be accessible locally or remotely to authorized research team members in Madison, Hershey, Boston and Salt Lake who will be able to view and/or enter data. Data provided online by the study participants will be "deposited" directly into the UW DFMCH-housed RedCap database, with required response to all questions, ensuring data are complete and updated in a timely manner. The REDCap database will be developed and managed by a UW database administrator experienced with the proposed methods.[17,46-48] Data from the in-person or virtual assessment sessions (at baseline and exit) and follow-up data collected online or by a trained researcher by phone will be recorded by the researcher through the participant's web link; or "on paper," prior to being entered by a research staff into the outcome database. All visits will be encouraged to be completed via electronic web link, regardless of meeting in-person or remotely, however phone / paper completion will be an option. The participant will be encouraged to access the web-link during their initial study visit, so they can have practice with the web-link surveys prior to completing them remotely on their own. Outcome data, labeled by the subject's study ID only, will be stored in an outcome database, separate from the identifiable data, used for subject tracking. If data on the prescribed opioids are extracted by a database analyst from the EHR, the UW database analyst will ensure standardized extraction of EHR data across the health systems and will facilitate linking of de-identified EHR data to other outcome data. The videorecorded activity and in-depth qualitative interviews will be stored on a secure UW server and managed by the UW Information Technology team.

9.4 Data Monitoring

Data and Safety Monitoring Plan Prior to the subject enrollment, a detailed data/safety monitoring plan will be submitted to the IRB and the PCORI for approval. Although we do not anticipate serious adverse events (see item 3), should any occur, the site PI will report it to the Research Subjects Advocate and the IRB and the Project Officer at the PCORI within 48 hours, using the subject ID number. Annual reports of adverse events will be submitted to the PCORI. The data and safety monitoring will be provided through the regular study team meetings and by the Data and Safety Monitoring Committee (DSMC).

Data and Safety Monitoring Committee The PI's prior RCTs evaluating MM intervention for opioid-treated CLBP and for alcohol dependence were both considered to be of "minimal risk" by the UW IRB.[17,46-48] Therefore, an independent Data and Safety Monitoring Board and an interim data analysis are not expected to be required. However, to maximize participant safety, and the validity and integrity of the data, we will form a DSMC, which we successfully implemented in our prior similar trials.[17,46-48] This committee will include 4 individuals who are not involved in the trial as investigators or research staff: two clinicians (Michael Miller, MD; Michael Gerst, LCSW, MSW, MDiv, MA); patient stakeholder and advocate (Janet House, member of the Community Advisors on Research Design and Strategies (CARDS); and a statistician (Kevin Buhr, PhD; Director, Statistical Data Analysis Center, University of Wisconsin-Madison– Chair of the DSMC). During the course of the study, the DSMC will meet twice a year for data and safety monitoring, and to approve continuation of the study protocol. Details of the DSMC operations and procedures are described in the Data Safety and Monitoring Plan and DSMC Charter document (see Appendix).

Study Team Meetings The study team meetings will be scheduled on a regular basis and will include Site Manager Meetings, and regular Site Team Meetings. A plan for communication within and between sites will be established and included in the Manual of Operations. The Investigator Meetings will be led by the study or site PIs, or the study

manager, with meetings scheduled on average every 1-2 months, will follow a written agenda and produce meeting minutes. The Investigator Meetings will invite participation of all Investigators, consultants, the study manager and site managers, and other team members.

Annual Site Visits The Study Manager and/or PI will conduct a site visit each site 1-2 times per year to monitor and ensure compliance with the study protocol and data integrity. Site visits will include monitoring/auditing of protocol compliance, study procedures, safety and related reporting, regulatory and other study documents, and random sampling of data collected. A report of visit results will be generated and sent to the Study PI, Site PI, and Site Manager for the audited site.

10 Assessment of Safety

10.1.1 Definition of an Adverse Event (AE)

We will report Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

10.1.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event is any of the following:

- Fatal;
- Life-threatening;
- Persistent or significantly disabling or incapacitating;
- An inpatient hospitalization or prolongation of hospitalization;
- A congenital anomaly or defect; OR
- A significant medical incident that, based upon appropriate medical judgement, may jeopardize the participant and requires medical or surgical intervention to prevent one of the outcomes listed above

10.1.3 Definition of an Unanticipated Problem (UP)

An Unanticipated Problem is an event that meets all of the following criteria:

- Is more likely than not related to the research;
- Negatively affects the risk/benefit ratio of the research (this includes physical as well as psychosocial risks); AND
- Was not described in the protocol, Investigator's Brochure, IRB application, or informed consent document OR exceeds the specificity, frequency, or severity described in these documents

10.2 Classification of an Adverse Event

10.2.1 Severity of Event

All AEs will be assessed by the clinician using the below grading system. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
Life-Threatening – Events that result in life threatening consequences, and urgent intervention is indicated.
Death – Events that result in death.

10.2.2 Relationship to Study Agent

For all collected AEs, the clinician will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definite – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to the study intervention and cannot be explained by concurrent disease or other interventions, drugs or chemicals.

Probable – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease or other the study interventions, drugs or chemicals.
Possible – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Unlikely – A clinical event whose temporal relationship to the study intervention makes a causal relationship improbable and in which other interventions, drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Unrelated – The AE is completely independent of the study intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.2.3 Expectedness

The Principal Investigator or other delegated PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

10.3 Time period and frequency for event assessment and follow-up

Monitoring for AEs, including UPs and SAEs, will be conducted by the study team at each of the assessment visits and other contact times. Any medical or mental health condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Participants will be asked if they experienced any potential side effects related to their participation in the study. AEs will be further assessed at the assessment sessions by the Short Opioid Withdrawal Scale. Any AE occurring any time after informed consent is obtained will be reported to the study or site PI, with SAEs reported immediately (or as soon as possible if the situation does not allow for immediate reporting). AEs/UPs and SAEs will be recorded by research staff on an ICTR's Adverse Events tracking log, and entered into the study database. See Section 10.4 for the timeline of reporting of AEs/UPs/SAEs.

10.4 Reporting procedures

Adverse Events, unanticipated problems (such as subject complaints, breach of confidentiality, etc.), and complications across all sites will be promptly reported to the site-PI and coordinating-center PI, who will evaluate, and report to the IRB in accordance with posted guidelines.

For reporting of UPs/AEs/SAEs, we will follow the UW IRB reporting procedures as described in the UW Health Sciences IRB Unanticipated Problems Reporting Decision Tree (https://kb.wisc.edu/images/group78/18324/AEdecisionguidewithFDAVAupdate2.6.13.pdf).

In case of the serious adverse events, the PI will complete a SAE Form within the following timelines:
All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study funder within 24 hours of site awareness. Other SAEs regardless of relationship, will be submitted to the DCC/study funder within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study funder and should be provided as soon as possible.

In case of the unanticipated problems (UPs), we will report UPs with the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

In addition, routine reporting of the number and type of adverse events (UPs/AEs/SAEs) will be compiled for the DSMC meetings and included in all PCORI-required progress reports.

10.4.1 Events of special interest

N/A

10.4.2 Reporting of pregnancy

Although we will not enroll women who report pregnancy, and later on do not obtain laboratory testing toward pregnancy, if a female participant reports pregnancy after the enrollment, we will discuss this situation with the DSMC to make a determination about further participation on a case by case basis.

10.5 Study Halting Rules

While the study interventions and procedures are minimal risk and not expected to produce any unanticipated serious adverse events, the study may be halted or temporarily suspended if it is discovered that the interventions pose a serious consistent life- or health-threatening risk to participants. Should SAEs occur, the DSMC and other study oversight agencies will be involved in a timely manner as specified above to determine further course of action.

10.6 Safety Oversight

Our Data Safety and Monitoring Committee (DSMC) will provide Safety Oversight. See Section 9.4.

11 Study Monitoring, Auditing, and Inspecting

11.1 Medical/Safety Monitoring

Safety protocol will be implemented by a trained researcher or therapist in case of presence of any worrisome symptoms, including inappropriate behavior during the study sessions or assessments. In case of worrisome symptoms during the intervention or assessment sessions, regardless of their mode of delivery (ie, in person, by phone, or via online platforms), a therapist or a research staff will discuss the concerns individually with the symptomatic participant, follow the Safety Protocol procedures, and call the study clinician as needed if concerns persist for further assessment and directions (see Section 2.5.2 for details). For those who are experiencing mental health problems, information on the resources available for counseling or other services to help with anxiety, distress, or feelings of sadness, will be provided. Depending on clinician's assessment, participants will be cleared to stay at home or go home (by themselves, with a family member or a friend, or via study-provided cab) or referred to the appropriate further assessment, including in the Emergency Department (ED) if needed. Participants who are excused from the assessment meeting will be asked to reschedule it; however, they will not be able to reschedule a missed intervention session. In case of emergency, the therapist or research staff will call hospital security or 911.

At each assessment session (baseline, 3, 6, 9, 12 months) participants will be screened for an intent to self-harm through their answers to item 5 on the existing outcome measure, the Current Opioid Misuse Measure (COMM): *"In the past 30 days, how often have you seriously thought about hurting yourself?" (with responses ranging from 0=Never, 1=Seldom, 2=Sometimes, 3=Often, to 4=Very Often).* Scores 3 (Often) and 4 (Very Often) will be considered a "positive screen" and trigger the research staff to initiate the Safety Protocol, which includes involving the designated study clinician for assessment of the participant's intent to harm and disposition. Depending on clinician's assessment, participants will be "cleared" or referred for appropriate further assessment, including in the Emergency Department (ED), if needed. All participants assessed by the study clinician will be provided information on the local resources available for counseling or other mental health services. COMM responses are monitored by the research staff during business hours.

If the Safety Protocol is implemented, the assessed participants will be encouraged to contact their regular providers for evaluation, if needed, and will receive a follow-up phone call from the study site clinician the following day, if needed. Notification of participant's regular provider or a designated emergency contact person will not be required unless an ED assessment is necessary. Participants who are excused from the assessment session will be asked to reschedule it; however, they will not be able to reschedule a missed intervention session. They will be encouraged to continue study activities. In case of ED referral, the site PI or designated study clinician will notify the receiving physician in the ED, participant's regular provider and the emergency contact person (this procedure is outlined in the consent/HIPAA form).

11.1.1 Study Monitoring Plan

Clinical site monitoring is conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are high-quality, accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, and with applicable regulatory requirement(s).

- The Study Manager and/or PI will conduct a site audit 1-2 times per year to monitor and ensure compliance with the study protocol and data integrity. Site visits will include monitoring/auditing of protocol compliance, study procedures, safety and related reporting, regulatory and other study documents, and random sampling of data collected.
- Scheduled independent audits are not planned, however, Patient Centered Outcomes Research Institute (PCORI) or UW Institute for Clinical and Translational Research may choose to conduct an audit of the study.
- Each Site Manager and/or PI will perform will perform internal quality management of study conduct, data collection, safety monitoring, documentation and completion.

11.2 Protocol Deviations

The PI, site PIs, Investigators and staff will be responsible for continuous vigilance to identify and report deviations from the protocol. Noticed protocol deviations will be reported to the IRB per existing guidelines. The PI / site PIs are responsible for knowing and adhering to the IRB requirements.

11.3 Auditing and Inspecting

Patient Centered Outcomes Research Institute, UW Institute for Clinical and Translational Research, and the UW IRB may require auditing/inspecting of all study related documents. The PI will ensure the capability for inspections of applicable study-related facilities. The Study Manager will audit each site in years 1 and 2, and as needed in years 3-5, to conduct site visits for compliance with the study protocol and data integrity

11.4 Participant Compliance Monitoring

The study team will assess and track participant compliance with the study interventions, through collection of home practice logs of home practice, attendance log for the intervention sessions, and phone follow-up with any participant that misses a given intervention session to collect any home practice data and set up a time to touch base with the intervention instructor to ensure the participant does not fall behind in the material.

The study team will monitor electronically received self-reported assessment data from participants, and if a given participant has not completed their assessments at 3, 6, or 9 months, they will be contacted by a member of the study team to facilitate collection of data either online or by phone.

12 Ethical Considerations

This study is to be conducted according to US and international standards of applicable government regulations, applicable local and state laws, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. See Appendix for a copy of the Participant Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a participant, using the EC/IRB-approved consent form, will be obtained before that participant undergoes any study procedure. The written consent form will be signed by the participant or legally acceptable surrogate during the in-person initial meeting. For those participants who are unable to sign the consent form in person, oral consent will be obtained by the research coordinator, and will be indicated in that participant's study record, all written consent forms will be signed by the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is funded through a contract with Patient Centered Outcomes Research Institute (PCORI) and internal funds of each participating site's institution: UW-Madison, Pennsylvania State University, University of Utah and Harvard University.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the IRB-recommended conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Patient Centered Outcomes Research Institute (PCORI) for the purposes of performing the study, will be published or passed on to any third party without the consent of PCORI and the PI. Any investigator involved with this study is obligated to provide PCORI and the PI with complete test results and all data derived from the study.

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