Mechanisms of Psychosocial Treatments on Opioid Use in Chronic Pain

Study Protocol

Version Date: March 7, 2022

IRB Title: **Mechanisms of Psychosocial Treatments *on Opioid Use in* Chronic Pain**
Short Title: Living in Full Even (LIFE) with Pain Study
NCT Number: NCT03916276

Mechanisms of Psychosocial Treatments on Opioid Use in Chronic Pain

A randomized, 3-group, parallel-design, 90-subject clinical trial to test the mediators and moderators of cognitive therapy, mindfulness meditation, and activation skills on individuals with heterogeneous chronic pain conditions who are at risk for opioid misuse.

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Contents

TOOL REVISION HISTORY

Version 2.31
Version Date: March 7, 2022
Summary of Revisions Made:

1. Revised exclusion criteria of “Current or past participation in a research study with treatment components that may overlap those in the current study” to “Current or past participation in a research study with components that may overlap, conflict, or affect those in the current study”.
2. Added using UW Medicine EHR research tools for recruitment.
3. Removed Andrea Thomas and Emily Stensland from Study Team Roster and Blinded/Unblinded Research Staff.
4. Updated Marcia Ciol’s phone number.
5. Added Importance of Treatment Outcomes measure to Table 1, Section D6g, Table 3, and Table 4.

Version 2.3
Version Date: July 14, 2021
Summary of Revisions Made:

1. In Section E4b., added more active monitoring of adverse effects during the study intervention for participants in the CT and MM treatment conditions.
2. Added Malka Dhillon to, and removed Madison Sherwood and Kala Phillips from, Study Team Roster and Blinded/Unblinded Research Staff.

Version 2.21
Version Date: June 24, 2021
Summary of Revisions Made:

3. In Section E4b., added more active monitoring of adverse effects during the study intervention for participants in the AS treatment condition.

Version 2.2
Version Date: June 1, 2021
Summary of Revisions Made:

1. Added Nikki Torres, Andrea Newman, and Emily Goldberg to and removed Kevin Gertz from Study Team Roster and Blinded/Unblinded Research Staff.
2. Changed Andrea Thomas from Blinded to Unblinded Research Staff.
3. Removed “If currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to this study” from inclusion criteria.
4. Removed “UW Department of Rehabilitation Medicine” from exclusion criterion “current or past participation in a UW Department of Rehabilitation Medicine research study with treatment components that may overlap those in the current study” so that any study with overlapping treatment is exclusionary, regardless of where study is from.
5. Expanded exclusion criterion “Any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study” to “Any planned surgery, procedure, hospitalization, treatment, or event that may conflict with or otherwise influence participation in the study”.
6. Fixed an error in Figure 1. Study Design that screening may be done ≤ 6 months before randomization; this was corrected to ≤ 3 months.
7. Revised all instances of “Re-Assessment of Opioid Use” to more broadly be “Re-Assessment of Eligibility”, as we re-assess for more than just opioid use and pain chronicity and frequency with this assessment.

8. Age, sex, gender, race, and ethnicity data may be collected after informed consent prior to the start of the Pre-Treatment Phase.
9. Revised D6a. Recruitment: expanded recruitment sources and revised language to be more flexible.
10. Added exception to when a resource list is provided to ineligible participants.
11. The collection and retention of assessment data outside the defined assessment window is allowed if that assessment had been started by the participant within window.
12. The collection and retention of assessment data collected outside window, if that assessment had been started within window, will not be considered a protocol deviation.
13. Revised F. Data Safety Monitoring to be consistent with DSMP version 1.2.

Version 2.1
Version Date: May 14, 2020
Summary of Revisions Made:

The revisions below were done to make this supplemental protocol consistent with the primary protocol, version 7.2, which was approved by NCCIH on May 8, 2020.

1. Removed Sam Battalio and Hannah Lessing from protocol, as both departed the study and our institution in fall 2019 to pursue graduate studies.
2. Updated titles for Emily Stensland and Andrea Thomas, due to promotions.
3. Removed ActiGraph Compliance Monitoring Period and reduced the number of ActiGraphs mailed out from two to one. Participants will now be compensated $70 for the return of one ActiGraph versus $20 for the first ActiGraph and $50 for the second.
4. Moved 3- and 6-month follow-up assessments to be completed online by the participant.
5. Added items on COVID-19's effects on mental health and well-being to extended assessments and the Qualitative Interview.
6. Added providing participants with a study schedule.
7. Added flexibility for contacting participants regarding missed EMAs and ActiGraph non-wear, due to the variability in participants' participation level and individual circumstances.
8. Lowered the randomization threshold of EMA survey completion from 10/14 EMAs to 7/14 EMAs during Week 1 of the Baseline Monitoring Period.
9. Removed ActiGraph Compliance Monitoring Period from required baseline procedures for randomization.
10. Removed limit on number of people enrolled for each cohort.
11. Removed limit on number of people in each treatment group.
12. Added language describing who may cover a treatment session if an emergency arises.
13. Added an email option to the Replacement Check Protocol.
14. In Table 3, corrected the number of items administered in the EMAs and extended assessments for the PAS, CSQ, PCPQ, and pain-related self-efficacy; this was researcher oversight in updating the table to reflect the number of items currently being administered and analyzed. Also corrected sub-scales for SOPA measure, added PGIC and PGATS measures to Tertiary Outcomes (researcher oversight), additional COVID-19 items to Exploratory Moderators, and additional cannabis use items to Secondary Outcomes.
15. Added COVID-19 items, cannabis use items, and additional details to various measures in Table 4.

Version 2.0
Version Date: January 31, 2020
Summary of Revisions Made:

The revisions below were done to make this supplemental protocol consistent with the primary protocol. With only a few exceptions, the majority of the supplemental protocol is identical to the primary protocol.

The following changes were newly added to the primary grant and supplemental grant protocols on January 31, 2020.

1. Added Calia Morais to Study Team Roster and Blinded/Unblinded Research Staff.
2. Revised window for re-assessment of opioid use (asked to ensure that opioid use still meets study entrance criteria) from 4 weeks to 5 weeks before start of Baseline Monitoring Period.
3. Added requirement for participants to use a response key during weekly telephone assessments.
4. Added flexibility to setting a participant's morning and evening EMA windows, should the participant be unable to utilize the study's pre-determined EMA windows.
5. Increased the maximum number of participants staff can enroll per cohort from 36 to 40.
6. Corrected omission in Table 3 – employment status and weight change questions are also asked at Baseline.
7. Expanded study clinicians to include those with a Masters-level degree or higher.

The following changes were previously approved in Version 7.0 of the primary grant's protocol, approved by NCCIH on December 19, 2019.

1. Added Andrea Thomas, Kala Phillips, and Madison Sherwood to Study Team Roster and Blinded/Unblinded Research Staff.
2. Updated phone numbers for staff in Study Team Roster.
3. Removed requirement that participants must have a formal "diagnosis" (e.g., as indicated on a medical record) of chronic pain; however, participants must still meet criteria for having chronic pain per the NIH Low Back Pain Task force guidelines.
4. Per phone meeting with NCCIH PO and committee on 10/7/19, removed inclusion criteria "Pain is consistent (pain is either always present or present most of the time, with only occasional periods of no pain, if any)" as this was confusing with inclusion criteria "Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in past 6 months)".
5. Added exclusion criteria of having a terminal illness.
6. Added exclusion criteria of inability to walk (defined as unable to walk at least 50 yards).
7. Added exclusion criteria of significant pain from a recent surgery or injury.
8. Removed blanket exclusion of autoimmune conditions; revised to having a serious medical condition that may interfere with study participation or with receiving potential treatment benefits.
9. Per phone meeting with NCCIH PO and committee on 10/7/19, added explicit statement specifying that all materials and procedures to be used for recruitment will be submitted to the University of Washington IRB for review and approval.
10. Added flexibility to clinic recruitment by removing requirement to send out an initial approach letter or email to patients prior to approaching them in clinic.
11. Added in-person efforts in clinics and other spaces, public ads, and print, online, and media advertisements as recruitment options.
12. Removed "diagnosis" verification process that involved accessing medical records or requiring a completed form from the participant's health care provider.

13. Clarified that re-screening for study eligibility will also be done if the screening questions are revised and the participant has not yet been randomized. Staff will re-screen participants on the most current approved version of the screening questions.
14. Per Westat site monitor during IMV on 9/4-9/6/19, removed letter of orientation from protocol. A physical letter is not being used as all enrollment information is emailed to the participant.
15. There was a typographical error in D6c. Consent Process that stated the informed consent process may only be done if within 7 weeks prior to the start of the treatment groups for that particular cohort – this was inconsistent with other areas of the protocol stating informed consent could occur up to 6 months before randomization. We revised D6c. to be consistent with other areas of the protocol. However, such participants will be re-screened to ensure they meet inclusion/exclusion criteria.
16. Clarified baseline and demographic information may be collected again if collection is not within 3 months of randomization.
17. Clarified a refresher technology training will be done if participant does not participate in the treatment groups for the cohort which they complete the initial technology training. In other words, the technology training will be done again so that it is within the cohort that the participant will receive the intervention.
18. Removed option for participants to wear ActiGraphs on the ankle.
19. Lowered the ActiGraph wear compliance percentage during the ActiGraph Compliance Monitoring Period from 70% to 50%.
20. Added option to re-contact participants who do not meet baseline criteria for EMA completion or ActiGraph compliance, should the cutoffs for these criteria change in the future.
21. Increased the number of study cohorts per year.
22. Clarified the maximum number of participants enrolled per cohort.
23. Clarified that homework submission will be done electronically, specifically via Google Drive.
24. Formally defined treatment completion as attending at least 4 out of 8 sessions in an intervention.
25. Added details on Intent-to-Treat (ITT) process. Per phone meeting with NCCIH PO and committee on 10/7/19, we have revised the details to explicitly state that no deferrals to a future cohort will be allowed for participants after they have been randomized.
26. Clarified that qualitative interviews will not be conducted for participants who do not attend any treatment sessions.
27. Corrected typographical error in Table 3 that incorrectly listed Treatment Credibility items being assessed during Extended assessments.
28. Per Westat site monitor during IMV on 9/4-9/6/19, removed “X” from Table 4. Study Assessment Schedule for PROMIS Pain Interference being assessed at the Baseline time point – this was a typographical error.
29. While reviewing Table 4 with Westat site monitor on 9/4-9/6/19, staff caught another error in this table, where “X”s were left off Employment Status and Weight being assessed at the Baseline time point. These omissions have been corrected.
30. Changed Jeffrey Borckardt from blinded to unblinded staff member, due to needing his expertise to help manage unblinded data.
31. Per phone meeting with NCCIH PO and committee on 10/7/19, provided more detail in table listing blinded and unblinded staff regarding the activities they will engage in. Included specifics clarifying that investigators who oversee study data may still listen to unblinded fidelity recordings and participate in final data analysis. Provided rationale for this allowance and noted when this permission was granted by the PO.

32. Per Westat site monitor during IMV on 9/4-9/6/19, added statement explicitly stating that participant non-completion of study components should not be counted as protocol deviations and included the date the NCCIH PO granted permission for this.
33. Revised re-screening window for inclusion/exclusion from 6 months to 3 months, per recommendation of NCCIH PO and committee.
34. Added verbiage to D6r. Data Collection and Management attesting that staff performing data collection/participant evaluations will not be analyzing and reporting study outcome data during the data collection phase of the study. Blinded/Unblinded Research Staff table updated.

The following changes were previously approved in Version 6.0 of the primary grant's protocol, approved by NCCIH on June 25, 2019.

1. Added exclusion criteria of headache as primary pain condition.
2. Removed exclusion criteria of having another confounding chronic pain condition.
3. Added additional flexibility to recruitment contact methods and contact order.
4. Added departmental Participant Pool and previous studies as recruitment source.
5. Added flexibility in randomization eligibility, such that exceptions to meeting all eligibility criteria may be made on a case-by-case basis.
6. Added option for participants to complete their home practice activities through electronic, cloud-based forms (e.g., Google Drive forms).
7. Clarified qualitative interviews will be coded by a transcription company and not research staff.

Version 1.1
Version Date: March 28, 2019
Summary of Revisions Made:

The following change was made relevant to this supplement:

1. We removed exclusion criterion "uncontrolled schizophrenia, bipolar affective disorder, or seizure disorder" because we realized that this criterion is already captured with exclusion criterion "Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months".

The following changes were previously approved in Version 5.1 of the primary grant's protocol, approved by NCCIH on March 15, 2019.

1. Changed both co-PIs from blinded status to unblinded status.
2. Added Emily Stensland as a staff member.
3. Clarified when staff may call participants to check on stabilized medications during the screening process.
4. Changed EMA compliance cutoff from 85% to 80% such that the DSMC Chair may call a meeting with study investigators should EMA completion compliance fall below 80%.

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PRÉCIS

Study Title: Mechanisms of Psychosocial Treatments on Opioid Use in Chronic Pain

Objectives

The goal of this administrative supplement is to examine the mediators and moderators of three psychosocial treatments for chronic pain, in the context of a population at risk for opioid misuse: Cognitive Therapy [CT], Mindfulness Meditation [MM], and Activation Skills [AS].The sample will consist of 90 individuals with heterogeneous chronic pain who are at risk for opioid misuse. Participants will be randomly assigned to eight (8), 1.5 hour telehealth group sessions of (1) CT, (2) MM, or (3) AS. Mechanisms and outcomes will be assessed twice daily during 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via cue-elicited ecological momentary assessment (EMA) and via weekly telephone interviews during this time period; activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Follow-up macro-level assessments will be conducted at 3- and 6-months post-treatment. The study will address two aims.

Aim 1 is to test the Limit Activate and Enhance (LA&E) model to investigate theory driven moderators of response to CT, MM and AS in a sample of individuals with chronic pain at risk for opioid misuse. To accomplish Aim 1, we will use omnibus groups regions of significance (OGRS) tests to evaluate the effect sizes associated with the extent to which baseline pain catastrophizing, mindfulness and activity level are respectively associated with reductions in opioid use following CT, MM and AS. Specifically, three OGRS models will test the LA&E predictions that (1) higher baseline levels of catastrophizing will be associated with greater reductions in opioid use in response to the CT intervention compared to MM or AS (Hypothesis 1a), (2) lower baseline levels of activity will be associated with greater reductions in opioid use in response to AS compared to CT or MM (Hypothesis 1b), and (3) higher baseline levels of non-judgment will be associated with greater reductions in opioid use in response to MM compared to CT or AS (Hypothesis 1c). We will test these baseline characteristics as moderators of response at post-treatment (primary analyses) and at 1-, 3- and 6-month follow-up (secondary analyses).

Aim 2 is to examine the mediators underlying the expected change in opioid use during CT, MM and AS in this at risk population. We will use PROCESS bootstrap mediation models to evaluate the extent to which early treatment changes in the primary mechanisms (pain intensity and emotional distress, i.e., depression and anxiety) will predict subsequent late-treatment changes in opioid use (primary outcome), and the extent to which these associations are shared across the three treatments, or if some are unique to one or a subset of treatments. If changes in pain intensity and emotional distress are mechanisms *shared* by CT, MM and AS, then changes in opioid use in all three treatments will be predicted to approximately the same extent by changes in the primary mechanisms (Hypothesis 2a). On the other hand, if changes in the primary mechanisms are *specific* to one (or a subset) of the three treatments, then Treatment Group X Assessment Period interactions will reveal that late-treatment changes opioid use will be substantially and uniquely predicted by early-treatment changes in the primary mechanism(s) in one (or a subset) of the three conditions only (Hypothesis 2b). As we plan to do for the parent study, we will also include secondary tests in the supplemental project to evaluate these mechanism variables as potential processes underlying post-treatment relapse, maintenance and continued gains in outcome (i.e., opioid use reduction for the supplemental project).

In addition to the planned primary analyses to address the supplemental project study hypotheses, we will also perform secondary tests to examine the effects of the three Aim 1 moderators (i.e., baseline levels of catastrophizing, mindfulness, and catastrophizing) on continued reductions in opioid use immediately post-treatment (i.e., to 1 month follow-up) and at 3- and 6-months follow-up. We will also perform exploratory tests to examine additional potential secondary moderators and mediators. We will additionally perform planned secondary tests to evaluate the moderation and mediation effects of these variables on secondary outcomes. We will describe these as secondary analyses (i.e., exploratory and not definitive) when the study is registered at clinicaltrials.gov and when the findings from these secondary analyses are disseminated.

Design and Outcomes

A randomized, 90-subject administrative supplement of a clinical trial that will test the mechanisms of cognitive therapy, mindfulness meditation, and activation skills on individuals with heterogeneous chronic pain who are at risk for opioid misuse.

Interventions and Duration

Participants will be randomly assigned to eight (8) telehealth group sessions of (1) cognitive therapy (CT), (2) mindfulness meditation (MM), or (3) activation skills (AS). Treatment groups will meet, on average, twice per week over the Zoom videoconferencing platform. Each session will last for a duration of about 90 minutes. Proposed mechanisms and outcomes will be assessed twice daily during 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via cue-elicited ecological momentary assessment (EMA) and via weekly telephone assessments during this time frame; activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Macro-level assessments will be conducted at pre- and post-treatment and at 3- and 6-months post-treatment.

The total time involved in the study (excluding between session skills practice) is approximately 37-42 hours over an 8 to 9-month period.

Sample Size and Population

We plan to enroll 90 participants with moderate to severe chronic pain who are also at risk for opioid misuse.

Enrolled participants who complete the required baseline components (baseline data and demographic questions, pre-treatment extended assessment period, technology training, pass the re-assessment of eligibility, and a minimum number of EMA surveys during one week of Baseline Monitoring (Days 1-7)) will be randomized to one of the three conditions.

A. SPECIFIC AIMS

A1. Problem Statement

This supplement study relates directly to the parent study's primary aim to understand the mechanisms that underlie the beneficial effects of non-pharmacological treatments. Chronic pain is a costly condition affecting millions of Americans. One of the most common treatments for chronic pain is the prescription of opioid analgesics. However, the long-term use of opioids is associated with increasing rates of misuse, serious negative side-effects and only modest pain relief. Thus, current guidelines put forth by the Centers for Disease Control recommend non-opioid therapy as the first line treatment approach for chronic pain. Non-pharmacological treatments such as those being tested in the parent project (Cognitive Therapy [CT], Mindfulness Meditation [MM] and Activation Skills [AS]) are potential viable alternatives to opioids, and have been shown to reduce opioid use. However, the mechanisms – that is, the moderators and mediators – of these treatments in individuals with chronic pain at heightened risk for opioid misuse are yet to be substantively investigated. Therefore, the dual-aim of this supplemental project is to increase our understanding of the moderators (Aim 1) and mediators (Aim 2) of CT, MM and AS in a sub-sample of individuals with heterogeneous chronic pain who are at risk of opioid misuse. Results of the supplemental project will benefit public health by providing an empirical basis that will inform the future streamlining of these treatments, as well as the development of algorithms for matching individuals with chronic pain who are at risk for opioid misuse to the specific treatment most likely to efficiently optimize benefit.

Actigraphy and ecological momentary assessment (EMA) consisting of multiple daily measures allows for the evaluation of longitudinal mechanism effects. In the context of a clinical trial, use of actigraphy and EMA data could determine the specific lag times of mechanism effects (i.e., how long it takes for a change in a mechanism to influence key outcomes). Thus, utilizing actigraphy and EMA throughout a controlled trial represents an innovative approach to assessing psychosocial pain treatment mechanisms at a micro-level.

A2. Specific Aims and Hypotheses

In the planned trial, 90 individuals with heterogeneous chronic pain who are at risk for opioid misuse will be randomly assigned to telehealth-delivered CT, MM, or AS. Mechanisms and outcomes will be assessed with actigraphy, twice daily EMA, and weekly telephone interviews during baseline, treatment, and for 4-weeks post-treatment. Mechanisms of longer-term maintenance of gains will be evaluated at 3- and 6-month follow-up. Given past research showing equivalent efficacy for active treatments, we expect no significant group level outcome differences between conditions. However, we do expect *individual* variability in treatment response and maintenance of gains that will allow us to examine mechanisms of change. This study will address two aims.

A2a. Primary Aim and Hypotheses

Aim 1: Test the LA&E model to investigate theory driven moderators of response to CT, MM, and AS.

To accomplish Aim 1, we will use omnibus groups regions of significance (OGRS) tests to evaluate the effect sizes associated with the extent to which baseline pain catastrophizing, mindfulness, and activity level are respectively associated with reductions in opioid use following CT, MM, and AS.

Hypothesis 1a: Higher baseline levels of catastrophizing will be associated with greater reductions in opioid use in response to the CT intervention compared to MM or AS.

Hypothesis 1b: Lower baseline levels of activity will be associated with greater reductions in opioid use in response to AS compared to CT or MM.

Hypothesis 1c: Higher baseline levels of non-judgment will be associated with greater reductions in opioid use in response to MM compared to CT or AS.

Aim 2: Examine the mediators underlying the expected change in opioid use during treatment.

To accomplish Aim 2, we will use PROCESS bootstrap mediation models to evaluate the extent to which early treatment changes in the primary mechanisms (pain intensity and emotional distress, i.e., depression and anxiety) will predict subsequent late-treatment changes in opioid use (primary outcome), and the extent to which these associations are shared across the three treatments, or if some are unique to one or a subset of treatments.

Hypothesis 2a: If changes in pain intensity and emotional distress are mechanisms shared by CT, MM, and AS, then changes in opioid use in all three treatments will be predicted to approximately the same extent by changes in the primary mechanisms.

Hypothesis 2b: If changes in the primary mechanisms are *specific* to one (or a subset) of the three treatments, then Treatment Group X Assessment Period interactions will reveal that late-treatment changes in opioid use will be substantially and uniquely predicted by early-treatment changes in the primary mechanism(s) in one (or a subset) of the three conditions only.

We also predict that change in the mechanism variables will precede and predict change in outcome, but not vice versa.

A2b. Secondary Aim and Hypotheses

We will test these baseline characteristics as moderators of long-term response at 1-, 3-, and 6-month follow-up as a secondary analysis.

As a further secondary aim, this study will also evaluate the post-treatment mechanisms that explain relapse, maintenance, and continued gains associated with these treatments. The Shared (Hypothesis 2a) and Specific (Hypothesis 2b) Mechanisms Models will also be applied to data collected via EMA and ActiGraph daily during the 4-weeks post-treatment to better understand the post-treatment mechanisms that underlie maintenance of gains and relapse.

Exploratory Hypothesis 3a: The Shared Mechanisms Model hypothesizes that if early post-treatment changes in pain intensity and emotional distress are shared maintenance mechanisms across the three treatments, then treatment condition will have small and non-

significant effects on early post-treatment changes in the mechanism variables (i.e., the effects of the three treatments on the mechanism variables early post-treatment will be similar; Shared Mechanisms Model).

Exploratory Hypothesis 3b: If early post-treatment changes (i.e., post-treatment to 2-weeks post-treatment) in pain intensity and emotional distress are *specific* to one of the three treatments, then Treatment Group X Assessment period interactions will identify that early post-treatment changes in one or more of the mechanisms will be significantly associated with late post-treatment changes (i.e., 2-weeks post-treatment to 4-weeks post-treatment) in opioid use (Specific Mechanisms Model).

A2c. Exploratory Moderation Aims and Hypotheses

In addition to the planned primary analyses to address the supplemental project study hypotheses, we will also perform secondary tests to examine the effects of the three Aim 1 moderators (i.e., baseline levels of catastrophizing, mindfulness, and activity level) on continued reductions in opioid use immediately post-treatment (i.e., to 1 month follow-up) and at 3- and 6-months follow-up. We will also perform exploratory tests to examine additional potential secondary moderators and mediators. We will additionally perform planned secondary tests to evaluate the moderation and mediation effects of these variables on secondary outcomes. We will describe these as secondary analyses (i.e., exploratory and not definitive) when the study is registered at clinicaltrials.gov and when the findings from these secondary analyses are disseminated.

B. BACKGROUND AND SIGNIFICANCE

B1. Significance of Research

Chronic pain affects millions of Americans and is associated with substantial economic cost.

Chronic pain affects approximately 116 million adult Americans, and prevalence is on the rise.[1] Recent estimates report the rate of chronic pain in the U.S. translates into an estimated annual cost of between $560 to $635 billion in direct healthcare costs, disease burden and lost productivity.[2] The most common treatment approach for chronic pain is the prescription of opioid analgesic medication, but their misuse is now recognized as a healthcare crisis.[1,3,4]

Long-term use of opioid analgesics for chronic pain is associated with misuse, serious negative side-effects, and only modest pain relief.

Between 1999 and 2010, there was a 300% increase in opioid analgesic consumption in the U.S.[3,5] Accompanying this increase in consumption was a dramatic increase in the rates of opioid misuse as well as a more than three-fold increase in death rates for poisoning involving opioid analgesics, resulting in over 16,000 opioid-involved overdose deaths in 2010 alone.[3,5] The increased use of opioids is driven partially by the increased reliance on opioids for the treatment of chronic pain, with a significant proportion of individuals who experience a chronic pain condition being prescribed opioid medications.[6,7] Despite the widespread use of long-term opioid therapy in the context of chronic pain, there is a lack of research to support its efficacy.[6,8-11] Moreover, the rates of improvement with opioids is only around 30%.[6] The long-term use of opioids for the treatment of chronic pain is also associated with other significant risks, including analgesic tolerance, physical dependence, opioid-induced hyperalgesia, and risk of misuse, addiction and diversion, and other negative impacts on function (e.g., sedation).[9,12-14] In the midst of this so-called "opioid epidemic", *current evidence-based guidelines put forth by the Centers for Disease Control recommend nonopioid therapy as the first line approach to chronic pain management*.[13]

Psychosocial interventions for chronic pain are viable treatments that lead to reductions in opioid use and entail few, if any, deleterious side-effects.

Research has demonstrated that cognitive, behavioral, and mindfulness-based interventions are efficacious for chronic pain management, and also often result in *positive* side-effects, such as improvements not only in pain, but also in mood, function and psychosocial outcomes.[15,16,17] The parent grant to this supplemental project is testing hypotheses related to the mechanisms (i.e., mediators and moderators) of three such nonpharmacological approaches with evidence for their effectiveness for chronic pain: (1) Cognitive Therapy (CT), (2) Mindfulness Meditation (MM), and (3) Activation Skills (AS). These programs teach patients skills they can continue to use after treatment to manage pain mechanisms, and it is necessary to examine more than one treatment in a mechanism study.

Few trials have investigated these approaches as an alternative to opioid medication for the management of chronic pain. The limited available research suggests that cognitive and behaviorally focused treatments do lead to reductions in opioid consumption within groups of individuals with chronic pain who are at risk for opioid misuse (i.e., dosage of ≥20 morphine milligram equivalents [MMEs] per day).[13,18] However, there is wide variability in response to these approaches. What is not known is (1) for *whom* are these approaches effective for reducing opioid use (i.e., moderators of outcome), and (2) *how* are these reductions in opioid use engendered (i.e., mediators of outcome).

Advancing the understanding of treatment moderators will inform the capacity to match patients with chronic pain who are at high risk for opioid misuse to the treatment most likely to be of benefit.

To date, there has been a lack of research that has critically examined the individual, moderating patient factors that may be causative mechanisms of treatment outcome in individuals with chronic pain who are at heightened risk for opioid misuse. Despite the lack of research devoted to this topic, development of the ability to match these at risk patients to the treatment most likely to efficiently reduce opioid use via elucidation of key moderating factors is of pivotal importance. We are operating in times when public healthcare resources are substantially limited, and when the misuse of opioids is on the rise. Thus, more than ever, there is a need to maximize the utility of available resources and interventions. Limited prior research has examined the moderators of treatment response in individuals with chronic pain who are at risk for opioid misuse. However, a recent systematic review identified that patient characteristics associated with treatment response in such a population may be similar to chronic pain populations without high opioid usage.[19] This suggests that the theory pertaining to the moderators of chronic pain treatment response may be similar across these populations, although this is yet to be empirically tested.

In the funded parent project, an exploratory aim is to examine a theory driven test of the moderators of response to CT, MM, and AS in a sample of individuals with low back pain. The theoretical framework that will be tested in this context is the Limit, Activate, and Enhance (LA&E) model.[20] This model proposes a set of testable hypotheses regarding the moderators of response and identifies a decision tree for matching patient baseline profiles to specific treatments. The LA&E model is based on the fact that psychosocial treatments can be classified with respect to the extent that they are designed to: (1) encourage individuals with chronic pain to reduce or *limit* their use of maladaptive coping responses (i.e., pain catastrophizing); (2) teach or encourage individuals with chronic pain to increase or *activate* their use of adaptive coping responses (i.e., activity levels); and (3) build on or *enhance* their signature strengths (i.e., mindfulness). Given research suggests that the moderators of treatment may be similar in chronic pain populations at both low vs high risk for opioid misuse, this framework may similarly apply across these groups.[19] Thus, the proposed supplemental project aims to test the utility of the LA&E model for matching individuals with chronic pain at risk for opioid misuse to the treatment approach most likely to be of benefit. Other moderators of potential importance in this group will also be explored, including use of other substances (e.g., nicotine, alcohol, benzodiazepines), emotional distress (e.g., depression, anxiety, Post-Traumatic Stress Disorder [PTSD] symptoms), and pre-treatment expectations and motivation for treatment-related opioid reduction.[20]

Understanding treatment mechanisms for reducing opioid use is also critical to the streamlining of psychosocial approaches for effective application in this high risk population.

Testing treatment mediators has been identified as a critical next step in the field as while equivalent efficacy is typically obtained *on average* when active treatments are compared, theory suggests that the mediation pathways across treatments are unique.[21-24] An innovative approach is being used in the parent project to test theory driven (as well as non-specific) mechanisms of CT, MM, and AS. The testing of the unique vs. shared mediators of these three different pain treatments in the parent project could lead to streamlined interventions that distill the most critical change factors into an efficient and cost-effective treatment package.

In this context of the parent project, we have a unique opportunity to leverage the existing resources and state-of-the-art mechanism methodology to extend this program of research into

the testing of how these theory driven mechanisms operate within the treatment of individuals with chronic pain who are also at risk for opioid misuse. It is possible that given the treatments – CT, MM, and AS – are theorized in the broad psychotherapy literature to target essentially the same unique mechanisms regardless of the setting/population applied (i.e., whether in chronic pain, depression, substance use, etc.)[e.g.,25-30] that the same mechanisms proposed in the parent project (i.e., change in cognitive content in CT, change in cognitive process in MM, and change in activity level in AS) will also apply in a population at risk for opioid misuse.

However, in terms of the *mechanisms specifically underlying the outcome of reduced opioid consumption in at risk populations*, there may be defining aspects of changes occurring during treatment that function as mechanisms unique to this population (that is, that do not mediate outcome in populations *not* at risk for opioid misuse). Specifically, given research that has shown a complex interaction between both pain intensity and emotional factors as drivers of opioid use within chronic pain populations,[31] it is plausible that treatment related changes in both pain intensity as well as emotion (e.g., anxiety, depression) might be mechanisms specifically underlying reduced opioid consumption in individuals with chronic pain who are at risk for opioid misuse. Our pilot data from a randomized controlled trial (RCT) comparing CT, Hypnosis, and Hypnotic-CT in a musculoskeletal pain sub-sample provide preliminary support for the premise that treatment-related changes in pain intensity and depression might be critical mechanisms underlying reductions in opioid use. In this pilot data, pre- to mid-treatment changes in these mechanisms evinced significant, large associations with later (i.e., mid- to post-treatment) changes in opioid use (*r*s of .58 and .68 for intensity and depression, respectively) across individuals prescribed opioids at baseline (N=18). Further, early changes in opioid use were not significantly correlated with later changes in intensity or depression (*r*s of -.22 and -.13 for intensity and depression, respectively). These lagged mechanism associations underlying treatment-related reduced opioid use were even larger in those individuals (N=9) who at baseline met criteria for at risk opioid use (*r*s of .69 and .94 for intensity and depression, respectively). Thus, this pilot data supports the potential mechanism role of treatment related changes in pain intensity and depression as drivers of reduced opioid use in at risk groups.

D. RESEARCH DESIGN AND METHODS

D1. Synopsis

The sample will include up to 90 adult participants with heterogeneous chronic pain who are at risk for opioid misuse. Study inclusion criteria include: (1) age ≥18 years; (2) meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months); (3) use of opioid medication in the past week[1]; (4) daily average opioid analgesic medication use in the past week of ≥20 MMEs; (5) average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months; (6) able to read, speak, and understand English to comprehend the worksheets, measures, and interventions implemented; and (7) availability of a telephone, webcam, and microphone through computer or telephone, as well as daily internet access.

Exclusion criteria include: (1) primary pain condition is headache; (2) severe cognitive impairment; (3) current alcohol or substance dependence; (4) active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus); (5) inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention; (6) significant pain from a recent surgery or injury; (7) pain condition for which surgery has been recommended and is planned; (8) any planned surgery, procedure, hospitalization, treatment, or event that may conflict with or otherwise influence participation in the study; (9) currently receiving or had received other psychosocial treatments for any pain condition (as this may influence these treatment results); (10) current or past participation in a research study with components that may overlap, conflict, or affect those in the current study; (11) current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years; (12) psychiatric hospitalization within the past 6 months; (13) psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months; (14) any psychiatric or behavioral issues as noted in the medical record or disclosed/observed during self-report screening that would indicate participant may be inappropriate in a group setting; and (15) presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others, or active delusional or psychotic thinking.

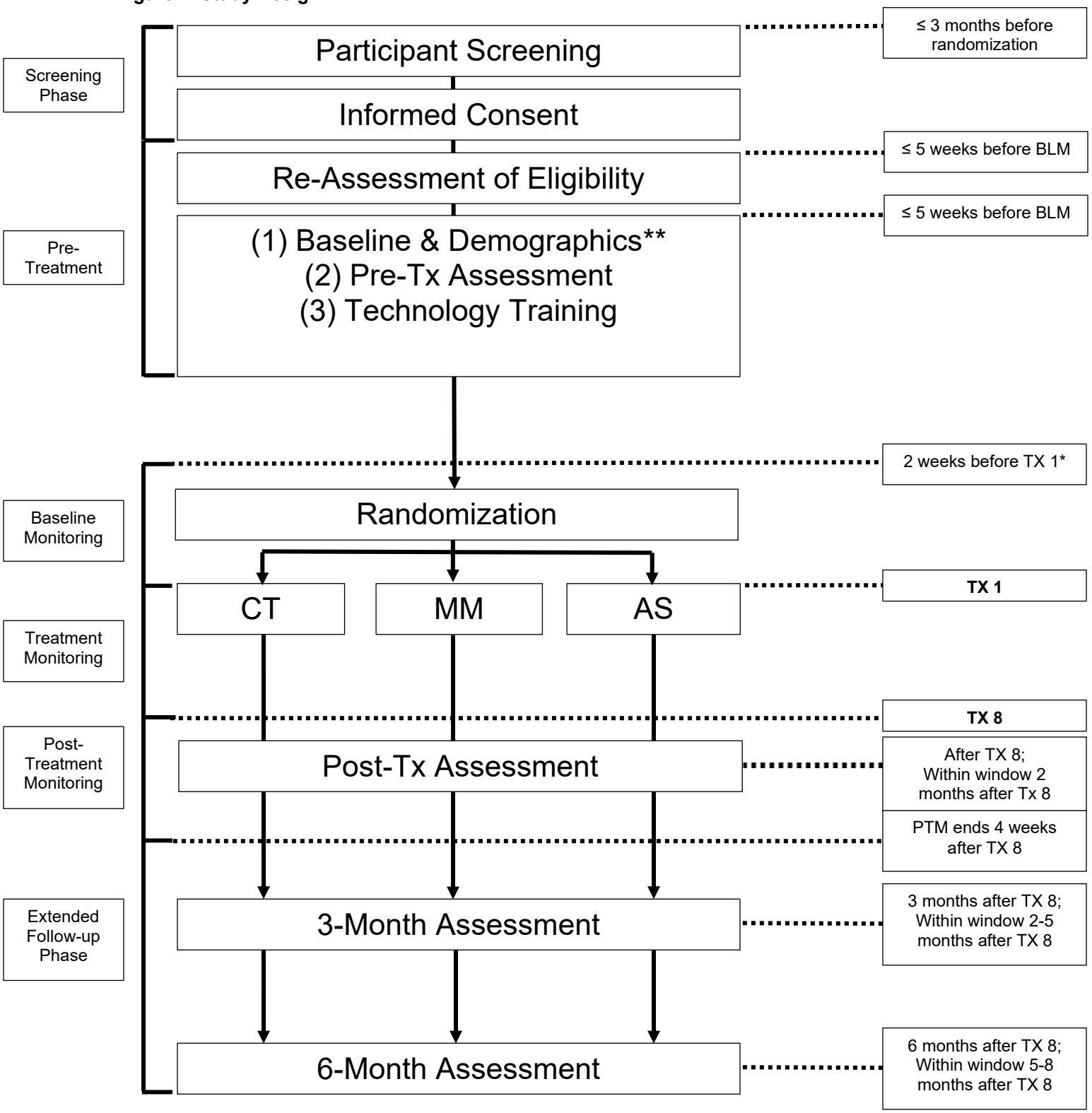
Study participants who meet study inclusion criteria and consent to participate will complete all required baseline components before being randomly assigned to eight, 1.5 hour videoconference-delivered group sessions (2 sessions per week on average) of one of three manualized treatments: (1) cognitive therapy (CT), (2) mindfulness meditation (MM), or (3) behavioral activation skills training (AS). Telephone outcome assessors will be blind to randomization group, and participants will not be told which treatment is expected to be most beneficial. Participants will be told, however, that each of the therapies to which they could be assigned is a type of “pain self-management” intervention that previous patients have found helpful, and that the purpose of the study is to determine how these interventions work.

All measures will be assessed by research staff over telephone at pre- and post-treatment and either by telephone or online at 3-month and 6-month follow-up. We will also invite participants upon completing each assessment period to participate in an optional assessment. Additionally, primary outcome measures and hypothesized mechanism variables will be assessed (via cue-elicited, twice daily EMA methodology accessible via smart phone, tablet, laptop, and/or desktop) during an approximately 2-week Baseline Monitoring Period, throughout the Treatment Period, and throughout the initial 4-weeks Post-Treatment. During the same time

period as EMA administration, participants will also complete abbreviated weekly telephone assessments that will assess study outcome and mechanism variables. Activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Exploratory moderator variables will be assessed at the initial screening (see Table 1).

The study uses a 3-group parallel design (see Figure 1). During their study participation, all participants will continue to receive their usual medical, psychiatric, and psychotherapeutic care.

Figure 1. Study Design



* Based on the Tx 1 date of the earliest group
** Age, sex, gender, race, and ethnicity data may be collected after informed consent prior to the start of the Pre-Treatment Phase

Table 1. Study Design		
Step	**Data Collected**	**How Often/When**
Re-Assessment of Eligibility	Opioid use, pain consistency, pain frequency, medications, current and planned treatments (collected to ensure participant is still eligible for randomization)	Once following consent, before treatment begins
Randomization Stratification	Opioid use (collected to determine randomization stratification)	Once following consent, before treatment begins*
Baseline Data and Demographics	Demographic and general health information, chronic pain history, chronic pain treatment history and surgery history, smoking and alcohol use, CT, MM, and AS treatment history and practice; treatment preference, the importance of various treatment outcomes, and pain medication beliefs	Once following consent, before treatment begins
Technology Training	N/A	Once following consent, before treatment begins
Pre-Treatment Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once following consent, before treatment begins
2-Week Baseline EMA Monitoring with Actigraphy and Weekly Surveys	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, and treatment credibility and expectancies; Actigraphy: Activity level and sleep Weekly Assessment: Medication use, pain intensity, anxiety, depression, catastrophizing, non-judgement	Approximately two weeks before treatment begins; starts two weeks before the date of the earliest treatment group
Randomization	N/A	Once following completion of all Baseline study procedures**
Treatment	Participant engagement as per clinician, amount of home practice per completed home practice documents	Eight sessions, on average twice per week

During Treatment EMA Monitoring with Actigraphy and Weekly Surveys	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, time spent practicing coping skills, therapeutic alliance, group cohesion, and treatment credibility and expectancies; Actigraphy: Activity level and sleep Weekly Assessment: Medication use, pain intensity, anxiety, depression, catastrophizing, non-judgement	Begins day of Session 1 and ends day of Session 8
4-Week Post-Treatment EMA Monitoring with Actigraphy and Weekly Surveys	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, and time spent practicing coping skills; Actigraphy: Activity level and sleep Weekly Assessment: Medication use, pain intensity, anxiety, depression, catastrophizing, non-judgement	Immediate four weeks following end of treatment
Post-Treatment Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, treatment modality, overall participant improvement since beginning treatment, open-ended items about experiences in group and feedback about program, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once following end of treatment; allowable window of up to 2 months after end of treatment
3-Month Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, overall participant improvement since beginning treatment, the importance of various treatment outcomes, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once three months following end of treatment; allowable window of 2-5 months after end of treatment

6-Month Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, overall participant improvement since beginning treatment, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once six months following end of treatment; allowable window of 5-8 months after end of treatment

* Will only be administered if participant is still eligible after Re-Assessment of Eligibility

** Only participants who have completed all required baseline study procedures will be randomized. Required procedures include: Baseline Data, Demographics, Pre-Treatment Assessment, Technology Training, Re-Assessment of Eligibility and Randomization Stratification, and completion of a minimum number of EMA surveys.

D2. Study Timeline

We designed a four-year study plan and timeline for achieving short-term study objectives. There will be approximately 35 months available to enroll 90 participants. The anticipated lost to follow-up rate for this study is 20% of the total enrollment number, or 18 participants. We anticipate that with 90 participants enrolled (although we may elect to continue to enroll beyond this if we have the resources to do so, as this would provide even more power for the planned analyses) and a 20% attrition rate, we will have complete data for 72 of our participants; the primary analyses are to be conducted with the intent to treat sample.

Months 01-06 in Year 01 (Year 02 of the parent grant) will be spent finalizing internal operating procedures surrounding the study. Participant enrollment will require approximately 3 years (36 months; Month 07, Year 01 through Month 06, Year 04). Data collection and cleaning will be ongoing through Month 12, Year 04. Data analysis and dissemination will occur following data collection and cleaning. Drs. Jensen and Day will closely monitor study flow and will hold regular conference calls to coordinate study procedures. Both PIs will be directly involved with the details of the study at every level. Intra-site team meetings with staff and Co-Is will be conducted to ensure any issues will be addressed as they arise.

Milestone	Year 1*				Year 2*				Year 3*				Year 4*			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Finalize administrative supplement protocol, data collection procedures, and obtain IRB approval	X	X														
Enroll 90 participants and execute study procedures			X	X	X	X	X	X	X	X	X	X	X	X		
Data analysis; evaluate benchmarks to determine whether to proceed to grant application for a larger study															X	X
Dissemination of study findings															X	X

*Add one year for time corresponding to parent grant

D3. Inter-Site Communication and Coordination

Routine communication and coordination between the investigators will occur primarily through joint teleconferenced executive meetings. The PIs will communicate bi-weekly (scheduled) or more often (if needed), either by phone, e-mail, or Skype/Zoom, as well as in-person 1-2 times per each year of the funded period, to discuss experimental design, data analysis, and all administrative responsibilities. They will work in close collaboration with the study investigators to discuss the direction of the research project and the reprogramming of funds, if necessary. Scheduled project wide meetings with all study investigators and study staff will be held on a monthly basis and will be chaired by Dr. Day; Dr. Day and other investigators not located on the University of Washington campus will primarily be present via Zoom for these meetings, and occasionally in-person and/or via conference call.

D4. Participant Recruitment and Feasibility

Potential participants with heterogeneous chronic pain conditions will be primarily identified via diagnostic codes in the University of Washington Medical Center (UWMC) / Harborview Medical Center (HMC) medical records. Recruitment approaches could also include several other modalities, if required. These include using our department's research participant pool and reaching out to past participants who indicated interest in contact about future studies, posting flyers and brochures in relevant clinics, such as Spine and Rehabilitation Medicine clinics at both HMC and UWMC; and announcements about the study on the hospital-wide electronic reader board and through the UW Medicine Newsroom (https://newsroom.uw.edu/), which publicizes studies that are enrolling participants through a variety of electronic, print, and social media sources. The pool of potential participants currently includes about 9,000 initially eligible individuals.

Clinicians in UWMC clinics (as well as clinics outside of the UWMC system that agree to participate in recruitment efforts) will be periodically alerted to this study and its eligibility criteria and encouraged to refer patients who meet criteria and for whom this would be clinically appropriate. Identified individuals will be added to a participant registry and will be contacted and sent information that describes the study and invites them to participate. Interested individuals may also be instructed to directly contact study investigators.

Additionally, research staff may pre-screen lists of patients with upcoming appointments in relevant clinics at both HMC and UWMC or use available research tools in the UW Medicine EHR system to search for potential participants. Participants meeting eligibility criteria will be contacted and sent information that describes the study and invites them to participate. Potential participants may also be approached in clinic about the study.

If needed, we will also recruit nationally. If so, we plan to post the study on ClinicalTrials.gov and we may also use social media sources and ResearchMatch.org if needed and appropriate. In addition, and again if needed, we would plan to seek input from other NCCIH investigators and colleagues regarding ideas for recruiting individuals with chronic pain from national samples.

In addition to these primary recruitment sources, we will also recruit using social media, online forums, websites, patient advisory networks, and other online mediums that are pertinent to chronic pain. We will also encourage providers, participants, and interested individuals to pass along our study information to others as they see fit.

The recruitment sources described above will provide participants who are representative of the general population with a history of heterogeneous chronic pain conditions and enhance the generalizability of the study results.

D5. Participants

We propose to enroll 90 participants. The anticipated lost to follow-up rate for this study is 20% of the total enrollment number, or 18 participants. We anticipate that with 90 participants enrolled (although we may elect to continue to enroll beyond this if we have the resources to do so, as this would provide even more power for the planned analyses) and a 20% attrition rate, we will have complete data for 72 of our participants; the primary analyses are to be conducted with the intent to treat sample.

Eligibility Criteria

Inclusion Criteria:

(1) Age ≥18 years;
(2) Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in past 6 months);
(3) Use of opioid medication in the past week;
(4) Daily average opioid analgesic medication use in the past week of ≥20 MMEs;
(5) Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months;
(6) Able to read, speak, and understand English; and
(7) Availability of a telephone, webcam, and microphone through computer or telephone, as well as daily internet access.

Exclusion Criteria:

(1) Primary pain condition is headache;
(2) Severe cognitive impairment;
(3) Current alcohol or substance dependence;
(4) Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
(5) Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
(6) Significant pain from a recent surgery or injury;
(7) Pain condition for which surgery has been recommended and is planned;
(8) Any planned surgery, procedure, hospitalization, treatment, or event that may conflict with or otherwise influence participation in the study;
(9) Currently receiving or had received other psychosocial treatments for any pain condition;
(10) Current or past participation in a research study with components that may overlap, conflict, or affect those in the current study;
(11) Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;
(12) Psychiatric hospitalization within the past 6 months;

(13) Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
(14) Any psychiatric or behavioral issues as noted in the medical record or disclosed/observed during self-report screening that would indicate participant may be inappropriate in a group setting; and
(15) Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.

Clinical discretion may be exercised as needed regarding mental health exclusion criteria above to determine appropriateness in a group setting.

We will not have an upper age cutoff for study participation because we have successfully treated individuals at all ages, including those over 80 years old.

D6. Procedures

D6a. Recruitment

IMPORTANT: All materials and procedures listed below to be used for recruitment will be submitted to the University of Washington IRB for review and approval.

Select Medical Record Review

Researchers will receive lists of patients who may potentially be eligible for the study who have received services at either the University of Washington Medical Center (UWMC) or Harborview Medical Center (HMC) systems. These lists may contain the patient's contact information and information related to the patient's UWMC/HMC visits. Such information could include, for example, clinics visited, reasons for visits, dates of visits, visit outcomes, diagnoses, problem lists, and medications taken, among others. This information would be used to sort and filter patients to determine preliminary eligibility for this study. Staff may review the medical records of these patients in the UWMC/HMC medical records system for pre-screening purposes to confirm study eligibility if the information contained in the list is not sufficient to make a determination. Research staff would send eligible patients an approach letter or email along with an information sheet about the study if they are deemed eligible. Patients may also receive an approach text message. The patient would then contact research staff via telephone if interested in participating in the study. Research staff would call patients following the initial contact attempt if there is no response to make sure the patient received the letter. Research staff would use a script to inquire whether the patient is interested in participating in the research study or not. Research staff would initiate the study self-report screening process over the telephone if the patient is interested in participating using the research recruitment script and electronic screening case report form (self-report screening protocol described in detail below).

Number of Contacts: Research staff would send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

Other Studies and Registries

Research staff may contact participants who participated in previous studies who agreed to be contacted for further research opportunities, or are enrolled in a registry (such as the department's Participant Pool, or others like it). We may also contact participants who are referred to us by other research studies, or use another study's participant lists/databases (provided by the other study with all IRB permissions in place).

Participants from these sources will be sent an approach letter or email with a FAQ sheet that will explain the study in more detail; participants may also receive an approach text message.

Number of Contacts: Research staff would send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

<u>If needed</u>, we will also recruit from the following sources:

Provider Referral

1) Health care providers from the UWMC/HMC Spine and Rehabilitation Medicine clinics, primary care clinics, and clinics/medical organizations outside of the UWMC/HMC system who agree to participate in recruitment efforts, may also provide research staff members the contact information of potential patients who expressed interest in participating in the research study or the provider deems may be a good fit for the study. Research staff would reach out via email or phone (depending on what contact information is provided) and initiate the study screening process if a patient is interested in participating using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

   Number of Contacts: Research staff may send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

2) Providers can also refer patients to the study by providing the patient with recruitment materials or study contact information and inviting them to follow-up independently. The patient would then contact research staff if interested in participating in the study.

   Number of Contacts: Following initial contact by patient, research staff would then attempt to reach the patient over phone or email. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

3) In addition, medical records may be reviewed for patients with upcoming visits to certain clinics (e.g., various Spine and Rehabilitation Medicine clinics) where we expect a high

rate of interest, relevance, and eligibility. Research staff may contact a provider to inform them when a particular patient who appears to be eligible for the study based on the medical record screening protocol will be attending an upcoming appointment, and that staff would like the provider to mention the study to the patient. Ideally this would then result in scenario #1 described above.

4) As needed, research staff will review the medical records of patients who have upcoming appointments at the UWMC or HMC Spine, Rehabilitation Medicine, or other relevant clinics for a chronic pain problem. If they are deemed eligible, research staff may send the patient an approach letter or email along with an information sheet about the study prior to their appointment that indicates why they are being approached, and informs them that they may be approached by research staff during their next appointment in the clinic. The patient would then contact research staff if interested in participating in the study. Research staff may approach the patient during their next appointment to see if they would be interested in participating if the patient does not contact the research team. Research staff may also approach patients directly in clinic without first using an approach letter or email if a specific clinic has provided permission for researchers to recruit with this method. Research staff would initiate the study self-report screening process if the patient is interested in participating using the research recruitment script and screening case report form in a private location, or set up a time to conduct the screening over the telephone (self-report screening protocol described in detail below).

Number of Contacts: Research staff may send one approach letter or email and may make one initial, in-person approach in clinic. If the patient indicates interest but does not want to discuss the study in clinic, staff will attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

In-Person Recruitment in Clinics and Other Spaces

Research staff may also recruit potential participants via in-person efforts in clinics where permission has been granted by clinic management/leadership or in other spaces as deemed appropriate. For locations where permission is needed to recruit in-person, researchers will seek and receive all approvals before engaging in such activities. Examples of in-person recruitment include, but are not limited to, setting up a table with a research staff member and recruitment materials, engaging waiting individuals or passerbys with recruitment materials (e.g., a brochure) and/or a short pitch about the study, or participating in an event targeting research or participant recruitment (e.g., a research fair). Staff may collect basic contact information such as name, telephone number, email address, etc. from in-person recruitment efforts; staff may also schedule a time with the potential participant to follow up with more details and/or start the screening process.

Self-Referral

If needed, flyers and brochures describing the study will be made available throughout clinics where we expect a high rate of interest, relevance, and eligibility. There may also be announcements about the study on the hospital-wide electronic reader board and through the UW Medicine Newsroom (https://newsroom.uw.edu/), which publicizes studies that are enrolling participants through a variety of electronic, print, and social media sources. Interested patients would then contact research staff via telephone or email.

If researchers are interviewed regarding the study, video or audio information about the study may be disseminated by news agencies in addition to any stories that may get published in print or online. Researchers may also place print or electronic advertisements or articles in publications such as newspapers, magazines, or newsletters. Additionally, researchers may take out advertisements in physical spaces such as on transit (e.g., buses, trains, trolleys) or at transit stations. If other viable locations for physical or electronic advertisements arise, researchers will work with the appropriate parties for permission and pricing considerations. All ads will display basic information about the study and study contact information. Interested people will contact the study directly after seeing the ad (or story, if researchers are featured in a news release). Research staff would initiate the study self-report screening process over the telephone if the patient is interested in participating in the study using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

If recruitment is opened up beyond patients in the UWMC/HMC system, potential participants will be able to contact research staff after seeing our listing on ClinicalTrials.gov or on any other websites, forums, blogs, patient advisory networks, and social media sites researchers decide to post the study. Research staff would initiate the study self-report screening process if the patient is interested in participating in the study using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

Number of Contacts: Following initial contact by the potential participant, research staff will attempt to reach the patient over the phone (or email, if contacted via email and participant did not provide a phone number). In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, if we have the potential participant’s mailing address, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

ResearchMatch.org

ResearchMatch is a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible. The database currently contains over 120,000 volunteers across the United States who have created profiles and are ready to be matched to appropriate research studies.

Research staff will search for appropriate matches amongst the non-identifiable ResearchMatch volunteer profiles in the system by entering in as much of the study's inclusion and exclusion criteria into ResearchMatch's Search Builder. The Search Builder will then yield a list of potential matches based on the search criteria. Staff will send out an initial recruitment message to these potential matches through ResearchMatch. The secure ResearchMatch clearinghouse will route the message to each of the potential matches and they will have the option of replying yes, no, or no response. By replying yes, ResearchMatch releases the volunteer's contact information so that researchers may follow up with the volunteer directly. A volunteer has the option of listing their mailing address, telephone number, and/or email address; some volunteers may only list one mode of contact while others may choose to list multiple.

Once the volunteer has authorized ResearchMatch to release their contact information to us, staff will contact the volunteer using their provided contact information. There are several possible routes we may contact volunteers, depending on what types of contact information the volunteer provides researchers. A specific approach letter and information sheet will be used when contacted via postal mailing, or a specific approach email when contacted via email. The research recruitment script will be used when contacted via telephone. If the volunteer is interested in being screened for the study, staff will go through the self-report screening process.

The recruitment approaches described above will provide participants who are representative of the general population with chronic pain, and enhance the generalizability of the study results. If needed, we would plan to seek input from other NCCIH investigators and colleagues regarding other ideas for recruiting individuals with chronic pain from national samples.

Research staff will use a combination of postal mail, email, phone, and/or text messaging during study recruitment, depending on recruitment source, participant preference, and/or what seems to be the easiest way to get a hold of the participant. Please note that only research staff members will screen, consent, or perform study procedures with potential participants.

D6b. Screening Procedures

The study screening procedures for participants will consist of the following:

Self-Report Screening

Research staff will ask potential participants a set of formalized IRB-approved questions to determine eligibility based on all of the study inclusion/exclusion criteria listed below with the assistance of the screening case report form.

Self-reported inclusion criteria include the presence of chronic pain, operationalized as follows:

- Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months);
- Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months.

Additional self-report inclusion criteria include:

- Age ≥18 years;
- Able to read, speak, and understand English;
- Use of opioid medication in the past week;
- Daily average opioid analgesic medication use in the past week of ≥20 MMEs;
- Availability of a telephone, webcam, and microphone through computer, telephone, or other mobile device; as well as daily internet access.

Self-report exclusion criteria include:

- Primary pain condition is headache;
- Severe cognitive impairment;
- Current alcohol or substance dependence;

- Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
- Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
- Significant pain from a recent surgery or injury;
- Pain condition for which surgery has been recommended and is planned;
- Any planned surgery, procedure, hospitalization, treatment, or event that may conflict with or otherwise influence participation in the study;
- Currently receiving or had received other psychosocial treatments for any pain condition;
- Current or past participation in a research study with components that may overlap, conflict, or affect those in the current study.

Self-reported exclusion criteria also include psychiatric or behavioral disorders that would interfere with ability to participate, as operationalized below:

- Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;
- Psychiatric hospitalization within the past 6 months;
- Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
- Any psychiatric or behavioral issues disclosed or noticed during self-report screening that would indicate participant may be inappropriate in a group setting;
- Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.*

Clinical discretion may be exercised as needed regarding mental health exclusion criteria above to determine appropriateness in a group setting.

* If during self-report screening the potential participant presents symptoms of active suicidal ideation, research staff will implement the emergent situations protocol (see section Suicide Risk Assessment Protocol). If there are any questions or concerns regarding the potential participant's psychological, behavioral, or cognitive appropriateness for the study, research staff will either (1) ask the participant if staff may call them back at a later time after consulting with a study investigator, or (2) ask for the potential participant's permission to have a licensed psychologist or a Masters-level or post-doctoral level clinician supervised by a licensed psychologist speak with the potential participant.

The psychologist or Masters-level or post-doctoral clinician (supervised by one of the study Co-PIs, Dr. Jensen, who is a licensed clinical psychologist) will use their clinical expertise and judgment to ask the potential participant some additional questions to assess the participant for the concerns (e.g., active suicidal or homicidal ideation or active delusional or psychotic thinking) raised by research staff. Clinical discretion may be exercised as needed regarding mental health exclusion criteria. The psychologist or Masters-level or post-doctoral clinician will relay the outcome of the call back to the staff member completing the self-report screening.

Ineligible Participants

Research staff will offer ineligible participants a list of resources with information about treatment of pain (e.g., books, internet resources, etc.) and any relevant clinical resources available. While staff will do their best in offering participants resources, there may be situations where there may not be an opportunity for staff to offer resources, or offering one may be inappropriate, e.g., the participant is hostile, aggressive, or disrespectful and/or terminates the conversation before staff are able to offer resources.

This resource list will also be available to enrolled participants who inquire about additional resources. The resource list will be accompanied with a cover letter if sent via mail.

Potential Participants who Decline

Research staff will collect basic demographic information from all participants who are deemed eligible to participate (following at least self-report screening) yet decline to participate. These data will be collected to determine if there are significant differences between eligible participants who enroll and those who do not.

Re-Screening

Research staff will re-screen eligible participants with the use of a re-screening script on the following mutable inclusion criteria if 3 months or more have elapsed between the initial screening and randomization OR if there is a revision of the screening questions used in determining eligibility. Re-screenings will always be done using the most current approved version of the screening form and will need to be done for participants who have not yet been randomized. The following criteria will be assessed:

1. Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months);
2. Daily average opioid analgesic medication in the past week of ≥20 MMEs;
3. Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months;
4. Availability of a telephone, webcam, and microphone through computer, telephone, or other mobile device; as well as daily internet access.

In addition, research staff will re-screen eligible participants on the following mutable exclusion criteria if 3 months or more have elapsed between the initial screening and randomization OR if there is a revision of the screening questions used in determining eligibility:

1. Primary pain condition is headache;
2. Severe cognitive impairment;
3. Current alcohol or substance dependence;
4. Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
5. Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
6. Significant pain from a recent surgery or injury;
7. Pain condition for which surgery has been recommended and is planned;
8. Any planned surgery, procedure, hospitalization, treatment, or event that may conflict with or otherwise influence participation in the study;
9. Currently receiving or had received other psychosocial treatments for any pain condition;
10. Current or past participation in a research study with components that may overlap, conflict, or affect those in the current study;

11. Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;
12. Psychiatric hospitalization within the past 6 months;
13. Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
14. Any psychiatric or behavioral issues disclosed or noticed during self-report screening that would indicate participant may be inappropriate in a group setting;
15. Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.*

* If during self-report re-screening the potential participant presents symptoms of active suicidal ideation, research staff will implement the emergent situations protocol (see Suicide Risk Assessment Protocol). If there are any questions or concerns regarding the potential participant's psychological, behavioral, or cognitive appropriateness for the study, research staff will either (1) ask the participant if staff may call them back at a later time after consulting with a study investigator, or (2) ask for the potential participant's permission to have a licensed psychologist or a Masters-level or post-doctoral clinician supervised by a licensed psychologist speak with the potential participant.

The psychologist or Masters-level or post-doctoral clinician will use their clinical expertise and judgment to ask the potential participant some additional questions to assess the participant for the concerns (e.g., active suicidal ideation or active delusional or psychotic thinking) raised by research staff. Clinical discretion may be exercised as needed regarding mental health exclusion criteria. The psychologist or Masters-level or post-doctoral clinician will relay the outcome of the call back to the staff member completing the self-report screening.

Screening procedures for this study will not require a physical examination or laboratory procedures.

The recruitment outcome for each participant will be captured using an electronic recruitment outcome case report form. The data collected will help ensure accurate reporting of recruitment and enrollment efforts in future publications.

The self-report screening component may take place up to 6 months prior to the randomization for that particular cohort.

D6c. Consent Process

All participants who meet eligibility criteria following all components of the screening procedures will then undergo the informed consent process if they wish to participate. Research staff will participate in and obtain informed consent from research participants after screening but prior to commencement of any further study procedures. The informed consent process will take place over the telephone at a time deemed mutually feasible for the participant and staff member and coordinated on a case-by-case basis.

Prior to the informed consent process, research staff will email (or postal mail, if the participant prefers) a copy of the information statement for the participant to review as well as the date and time of the appointment. Participants will be encouraged to read the information statement prior to the scheduled consent session and to be prepared with any questions. If the

informed consent session is scheduled more than two business days in advance, research staff will ask to call, text, and/or email participants as a reminder. Participants will be requested to have the information statement in front of them during the consent session.

A research staff member will review each section of the information statement approved by the UW IRB, inviting discussion to ensure comprehension. Staff will be trained by study investigators to ensure competency to discuss informed consent and strategies to ensure there is no coercion.

Participants will be provided with as much time as needed to review the information statement and ask the research staff member questions about the information statement, their rights as human participants, and participation in the study. Potential participants will be fully informed of all risks and benefits prior to giving their verbal informed consent and prior to enrollment in the study. **Potential participants will also be informed that providing consent for enrollment into the study does not guarantee assignment to a treatment intervention, as this is contingent on completing certain required baseline procedures (see randomization section below).**

If during the course of this contact the potential participant has questions that cannot be addressed by research staff, one of the study investigators or the research coordinator (depending on the nature of the questions) will follow up with the potential participant to answer the questions. Participants may take time to think about participating and render a decision at a subsequent time.

Potential participants will be asked to repeat back to research staff their understanding of the information statement material as necessary. Individuals will not be permitted to participate if there is any question as to whether a person has capacity to provide informed consent.

When all questions have been answered, research staff will ask the participant if they would like to participate in the study. The participant will then be asked to provide verbal consent to participate. The participant will not need to sign the information statement, as we have a Waiver of Documentation of Informed Consent through our institution's IRB.

Research staff may also ask the participant if they would like to learn more information about enrolling into the department's research participant pool. The participant pool consists of individuals who indicated interest in participating in Department of Rehabilitation Medicine research studies and who have agreed to be contacted by researchers for future studies. If the participant indicates interest, research staff will pass along to the participant information on how to enroll in the participant pool. Participants may decline to participate in the participant pool and still participate in the research study.

Research staff will provide participants with staff contact information (emailed) after the consent process. Participants will be sent a response key to help answer questions asked during the extended telephone assessments. Staff will also provide the participant with a schedule of the study procedures. If anything is mailed, it will be accompanied by a cover letter.

Research staff will complete an electronic enrollment case report form as well as documenting the consent process form in REDCap for each enrolled participant that will be included with study data. The REDCap system will allow researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered.

Participants may be screened and enrolled up to 3 months from the date they are randomized to a treatment intervention. However, if a participant is enrolled but more than 3 months will have passed between their date of consent and date they will be randomized, staff will re-screen the participant to ensure they are still eligible for the study.

D6d. Baseline Data and Demographic Information

After providing informed consent, research staff will ask the participant to provide demographic data (e.g., age, sex, gender orientation, ethnicity/race, marital status, education level, height and weight, income, household size, disability compensation status, lawsuit status, employment status) for descriptive purposes. We will also ask participants about their chronic pain history, chronic pain treatment and surgery history, whether they have been out of work due to chronic pain, smoking and alcohol use, treatment preferences, the importance of various treatment outcomes, pain medication beliefs, and CT, MM, and AS treatment history and practice.

The baseline data and demographic questions will take approximately 20-30 minutes to complete, and may be completed following enrollment during the same phone call as the informed consent session or during a later call if more convenient for the participant. Research staff will record baseline and demographic data on an electronic case report form in REDCap.

The collection of baseline data and demographic information may take place up to seven weeks prior to the start of the treatment groups for that particular cohort. Staff may collect information on a participant's age, sex, gender, race, and ethnicity immediately after informed consent and prior to the start of the Pre-Treatment Phase (i.e., before the window for baseline and demographic data collection opens).

We will re-collect baseline and demographic information if 3 months or more have passed since collection of this information and randomization. In other words, if a participant has already provided baseline and demographic information, but continues to defer to later cohorts without yet being randomized, the last instance of baseline and demographic information on file for them must have been collected within 3 months of randomization, regardless of the number of times the baseline and demographic information was already collected.

D6e. Personal Contact Information

Research staff will collect the following information from participants: (1) contact information; (2) preferred telephone number to reach an individual if they have more than one line; (3) permission to leave message on mobile/landline phones; (4) permission to send a text message and, if yes, cell phone carrier; (5) best times/days to reach participant; (6) email address; (7) preferred communication method; (8) an emergency contact; and (9) names and contact information of people staff are allowed to contact if participant is lost to follow-up or otherwise cannot be contacted (i.e., collateral contacts). The purpose of this is to maximize the likelihood of reaching a participant to complete the study procedures. Furthermore, asking permission to leave a voicemail at a specified contact number ensures a greater level of privacy for the participant.

The information may be collected following enrollment either during the same phone call as the informed consent session or during a later call if more convenient for the participant.

D6f. Technology Training Session

After providing informed consent but prior to randomization, a staff member will schedule a time mutually feasible with the participant to test their ability to use the HIPAA-compliant Zoom videoconferencing platform used to deliver the treatment sessions (https://zoom.us) and additionally review other study components. Zoom videoconferences allow participants to see and hear each other, and also allows screen sharing, giving therapists the opportunity to display visual information (e.g., PowerPoint slides) during the session. Staff will send the participant an invitation to join a test meeting where they will give a brief overview on how to operate the basic Zoom functions as a participant in the treatment sessions. Staff will also review the EMA and ActiGraph technologies with the participant during this training session. This training serves as an opportunity for staff to help address any technological issues, concerns, or questions the participant may have with their smartphone, computer, webcams, microphones, etc. and using the videoconferencing software, or with the EMA software or ActiGraph. A participant may request refresher training at a later date. Staff can also offer refresher trainings during later cohorts if a participant does not participate in the treatment groups for the cohort which they complete the technology training.

The participant must verbally agree during the training session that they are comfortable with using all study-required software and with participating in group sessions using the videoconference software. We want participants to feel comfortable using all required technology before treatment starts to minimize the risk of disruptions during the treatment sessions (although staff will be on hand to help if such technological issues arise).

Written instructions on using the videoconference platform and some etiquette guidelines will also be provided to the participant.

If a participant defers to another cohort after completing the technology training session, they will need to redo the technology training (could be a refresher) at the time of the cohort for which they will receive treatment.

D6g. Assessments: General Assessment Overview

Participants will complete a Pre-Treatment extended outcome assessment with research staff following enrollment into the study. Extended outcome assessments at Pre- and Post-Treatment will be administered over the telephone by research staff blind to participant treatment assignment. The Pre-Treatment assessment may be scheduled to be done on the same day as the initial intake after the participant has provided informed consent or on a later day that works better for the participant.

During the Pre-Treatment assessment, research staff will ask participants questions on pain interference, pain catastrophizing, cognitive processes, activity level, average intensity of chronic pain over the past 7 days, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in activities, quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, pain medication beliefs, and perceived cognitive abilities. Effective 2020, there are also questions on COVID-19's impact on mental health and well-being. Research staff will record extended outcome assessment data on an electronic case report form in REDCap.

The entire time required to answer questions during the Pre-Treatment assessment is 45-60 minutes. Participants must complete the Pre-Treatment assessment no more than 7 weeks before starting treatment and before beginning the 2-Week EMA and ActiGraph Baseline Monitoring Period described below. Participants who do not complete the Pre-Treatment assessment within this window will not be randomized and will be offered the option to defer to a later cohort. If a participant completes the Pre-Treatment assessment but defers to a future cohort before getting randomized, they will need to redo the Pre-Treatment assessment at the time of the future cohort as we require this data within 7 weeks of treatment.

The assessment period described above will be completed prior to initiating treatment, post-treatment (after session #8), and 3 and 6 months following the end of treatment for a total of four times. These assessment periods that occur following the start of treatment will also include questions about amount of time spent practicing skills learned in treatment, treatment satisfaction and treatment modality, the importance of various treatment outcomes, and overall improvement since the participant began the treatment program. The assessments done at 3 and 6 months following the end of treatment may be completed online by the participant via REDCap instead of verbally over the telephone with research staff. Regardless of modality, the items on both the online and verbally administrated versions of the extended assessments will be the same.

The participant will also be asked additional questions at post-treatment about their experiences in the group, as well as any feedback about the treatment program. Effective 2020, there will also be a question on COVID-19's impact during treatment. These questions will be collected by an unblinded staff member and should take approximately 15-30 minutes to complete. We will audio record and code up to 100 of these interviews until we reach saturation of themes. The audio recordings will not be labeled with any identifying information. The only identifying information that will be contained within the recordings will be participants' voices and if the staff member states a participant's name during the interview.

Staff will send the participant a reminder through their preferred method of communication prior to the 3- and 6-month assessment periods. All scheduled telephone assessments will be completed at a time deemed mutually agreeable by both the participant and research staff. For assessments completed online, the participant will be allowed to independently complete the assessment on their own time, with limits set by researchers on how long they may spend completing the assessment (e.g., once opened, the assessment must be completed within 24 hours, 48 hours, etc.). If a participant starts an assessment within window for an assessment period but continues to provide data for that assessment after the window closes, researchers will keep the out-of-window data. This scenario could occur if the participant, for example, begins an assessment over the phone or online, has to stop, and does not complete the remainder of the assessment until after the window has closed. Although research staff have internal protocols on reminding participants a reasonable number of times to complete unfinished and partial assessments, it is ultimately on the participant to agree to finish what they started. In some cases, participants may have circumstances that prevent them from timely finishing what they started in window, despite the best efforts of research staff. Collecting and retaining the out-of-window data will NOT be considered a protocol deviation.

As mentioned above, during the consent process research staff will provide participants with a response key to help answer questions asked during the telephone assessment periods.

Participants may request research staff send another response key to them if they lose the key during study participation. Research staff will send the response key along with a cover letter if the participant requests it via USPS mail or through email if the participant prefers email.

Participants will also complete abbreviated, weekly telephone assessments during the active monitoring phases of the study (Baseline Monitoring through Post-Treatment Monitoring). This weekly assessment will be procedurally similar to the extended assessment, but much briefer (under 15 minutes). It will only assess primary mechanism and mediator variables (medication use, pain intensity, catastrophizing, non-judgment, depression, and anxiety). Participants will also be required to use a response key to help answer questions during weekly assessments.

Participants will be compensated $25 for the completion of each assessment extended telephone assessment and $10 for each weekly telephone assessment via a check. The check will be sent via USPS mail and accompanied by a payment cover letter.

D6h. Optional Assessments

For all extended assessment periods, upon completing the main assessment, participants will be invited to participate in an optional assessment consisting of measures that were not included in the main assessment due to concerns regarding assessment length and participant burden. The optional assessment should take approximately 20-30 minutes to complete, and consists of questions regarding further responses to pain, goals, and future expectations. Optional outcome assessment data will be recorded on an electronic case report form in REDCap.

Participants are informed all optional assessments are completely voluntary, and that they may refuse to complete the optional assessments (or stop them at any time) with no effect on their payment for their completion of that particular assessment period. Participants will be informed they will not be compensated for completing the optional assessments.

D6i. Re-Assessment of Eligibility

A participant's eligibility will be re-assessed following consent and enrollment into the study to ensure that they still meet study entrance criteria. Participants will be asked similar questions to the screening questions they were asked initially. Items that could be re-assessed may include items on opioid use, pain chronicity, pain frequency, medications, and current and planned treatments, among others. Participants who are no longer eligible for the study will be thanked for their time and deferred or withdrawn from the study, depending on reason for ineligibility.

This re-assessment of eligibility may be completed up to 7 weeks before the start of treatment. Participants will not be compensated for completing this assessment.

D6j. General EMA and ActiGraph Monitoring

EMA Surveys

Cue-elicited EMA will be administered via EMA software programmed to alert participants daily within two pre-set 120-minute blocks (via notifications for smart phone users and email

messages for tablet, laptop, or desktop users) to complete the EMA surveys in the morning and evening. Participants will have the option to complete the survey via smart phone, tablet, laptop, and/or desktop. EMA surveys will be completed during three time periods: 2-Week Baseline, Treatment, and 4-Week Post-Treatment. The EMA software is both HIPAA-compliant and fully validated for 21 CFR Part 11; the software itself and collected EMA data will also be hosted on a secure server. Research staff will periodically download de-identified survey data from the EMA system directly onto our department's secure server for indefinite storage.

Staff will use the participant's chosen method of receiving EMA surveys to program this modality for the participant in the EMA software. That is, for participants electing to receive survey notifications through smart phone, research staff will set up the participant in the EMA management system to receive notifications with access to the survey during each morning and evening time window. For participants electing to complete surveys through a web browser, research staff will employ a similar system in which emails with a link to access the survey will be automatically emailed during each morning and evening time window. All participants will be given three pre-determined options for the morning and evening blocks for receiving surveys: for example, 5-7 AM and PM, 6-8 AM and PM, or 7-9 AM and PM. If none of the pre-determined time blocks work for the participant, the research team may work with the participant to find suitable morning and evening blocks where the participant is better able to complete their surveys.

Research staff will provide the participant with verbal instructions on how to complete the EMA surveys based on their preferred survey modality during the technology training session. These instructions will also be mailed/emailed to the participant so they can refer to them in the future.

The 2-Week Baseline Monitoring Period will consist of an approximately 14-day period before the participant begins their first session of treatment. We will schedule all participants to start the Baseline Monitoring Period 14 days before the start of the first group of that cohort. This means, for example, if the first session of CT will be 4/16, the first session of MM will be 4/17, and the first session of AS will be 4/18, all participants will begin the Baseline Monitoring Period on 4/2, which is 14 days before the start of the first group (4/16). Participants will complete Baseline EMA surveys until the day before their first treatment session.

The 2-Week Baseline EMA survey asks questions on pain interference, pain catastrophizing, cognitive processes, average pain intensity during the past 12 hours, mood, pain self-efficacy, sleep/wake times, and activity level and activity monitor wear. On days before Session 1 in the evening EMA there will also be questions on treatment credibility and expectancies. Each EMA survey should take approximately 5 minutes to complete. There are a minimum of 28 EMA surveys for the participant to complete during the Baseline EMA Monitoring Period.

The Treatment Monitoring Period begins on the day the participant is scheduled for Session 1 and ends the day they are scheduled for Session 8. The Treatment EMA survey asks the same questions as the 2-Week Baseline EMA survey described above, with the addition of items on therapeutic alliance, group cohesion, and time spent practicing skills learned in treatment. The therapeutic alliance and group cohesion items will be added after the Session 4 and 8 evening EMAs, while the time spent practicing skills items will be asked daily during the evening EMA beginning with Session 1. Additionally, items on treatment credibility and expectancies will be asked once again after Session 1 and before Session 2. While not collected as data, there is also an additional question asked the evening before each treatment

session on whether the participant has completed their homework activities; this question is used as a reminder to prompt participants to complete their homework activities if they have not already done so.

The total number of EMA surveys for the participant to complete during the Treatment Monitoring Period will vary depending on the schedule of the sessions. While we aim to have sessions twice a week for four consecutive weeks, this may not be the case if there is a holiday which the UW is closed or a session needs to be rescheduled for a variety of reasons. Participants will continue to complete EMAs daily during the entire Treatment Monitoring Period, regardless of the scheduling of sessions.

Finally, the 4-Week Post-Treatment Monitoring Period begins the day after Session 8 and extends for four weeks. The 4-Week Post-Treatment EMA survey asks the same questions as the Baseline EMA survey described above minus the items on treatment credibility and expectancies but with the addition of time spent practicing skills items. There will be a total of 56 EMA surveys for the participant to complete for the 4-Week Post-Treatment Monitoring Period.

Research staff will monitor the EMA data daily for possible missing responses and employ an internal protocol for contacting the participant regarding missed surveys. This protocol will be strict enough such that participants who are not completing surveys are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment due to issues of time commitment but remains intent-to-treat may warrant less frequent contacts about missed surveys compared to someone who remains in treatment and is fully engaged.

If a participant defers to a future cohort after starting the 2-Week Baseline Monitoring Period but before getting randomized, they will need to redo the 2-Week Baseline Monitoring Period at the time of the future cohort as we require a minimum 14 days of EMA collection prior to treatment.

Participants will be compensated $1 for the completion of each EMA survey, plus a $6 “bonus” for each week they complete ≥12 surveys. At the end of each EMA Monitoring Period, the number of EMA surveys completed will be tallied and total payment calculated for the entire period. A single check for the total payment for EMA surveys completed for that period will be sent via USPS mail and accompanied by a payment cover letter.

ActiGraphs

Activity levels and sleep will also be measured during these three time periods using the ActiGraph wGT3X-BT, which uses triaxial accelerometry that has been shown to be a valid measure of daily physical activity in people with chronic pain, and provides a more valid and reliable assessment of activity level than self-report methods. The ActiGraph will be worn all day (except when the participant is showering, swimming, etc.), including during sleep. The participant would wear the ActiGraph like a wrist watch on their non-dominant arm. There is no risk of electric shock with this device.

Research staff will provide the participant with verbal instructions on the use and care of the ActiGraph during the technology training session. These instructions will also be mailed/emailed to the participant so they can refer to them in the future.

ActiGraphs will be mailed out to all participants in a cohort about one week prior to the beginning of the 2-Week Baseline Monitoring Period to minimize the risk of participants losing the ActiGraph. ActiGraphs will only be mailed if the participant has completed all of the required baseline procedures that are scheduled to occur before the beginning of Baseline Monitoring (including the Baseline Assessment, Pre-Treatment Extended Assessment, Re-Assessment of Eligibility, and Technology Training). Participants will also be instructed to fully charge the ActiGraph using the provided charging cables before first use, and as needed throughout (i.e., when the monitor light begins to flash red – typically after approximately 1-week of consistent wear-time).

The participant will be instructed to send back the ActiGraph in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Research staff will download all data collected by the ActiGraph and link it to the participant's other data via their participant identification number. Data may be downloaded directly from the ActiGraph only with the assistance of ActiLife software that is unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer). The data will be stored on a secure server in de-identified form indefinitely.

Research staff will monitor ActiGraph wear compliance through questions on the EMA survey. Specifically, there is a question on the evening EMA asking the participant if they wore the device at all times during the past 24 hours. If a participant answers "No", a follow-up question will ask approximately how long they were not wearing the device. A staff member will employ an internal protocol for contacting the participant regarding ActiGraph non-wear. This protocol will be strict enough such that participants who are not wearing the device are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment but remains intent-to-treat AND who has reported difficulties with wearing the ActiGraph may warrant less frequent contacts about non-wear compared to someone who remains in treatment and is fully engaged.

If a participant defers to a future cohort after starting the 2-Week Baseline Monitoring Period but before getting randomized, they will need to redo the 2-Week Baseline Monitoring Period at the time of the future cohort (i.e., they will need to wear the ActiGraph again).

Participants will be compensated $70 for the return of the ActiGraph after the 4-Week Post-Treatment Monitoring Period. The check will be sent via USPS mail and accompanied by a payment cover letter.

To encourage wear compliance and the timely return of activity monitors, we will also offer participants the option to receive a summary of their ActiGraph data at study completion (after they have finished the 6-Month Extended Assessment). If the participant desires, we will send them either via USPS postal mail or email a document that may include data on one or more of the following: activity counts, energy expenditure, MET rates, steps taken, physical activity intensity, sleep latency, total sleep time, wake after sleep onset, and/or sleep efficiency. This information will be sent with a cover letter.

Participants who do not return their ActiGraphs within a reasonable amount of time will be contacted by research staff via phone, email, text, and/or letter to encourage the participant to send the device back as soon as possible. We will only have a limited number of devices on

hand and need the devices back promptly to ensure we can 1) collect the stored data and 2) have enough devices ready to deploy for the next return point/next cohort of participants.

D6k. Randomization

We will begin randomizing participants no sooner than six days after the start of the 2-Week Baseline Monitoring Period and continue to randomize until the day before the first treatment group starts. All participants in the current cohort will be reviewed to see if they completed all required baseline procedures and are thus eligible for randomization. The required baseline procedures are as follows:

1. Provided Baseline data and Demographics;
2. Completed Pre-Treatment Assessment;
3. Participated in technology training session and verbally agreed they are comfortable with all study software and with participating in group sessions using the videoconferencing software;
4. Completed re-assessment of eligibility;
5. Completed at least 7/14 EMA surveys during Week 1 of the Baseline Monitoring Period.

All participants need to complete the above required baseline procedures before they will be randomized; however, exceptions to meeting all randomization criteria may be given by researchers on a case-by-case basis should there be any extenuating circumstances that prevent the participant from meeting all randomization criteria. For example, a participant could have trouble accessing or completing EMAs not due to lack of participant effort. Participants who do not meet the EMA completion criterion above may be offered the opportunity to be contacted in the future should the criterion be revised. At that point, they would be re-screened for eligibility and will re-complete any Baseline procedures that are needed. If the Baseline procedures are completed the subsequent time around, then the participant will be eligible for randomization.

Participants who are not randomized will be asked to mail back any ActiGraphs still in their possession. Randomization will occur in stratified blocks to ensure that participants with each sex and baseline MME units (average daily in the past week, assessed at Re-Assessment of Eligibility; 20-49 or >49 MMEs)[31] have an equal chance of being randomized to one of the three conditions. Stratification will assure that the treatment groups are balanced regarding each stratification variable, so that the estimated effect of the treatment is not biased due to differences in distribution of sex or opioid use. The randomization procedures will also increase balance of treatment group sizes within each cohort.

Assignment to one of the three groups will be accomplished with randomization lists generated in Excel. The staff member in charge of conducting the randomization will receive training from the study statistician on how to generate the randomization lists. There is no potential for staff bias to interfere with creating these lists or randomizing participants. ***This is because the staff member conducting randomization will never have access to any person level information (other than sex and opioid use category), nor will the staff member have any direct communication with study participants at any point.*** Further, even if the staff member was familiar with person level details, this would not impact the structure of the randomization list, given that the order in which participants from each block are randomized is determined automatically by the software (using randomly generated numbers).

To further safeguard against potential bias, individuals will be randomized in the order that they become eligible for randomization (based on the completion of the pre-randomization procedures). After a participant has been randomized, the research staff member in charge of randomization will update the randomization form in REDCap to reflect the participant's treatment allocation. Only staff members who do not have access to study data during participant enrollment will know which treatment intervention corresponds with which group. Research staff will complete an electronic randomization case report form for each randomized participant that will be included with study data. The master list of participants will also be updated with the participant's assignment.

An unblinded staff member will call the participant to convey assignment and the schedule of treatment sessions. Brief (1 page) reading material specific to the treatment group will also be made available to the participant in preparation for Session 1; the reading material is informative only and not home practice. The group schedule and reading material will be provided to the participant electronically, unless the participant requests otherwise. The unblinded staff member may also provide the participant part or all of their participant treatment handbook prior to the first session (excluding instances in which the treatment mandates that a given portion of the treatment materials not be provided before a particular treatment session).

Research staff will re-screen participants on approved mutable eligibility criteria (e.g., pain intensity, frequency, etc.) if three months or more has elapsed between the consent process and randomization.

D6l. Treatment Scheduling

Cohorts of study treatment groups will be offered 3-5 times per year.

Trained clinicians will commit to offering at least three groups per year: one of each treatment type. This will reduce the potential for therapist bias on the outcomes.

An unblinded staff member will maintain lists of group assignments and coordinate the scheduling of sessions. Staff will provide clinicians with a list of participants who were assigned to each class.

Treatment reminders will be provided for each session using the participant's preferred method of communication. If a participant misses a session, the therapist or another staff member may contact the participant about the missed session. If the therapist or other staff member is not able to get a hold of the participant, additional follow-up may be conducted by research staff.

D6m. Treatment

Participants will attend eight 90-minute group treatment sessions scheduled on average twice per week for four weeks. In all three treatment conditions, group sessions will be conducted via the online, HIPAA-compliant Zoom videoconferencing platform (https://zoom.us/) with support from UW IT Services. Zoom videoconferences allow participants to see and hear each other, and also allows screen sharing, giving clinicians the opportunity to display visual information (e.g., PowerPoint slides) during the session. In the event that a participant cannot

access the videoconference during a specific session, we will provide workbooks to follow along with and to facilitate skills practice outside of sessions.

Participants may participate in Zoom sessions through a smart phone, tablet, laptop, or desktop computer. All participants will be provided instructions and training prior to their first scheduled session on how to log in, join the session, set up their video/audio components, and how to navigate the various menus/buttons within Zoom. Finally, participants are required to participate in sessions in a quiet, private location free from distractions to maximize treatment engagement and to protect the privacy and confidentiality of the sessions (e.g., their home or private office).

The group sessions will be conducted by PhD- or Masters-level clinicians with at least two years of clinical experience and who have undergone training that prepares clinicians to conduct each of the three treatment interventions in a group setting. The study clinicians will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. The clinicians will be provided with a detailed treatment manual and protocol outline, and Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled (weekly for the first two cohorts facilitated by any new study clinician; this may decrease to twice monthly once the study clinician has experience with the interventions and has demonstrated at least 90% treatment fidelity for the interventions provided) supervision for the study clinicians.

We will have a goal of having each group led by one or two clinicians allowing for groups to continue as scheduled in the event one of the clinicians is unable to attend a particular group.

Additional participants will be scheduled for the groups until they reach the maximum size. Clinicians will be expected to follow closely the treatment manuals to ensure all scheduled material is covered, and to ensure the consistency and replicability of treatment.

In all conditions, home practice activities will be assigned to build skill and competence in the coping techniques taught in the treatment sessions. While the exercises in MM are experiential in nature, the CT and AS conditions include didactic, written exercises. To assist with facilitation of learning between sessions, and to have record of engagement in home practice, all participants will be asked to keep an electronic record of their between-session activities. Participants in the CT and AS conditions will be asked to record the didactic components on Google Drive forms that are electronic versions of the forms provided in the participant handbooks; participants in the MM condition will be asked to write about the nature of their experiential learning during the MM practice on Google Drive forms that will also be electronic versions of the forms provided in the MM participant handbooks. Participants will be asked to complete electronic versions of these forms by the evening before each treatment session (with the exception of the first session); participants may also directly email their homework to clinicians. Participants will be instructed not to put their names or any identifying information on the forms. Clinicians will review these forms before the sessions in order to clarify any problem(s) the participants may have had between sessions. The completed forms will be downloaded and engagement in home practice data will be extracted and stored. Copies of these home practice forms will be stored on the department’s secure server.

Participants who have not completed the form by the morning of the session may, time permitting, be called to remind them to complete the form before the session starts.

We realize that adherence to interventions assigned outside of treatment sessions may influence study outcomes so will utilize EMA data collected about homework compliance. In addition, all participants in all interventions will be given a treatment workbook with materials to refer to and discuss during the group sessions as well as additional materials to read between sessions.

Cognitive Therapy (CT) condition

The cognitive-restructuring technique will be used to help patients recognize the relationships between thoughts, feelings, behaviors and pain. This technique will help patients: (1) identify negative or unrealistic automatic thoughts; (2) evaluate automatic thoughts for accuracy, identify sources of distorted thoughts, recognize the connection between automatic thoughts and emotional/physical shifts; (3) challenge negative, distorted automatic thoughts via "weighing the evidence"; (4) develop new realistic alternative cognitive appraisals; and (5) practice applying new rational appraisals and beliefs.

Participants in the CT condition will be asked to complete a Record of Automatic Thoughts Concerning Pain each day between sessions throughout the duration of treatment. It includes identification of the situation, automatic thoughts, emotional responses, and physical responses, as well as questions designed to challenge automatic thoughts and generate more reassuring thoughts. Other less formalized homework assignments may also be assigned, including practicing other cognitive skills learned in treatment (e.g., thought-shifting techniques, coping statements).

Mindfulness Meditation (MM) condition

Participants will receive training in mindfulness meditation, specifically Vipassana, which is the form of meditation typically implemented in mindfulness research. With this technique, the emphasis is placed upon developing focused attention on an object of awareness, e.g., the breath. This focus is then expanded to include a more open, non-judgmental monitoring of any sensory, emotional, or cognitive events. A standard script will be implemented by the clinician, and participants will be seated in a comfortable yet alert position.

In addition, participants will be given pre-recorded recordings of the meditation technique taught in the sessions and encouraged to practice MM daily (first using the recordings, and then later, on their own without recordings). Participants will be asked to listen to the recordings as often as they find helpful, but particularly at the time of the day they feel more alert, avoiding using them before going to sleep. Both a 20-minute as well as a 40-minute version will be provided to participants; although clinicians should encourage participants to practice the full 40-minutes, the 20-minute version is provided as this shorter version may especially be helpful early on in treatment, when participants are introducing a "new habit" of meditation in to their daily routine. They will also be encouraged to experience mindfulness meditation multiple times during each day (at least 3 times) by engaging in a short, 3-minute breathing space meditation focusing on the movements of the breath. Participants in the MM condition will be asked to fill out a practice log where they will describe what the mindfulness meditation practice experience was like for them.

Activation Skills (AS) condition

Participants will be educated about the role of inactivity and behavioral avoidance in chronic pain and functioning. They will learn how to be aware of the activities they avoid because of pain, and how to set effective goals so that, step by step, they can start being more active and resume some activities they enjoyed in the past but are currently avoiding. Explanation and

practice of a set of specific skills – including appropriate pacing skills – to facilitate an increase in appropriate activity level will be provided.

Participants in the AS condition will be asked to complete an activity log where they self-record their daily activities. Participants will also be asked to complete daily Goals Review and Success Logs, where they will record their short-, medium-, and long-term activity goals, taking into account different types of goals and the characteristics of effective goals (specific, measureable, achievable, relevant, and time-bound [SMART]).

Please note that the overall content of the treatment interventions as described above will not change during the course of the study. However, minor revisions of the actual therapist manual and participant workbook, such as minor changes to formatting and specific language (i.e., revisions that do NOT result in a change in the risk/benefit ratio or to the substance of the material covered), are anticipated throughout the study due to the iterative process of developing a psychotherapeutic treatment intervention.

Attendance Records

Group leaders (clinicians) will be given an electronic roster of the anticipated participants in their group. The roster will only include a participant's name, participant ID, and basic contact information should the clinician need to get a hold of the participant. The clinician will record the participant's absence or presence for each session on an electronic attendance form in REDCap. Only unblinded staff members will have access to these records, and the records will be password-protected and stored on a limited access folder on our department's secure server.

Treatment completion will be defined as attending at least 4 of the 8 total group sessions.

Data Collected during Treatment Sessions

Participants will complete via Google Drive a form regarding their completion of tasks or "homework" assigned by the clinician from the previous session. This form does not contain identifying information and the participant will be instructed not to put their name on it. Clinicians will review these forms before the sessions in order to clarify any problem(s) the participants may have had between sessions. All homework forms will be downloaded and stored on our secure network drive.

Study clinicians will also complete for each participant in that particular session a measure of perceived engagement within group after the session is over.

In this way, we address an important scientific question (i.e., whether engagement in homework and experience within sessions is associated with outcomes), but none of the clinicians are directly engaged in outcome data collection, and there is no additional burden to the participants.

Audio Recordings

All group treatment sessions will be audio recorded using Zoom's built-in recording function to ensure compliance to treatment procedures. These recordings may also be used for training purposes. A portion of treatment sessions will be randomly selected and reviewed/coded by study researchers to ascertain fidelity to protocol. Study clinicians will receive feedback during regularly scheduled supervision sessions with either Drs. Ehde, Day, or Jensen (depending on treatment condition) and corrective feedback will be provided as needed if they diverge from protocol.

The study clinicians will notify participants before the start of the session that they will be recording the session, and all participants in the group must have provided consent to audio record during the informed consent process. Participants who withdraw their consent to record after the groups start but who still want to participate in the study may still complete all remaining study procedures with the exception of treatment sessions.

Audio recordings will only be reviewed by study personnel and used for assessing consistency between study clinicians. The audio recordings will not be labeled with any identifying information. The only identifying information that will be contained within the recordings will be participants' voices and if the study clinician or if group members state participants' names during the discussion.

Treatment Intervention Discontinuation

A participant will be withdrawn from the treatment intervention if they (1) engage in behavior that is disruptive to the group, and/or (2) engage in behavior that interferes with the appropriate administration of the group treatment.

However, participants who are withdrawn from the study treatment intervention will be invited to complete study assessments at post-treatment, 3-month, and 6-month follow-up as well as any remaining EMA surveys and continue to wear the ActiGraph to allow for complete data for the planned intent-to-treat analyses (see below). Participants will receive payment for the time it takes to provide outcome data at each assessment point.

An electronic treatment withdrawal/termination case report form will be completed for participants who withdraw or are terminated from treatment.

Intent-to-Treat (ITT)

For all participants who are randomized to receive one of the three study treatments but are unable to participate in that cohort's treatment sessions, the participant will always be asked to complete study assessments for that cohort and included in study analysis unless they withdraw their participation from the study. This means that, post-randomization, if a participant is unable to attend the treatment they were assigned to OR decides to withdraw from treatment, they will be offered the opportunity to continue with EMAs, wear the activity monitor, and complete extended assessments for that cohort in which randomization had occurred. The participant will not be allowed to defer to another cohort to participate in treatment. Once a participant is randomized, they cannot be deferred to a later treatment cohort, even if they do not participate in a single session of the cohort they are randomized in. If a participant needs to defer to another cohort, this is only allowed **before** they have been randomized.

D6n. Study Design Enhancements: Treatment Fidelity, Missed Sessions and EMA Assessments, Participant Engagement, and Study Retention Strategies

We will take a number of steps to ensure uniform treatment protocol delivery. First, all treatments will be provided by a Masters-level or postdoctoral senior fellow or licensed psychologist (the study "clinician") who has at least two years of clinical experience in delivering psychosocial treatments or by one of the study investigators. The clinician will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. If one of the study clinicians is unable to deliver a session as planned, and no other study clinicians are available to fill in, a clinician who has experience in delivering the treatment content may be asked to fill in during emergency situations. This emergency clinician would

have documentation of training from any of the study investigators or consultants demonstrating training in the content of the session being covered. Second, the clinician will be provided with a detailed treatment manual and protocol outline. Third, Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled supervision to the study clinicians. Weekly supervision will occur for the first two cohorts of every study clinician new to the program; these are anticipated to become less frequent as the clinicians gain more experience and the need for frequent supervision sessions decreases. However, all clinicians at all times will have easy access to the clinical supervisors (either in person, via telephone, via email, or via Skype) at any time between the supervisory sessions as needed and as issues arise. Fourth, adherence and fidelity will be monitored using session audio recordings. Masters-level or above clinicians supervised by the investigators will review a random selection of 25% of the recordings (2-3 randomly selected sessions per group, to be coded by the start of treatment for the following cohort) to ensure procedures are followed. Protocol quality and adherence criteria will be developed for each session with satisfactory adherence defined as ≥90% of the maximum possible score. Corrective feedback will be provided to the clinician during regularly scheduled supervision sessions; didactics and role plays to correct "drift" will be implemented if needed.

We will monitor session attendance and session dates to track percentage of attendance and to account for absenteeism and reasons for any missed sessions. Reasons for attrition will be assessed for participants who withdraw. Given clinician-rated participant engagement during sessions was associated with dropout in our preliminary research, we will assess this at each session for each participant. Enactment of treatment-specific changes will be assessed by homework practice, assessed via EMA. Comparisons between the treatment conditions in dropout rates will be made, and variables shown to differentiate the groups will be included as covariates.

To minimize possible missed EMA data, we will provide financial incentives for completing the EMA surveys (i.e., $1.00 per assessment, plus a $6.00 "bonus" for each week they complete ≥12 assessments). In addition, a staff member will monitor the EMA data daily for possible missing responses and employ an internal protocol for contacting the participant regarding missed surveys. This protocol will be strict enough such that participants who are not completing surveys are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment due to issues of time commitment but remains intent-to-treat may warrant less frequent contacts about missed surveys compared to someone who remains in treatment and is fully engaged.

To minimize possible missed ActiGraph data, research staff will monitor ActiGraph wear compliance through questions on the EMA survey. Specifically, there is a question on the evening EMA asking the participant if they wore the device at all times during the past 24 hours. If a participant answers "No", a follow-up question will ask approximately how long they took the device off. A staff member will employ an internal protocol for contacting the participant regarding ActiGraph non-wear. This protocol will be strict enough such that participants who are not wearing the device are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment but remains intent-to-treat AND who has reported difficulties with wearing the ActiGraph may warrant less frequent contacts about non-wear compared to someone who remains in treatment and is fully engaged. If the participant says they cannot wear the

ActiGraph due to skin irritation, researchers will provide the participant with a more comfortable way of wearing the ActiGraph on the wrist (e.g., using a softer material on the wrist strip).

To encourage wear compliance and the timely return of ActiGraphs, we will also offer participants the option to receive a summary of their ActiGraph data at study completion (after they have finished the 6-Month Extended Assessment). If the participant desires, we will send them either via USPS postal mail or email a document that may include data on one or more of the following: activity counts, energy expenditure, MET rates, steps taken, physical activity intensity, sleep latency, total sleep time, wake after sleep onset, and/or sleep efficiency.

Participants who do not return their ActiGraphs within a reasonable amount of time will be contacted by research staff via phone, email, text, and/or letter to encourage the participant to send the device back as soon as possible.

We will implement a number of strategies to maximize participant retention. For example, sessions will be offered at different times, on a recurrent basis, giving participants scheduling flexibility. All research staff that interact with participants will be taught listening skills and encouraged to be warm in all interactions to enhance rapport. The on-site co-PI, Dr. Jensen, will receive weekly reports from staff so the investigators can discuss recruitment and retention during the scheduled research meetings and quickly implement changes if needed.

Finally, participants will receive up to $100 remuneration for completing all telephone-administered extended assessments, $1.00 per each EMA survey, plus a $6.00 “bonus” for each week they complete ≥12 EMA surveys, and up to $70 for mailing back their ActiGraph(s). We have successfully used these and other strategies in our past trials, with a retention rate of 85% to 97%.

Replacement Check Protocol

Research staff will send participants with a check that is outstanding 180 days after issuance of a letter/email that:

- Notifies the participant that the check remains uncashed;
- Requests the participant indicate whether they would like a new check(s) or decline payment; and
- If they would like new check(s), they will need to sign the reissuance form and send it back to research staff.

Research staff will then issue a new check to participants who request new check(s). Research staff will contact participants who have not returned the signed form within 2-3 weeks of mailing. Research staff will send out the same letter/email again if requested by participants.

Research staff will send the same letter/email described above to participants who notify staff that they did not receive the check/lost it, and request a replacement check.

D6o. Study Completion

Participants we are unable to get a hold of during the course of the study may be mailed an “unable to contact letter” requesting they contact study staff as soon as possible to discuss their participation. We will also attempt to reach these participants via phone, email, text, and/or through their collateral contacts.

Research staff will complete an electronic study completion form when either (1) a participant completes the 6-month assessment period, or (2) withdraws or is withdrawn from the study. Participants who complete the 6-month assessment period will be sent a cover letter along with their final remuneration with language indicating completion of the study. Participants who fail to complete the 6-month assessment period will be sent a letter/emailed informing the participant that their participation in the study has ended.

Table 2. Participant Involvement

Procedure	Number of Assessments	How Often / When	Time Required for Participants	Compensation
Re-Assessment of Eligibility	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 3 minutes	$0
Randomization Stratification	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 5 minutes	$0
Baseline Data and Demographics Collection	One telephone assessment	Once, following informed consent process; before treatment begins	About 30-40 minutes	$0
Pre-Treatment Extended Assessment	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 45-60 minutes	$25
Technology Training	One videoconference training session	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 30-45 minutes	$0
Baseline Monitoring Period*	At least twenty-eight (28) EMA assessments; two (2) weekly abbreviated phone assessments	Twice daily EMA assessments for approximately 2 weeks prior to first treatment session	About 5 minutes per EMA assessment; 15 minutes per weekly assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed; $10 for each weekly assessment
Treatment	Eight (8) videoconference group treatment sessions	Average of twice per week for approximately 4 weeks	90 minutes per session	$0

Treatment Monitoring Period*	Twice daily EMA assessments for duration of treatment; weekly abbreviated phone assessments	Twice daily EMA assessments, commencing on day of first treatment session, ending on day of last session	About 5 minutes per assessment; 15 minutes per weekly assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed; $10 for each weekly assessment
Post-Treatment Extended Assessment	One telephone assessment	Once following end of treatment	About 45-60 minutes	$25
Post-Treatment Qualitative Assessment	One telephone assessment	Once following end of treatment	About 15-30 minutes	$0
Post-Treatment Monitoring Period*	Fifty-six (56) EMA assessments; four (4) weekly abbreviated phone assessments	Twice daily EMA assessments for 4 weeks following end of treatment	About 5 minutes per assessment; 15 minutes per weekly assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed; $10 for each weekly assessment
Return Activity Monitor	N/A	Once, following end of Post-Treatment Monitoring Period	N/A	$70
3-Month Extended Assessment	One online or telephone assessment	Once, approximately three months following end of treatment	About 45-60 minutes	$25
6-Month Extended Assessment	One online or telephone assessment	Once, approximately six months following end of treatment	About 45-60 minutes	$25

* Participants will wear ActiGraphs for the duration of monitoring periods

D6p. Study Data

We list the demographic and descriptive information we propose to collect from the study participants in the next paragraph. The outcome variables, covariates (variables to control for in planned analyses if needed), and mechanism (mediator and moderator) variables for this study are listed in Table 3. Specific measures by time point are provided in Table 4.

Descriptive/Demographic Variables

All participants will be asked to provide demographic data (age, sex, gender orientation, ethnicity, race, marital status, education, alcohol/drug use, smoking behavior, height and weight, income, household size, disability compensation status, lawsuit status, and employment status). We will also ask about their history of MM, CT, and AS treatment and practice, as well as general chronic pain history (pain duration, pain frequency, pain intensity, other pain sources/types, surgery history, and pain interference with employment). We will also ask questions regarding co-morbid conditions (spinal stenosis and sciatica), pain medication use, and treatment preferences.

Outcome variables, covariates, and mechanism variables

Outcome variables, covariates, and mechanism variables will be assessed through a combination of extended assessments, EMA monitoring, and abbreviated weekly phone assessments. In some cases, slightly abbreviated versions of a measure will be administered during EMA assessments in order to minimize participant burden and encourage compliance (e.g., positive and negative affect, two items are asked in EMA and ten items are asked in extended assessments). The number of items for each measure in the EMAs was selected on the basis of content validity, factor loadings established during initial measure development and validation studies, brevity, and pilot data. Building on this, the minimum number of items was then selected that achieved at least good internal consistency reliability ($\alpha \geq .80$) for the mechanism variables and excellent reliability ($\alpha \geq .90$) for the primary outcome variable of pain interference in our pilot data. All outcome measures will be administered by research staff members blind to group allocation.

Qualitative Outcomes

A one-time qualitative interview assessing participant experiences in group, as well as any feedback about the treatment program will be completed following the completion of treatment by an unblinded staff member. Effective 2020, there will also be a question on COVID-19's impact during treatment. Qualitative interviews will not be conducted for participants who do not attend any treatment sessions.

Table 3. Primary, Secondary, Co-Variate, and Mechanism Variables

Variable Type	Domain	Measure (# items EMA, extended, weekly)
Primary Outcome	Morphine Milligram Equivalents (MMEs); average daily dose in past week	Self-reported opioid medication use (questionnaire, extended, and weekly)
Primary Mechanisms and Moderators	Cognitive Content	Pain Catastrophizing – Items from Pain Appraisal Scale (3, 5, 5), Coping Strategy Questionnaire (CSQ) (0, 2, 2)
	Cognitive Process	Pain-Related Cognitive Process Questionnaire (PCPQ) Non-Judgment Scale (2, 6, 6)
	Activity Level	Actigraphy, Godin Leisure-Time Exercise Questionnaire (3, 3, 0), Hours spent sitting without exercising (EMA only)
	Average Pain Intensity	Numerical Rating Scale (NRS), 0-10 (1, 1, 1)
	Depression	PROMIS-29 Depression (0, 4, 4)
	Anxiety	PROMIS-29 Anxiety (0, 4, 4)
Secondary Outcomes	Mood	Positive and Negative Affect Schedule (PANAS) (2, 10, 0)
	Physical Function	PROMIS-29 Physical Function (4 items ext. only)
	Sleep Quality	Actigraphy, PROMIS-29 Sleep Disturbance (4 items ext. only)
	Medication Use	Medication Use Questionnaire (Extended only)
	Cannabis Use	Investigator-developed items on cannabis use (3 items ext. only)
	Medication Use Attitudes	Survey of Pain Attitudes (SOPA) Medication Beliefs Sub-Scale (6 items ext. only), Pain Medication Questionnaire (PMQ) (26 items Baseline only)
	Post-Traumatic Stress Disorder	PTSD Checklist – Civilian Version (PCL-C) (0, 17, 0)
	Pain Interference	PROMIS Pain Interference (5, 5, 0)
Secondary Mechanisms	Pain Self-Efficacy	UW Pain-Related Self-Efficacy Scale (3, 6, 0)
	Patient Engagement	Clinician reported patient engagement (5 items rated by clinician)
	Therapeutic Alliance	Working Alliance Inventory (WAI) (12 items EMA only)
	Group Cohesion	Group Climate Questionnaire (GCQ-S) Engagement Scale (5 items EMA only)
	Skills Engagement	Duration and number of times practicing skills (EMA), number of days and duration of time practicing skills (Extended)
Tertiary Outcomes	Health Care Use	# visits to health care professional in last month (1 item ext. only)
	Pleasurable Activity	Pleasant Events Schedule SF (10 items ext. only)
	Behavior Activation	Behavioral Activation for Depression Scale (BADS) (9 items ext. only)
	Quality of Life	Global quality of life (1 item ext. only)
	Employment Status	Employment question (1 item Baseline & ext. only)
	Weight Change	Weight question (1 item Baseline & ext. only)
	Patient Global Impressions of Change	Patient Global Impressions of Change (PGIC) (6 items post-treatment and follow-up ext. only)
	Patient Global Assessment of Treatment Satisfaction	Patient Global Assessment of Treatment Satisfaction (PGATS) (1 item post-treatment and follow-up ext. only)
	Importance of Treatment Outcomes	Investigator-developed items (14 items Baseline and ext. only)
Tertiary Mechanisms	Mindfulness	Mindful Attention Awareness Scale (MAAS) (15 items ext. only)
	Resilience	Pain Resilience Scale (14 items ext. only)
	Other Cognitive Processes	All other PCPQ items (47 additional items ext. only, 53 total items)
	Pain Beliefs	Survey of Pain Attitudes (SOPA) Harm, Control, and Disability Scales (18 items ext. only)
Exploratory Moderators	Cognitive Abilities	PROMIS Cognitive Function Abilities (6 items ext. only)
	Treatment Credibility	Treatment Credibility & Expectancies items (5 items EMA only)
	COVID-19	Investigator-developed items on COVID-19's effects (6 items ext. & 1 item Qualitative Interview)
Optional Assessments	Responses to Pain	Positive & Negative Response to Pain Scales (85 items)
	Future Self	Future Self Questionnaire (FSQ) (16 items)
	Values-Consistent Goals	Valued Living Scale (VLS) (8 items)
Qualitative Outcomes	Experiences in group & program feedback	15-30" of investigator-developed qualitative items

Table 4. Study Assessment Schedule

Measures	EMA	Baseline	Pre-Treatment	Weekly Phone	During Treatment	Post-Treatment	3-Month	6-Month
Demographic Information		X						
Pain and Treatment History		X						
Start Back Tool		X						
Pain Medication Questionnaire (PMQ)		X						
Roland Morris Disability Questionnaire SF (RMDQ)		X						
PROMIS Pain Interference	X		X			X	X	X
Pain Appraisal Scale (PAS)	X		X	X		X	X	X
2-item Catastrophizing Scale from the Coping Strategy Questionnaire (CSQ)			X	X		X	X	X
Pain-Related Cognitive Process Questionnaire (PCPQ) Non-Judgment Scale	X		X	X		X	X	X
Godin Leisure-Time Exercise Questionnaire	X		X			X	X	X
Hours Spent Sitting w/o Exercising	X							
Pain Intensity NRS	X	X	X	X		X	X	X
Positive and Negative Affect Schedule (PANAS)	X		X			X	X	X
PROMIS-29 Sleep Disturbance			X			X	X	X
PROMIS-29 Physical Function			X			X	X	X
PROMIS-29 Depression			X	X		X	X	X
PROMIS-29 Anxiety			X	X		X	X	X
PTSD Checklist (PCL-C)			X			X	X	X
Medication & Cannabis Use			X	X		X	X	X
UW Pain-Related Self-Efficacy Scale	X		X			X	X	X
Participant Engagement					X[a]			
Working Alliance Inventory (WAI)	X[b]							
Group Climate Questionnaire (GCQ-S)	X[b]							
Duration and Times Practicing Skills	X					X	X	X
Sleep/Wake Times	X							
Health Care Utilization			X			X	X	X
Pleasant Events Schedule SF			X			X	X	X
Behavioral Activation for Depression Scale (BADS)			X			X	X	X
Global Quality of Life			X			X	X	X
Employment Status		X	X			X	X	X
Weight		X	X			X	X	X
Mindful Awareness and Attention Scale (MAAS)			X			X	X	X
Pain Resilience Scale			X			X	X	X
Pain-Related Cognitive Process Questionnaire (PCPQ) – Full			X			X	X	X
Control, Harm, Disability, and Medication Scales from the Survey of Pain Attitudes (SOPA)			X			X	X	X
PROMIS Cognitive Function Abilities			X			X	X	X
COVID-19 Impact Questions			X			X	X	X
Treatment Credibility and Expectancies	X[c]							
Patient Global Impression of Change (PGIC)						X	X	X
Patient Global Assessment of Treatment Satisfaction (PGATS)						X	X	X
Treatment Modality & Preferences						X		
Importance of Treatment Outcomes		X					X	
Qualitative Outcomes						X		
Optional Measures: Positive & Negative Response to Pain Scales, Future Self Questionnaire (FSQ), Valued Living Scale (VLS)			X			X	X	X

[a] Will be assessed for each participant and reported by the clinician following every treatment session. [b] Will be assessed during the evening EMA following Sessions 4 & 8 only. [c] Will be assessed once before Session 1 and once following Session 1 but before Session 2.

D6g. Treatment Fidelity Monitoring

We will take a number of steps to ensure uniform treatment protocol delivery. First, all treatments will be provided by a Masters-level or postdoctoral senior fellow or licensed psychologist (the study "clinician") who has at least two years of clinical experience in delivering psychosocial treatments or by one of the study investigators. The clinician will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. If one of the study clinicians is unable to deliver a session as planned, and no other study clinicians are available to fill in, a clinician who has experience in delivering the treatment content may be asked to fill in during emergency situations. This emergency clinician would have documentation of training from any of the study investigators or consultants demonstrating training in the content of the session being covered. Second, the clinician will be provided with a detailed treatment manual and protocol outline. Third, Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled supervision to the study clinicians. Weekly supervision will occur for the first two cohorts of every study clinician new to the program; these are anticipated to become less frequent as the clinicians gain more experience and the need for frequent supervision sessions decreases. However, all clinicians at all times will have easy access to the clinical supervisors (either in person, via telephone, via email, or via Skype) at any time between the supervisory sessions as needed and as issues arise. Fourth, adherence and fidelity will be monitored using session audio recordings. Masters-level or above clinicians supervised by the investigators will review a random selection of 25% of the recordings (2-3 randomly selected sessions per group, to be coded by the start of treatment for the following cohort) to ensure procedures are followed. Protocol quality and adherence criteria will be developed for each session with satisfactory adherence defined as ≥90% of the maximum possible score. Corrective feedback will be provided to the clinician during regularly scheduled supervision sessions; didactics and role plays to correct "drift" will be implemented if needed.

D6r. Data Collection and Management

Overview

Data will be collected at the University of Washington via telephone, online, or in person in an outpatient setting with the following two exceptions:

1. Ecological Momentary Assessment (EMA) data, which will be entered by the participant via a web portal (desktop, laptop, tablet, mobile device);
2. ActiGraph data, which will be collected via the ActiGraph device the participant will wear during participation in the study.

All study data collected for purposes of data analysis will be de-identified, labeled with a code number that is unique to each research participant, and maintained separate from any identifying information. The participant code numbers will consist of an arbitrary number consecutively numbered in order of screening/medical record review/approach. An electronic Master List key code will be maintained that links the participants with their code number. This key code along with identifying information will be stored in a password-protected Microsoft Access database that does not contain any study data. This database will also reside in a limited access folder on the UW network drive. Only approved study personnel will have access to the Master List key code, participant identifying information, and de-identified study data. We will analyze and report participant data in aggregate form and no PHI will be entered into these analyses or reports.

De-identified data collected by research staff or online will be entered directly into a database created in REDCap, a secure HIPAA-compliant web-based system. Web forms will be created to enhance functionality and proper data entry. The REDCap system also allows researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered. Both pieces will be utilized during data collection (i.e., we will create audit trails and require research staff to provide electronic signatures on all our electronic case report forms). Data will be downloaded to a limited access folder on the secure UW network drive.

Ecological Momentary Assessment (EMA) data will also be encrypted and stored on a HIPAA- and IRB-compliant web-based storage database. The EMA data will also be downloaded and stored in a limited access folder on the secure UW network drive.

Lastly, ActiGraph data is temporarily stored on the actual ActiGraph device until the participant returns the device to researchers. The data will then be downloaded by research staff and stored in a limited access folder on the secure UW network drive.

Recruitment and Screening

Trained study personnel will conduct the screening interview either in person or via telephone at the UW using a structured format in which the interviewer asks questions from a script. Study personnel will note the answers directly into a database if conducted via telephone or on the case report form if conducted in person. An electronic screening form as part of a REDCap database will be used to guide the screening to ensure that the same information is gathered and coded for all participants. Also, study personnel will enter basic recruitment outcome data for each prospective participant approached directly into the database using a standardized electronic case report form.

Telephone and Online Assessments

The self-report extended assessments consist of standardized protocols with specific/scripted questions. All study personnel who will be gathering data from these sources will be trained by the PIs regarding the collection of data and will have professional education and training as required by these instruments. Study personnel will enter the telephone assessment data directly into the database using a standardized electronic form in REDCap.

If the participant completes the self-report assessments online, they will be provided a secure link to a standardized electronic form in REDCap. The participant will directly complete the survey in REDCap.

EMA Data

Study participants will enter EMA data before, during, and after treatment. Study participants will be prompted via notifications to enter the data twice a day during those assessment periods. The data will be entered through a secure web portal with a link that is sent through (1) a notification on a smart phone; or (2) email, which can be accessed via desktop, laptop, tablet, or other mobile device. The data will then reside in a HIPAA- and IRB-compliant cloud-based storage database. Study personnel will check the EMA data in this database periodically to ensure participant compliance. In addition, study personnel will regularly download the data for storage in a limited access folder on the secure UW network drive.

ActiGraph Data

Activity levels will be measured before, during, and after treatment using the ActiGraph wGT3X-BT, which uses triaxial accelerometry. The participant will be instructed to wear the ActiGraph device on their non-dominant wrist during those periods of time. Each ActiGraph monitor will be initialized with the participant ID number for each specific participant prior to the device being sent to the participant. No identifying information is programmed into the device (although we will input the participant's study ID, planned wear location [i.e., wrist], side (right/left), height, weight, race, and sex, as reported to us by the participant). Thus, all activity and sleep data collected from participants will not contain any information that will reveal the identity of its user.

The participant will send back the ActiGraph to study personnel in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Study personnel will download the data collected by the ActiGraph and link it to the participant's other data via their participant identification number. The data will be stored in the same limited access folder on the secure UW network drive as the other data used for data analysis purposes. Data may be downloaded from the ActiGraph only with the assistance of ActiGraph software that is unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer).

Exceptions to Separation of Study Data from Identifying Information

There are four exceptions to the protocol of separating all study data from participant identifying information.

1. The group treatment sessions will be audio recorded to make sure study clinicians are following study procedures. These recordings may also be used for training purposes. The study clinicians will notify participants before the start of the session that they will be recording the session. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be (1) reviewed by study personnel and used for assessing fidelity to treatment study procedures by study clinicians, and (2) for training purposes. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be participants' voices and if the study clinician or group members state a participant's name during the discussion.

2. The qualitative interviews collected after the conclusion of treatment will also be audio recorded. Specifically, unblinded research staff will use open-ended questions to interview participants about their experiences in the treatment program and collect study feedback, if any. Effective 2020, there will also be a question on COVID-19's impact during treatment. Research staff will notify participants before the start of the interview that they will be recording the interview. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be transcribed (by third party software) and reviewed and coded by unblinded study personnel for themes that may highlight information about the program not captured by study outcome data. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be the participant's voice and if the staff member states the participant's name during the interview. No blinded staff members will have access to these qualitative interviews.

3. Reminders/notifications to complete the EMA assessments will be sent to either a participant's email address or mobile phone number. The participant's unique ID number may be included in the reminder/notification, creating a crosswalk between the

participant's identity and participant data. Please note, however, that the EMA data that will be collected will not be stored with any identifying information.

4. Participants will be asked to complete a document outlining home practice completion. The document itself will not contain any identifying information, but since it will be on Google Drive, identifying information may be included (e.g., name or participant ID). The documents will then be downloaded from Google Drive and engagement in home practice data will be extracted and stored. The documents will be stored in a limited access folder on the secure UW network drive only accessible by unblinded research staff.

Hard Copy Data

Any hard copies of study forms will be stored on a secure, badge-protected floor in the Ninth and Jefferson Building. Any hard copy forms containing participant identifiers will be stored in locked filing cabinets in a locked cabinet separate from the de-identified study data.

Blinded/Unblinded Research Staff

The following table describes details regarding who among the study investigators and research staff will be blinded and when they will be blinded.

Staff Member	Blinded / Unblinded	When Blinded
Mark P. Jensen, Ph.D.	Unblinded (Study Co-PI, will oversee data fidelity, provide supervision to study clinicians, participate in study analysis and reporting)	N/A
Melissa Day, Ph.D.	Unblinded (Study Co-PI, will provide supervision to study clinicians, participate in study analysis and reporting)	N/A
Marcia Ciol, Ph.D.	Blinded (will help manage outcome data, design and oversee randomization procedures, primary investigator responsible for data analysis)	Blind during data collection phase of study
Dawn M. Ehde, Ph.D.	Unblinded (will provide supervision to study clinicians, help address adverse events, participate in study analysis and reporting)	N/A
Elena Mendoza, Ph.D.	Unblinded (will administer intervention)	N/A
Jennifer Altman, Ph.D.	Unblinded (will administer intervention)	N/A
Andrea Newman, Ph.D.	Unblinded (will administer intervention, may participate in study analysis and reporting)	N/A
Calia Morais, Ph.D.	Unblinded (will administer intervention)	N/A
Janna Friedly, M.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
John Burns, Ph.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
Jeffrey Borckhardt, Ph.D.	Unblinded (will help manage unblinded data, may participate in study analysis and reporting)	N/A
Beverly Thorn, Ph.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
Joy Chan, B.S.	Blinded (will manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Sydney Drever, B.A.	Unblinded (will manage and collect unblinded data)	N/A

Nikki Torres, B.S.	Unblinded (will help manage and collect unblinded data)	N/A
Emily Goldberg	Blinded (will help manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Malka Dhillon, B.S.	Blinded (will help manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Erica Wasmund	Unblinded (will only randomize participants to treatment)	N/A
Laurel Peabody	Unblinded (will only randomize participants to treatment)	N/A

D6s. Statistical Analyses

The measures and assessment time-points administered in this sub-sample will match those that are collected as a part of the parent grant, with three exceptions. In addition, this sub sample will also complete the Pain Medication Questionnaire, PTSD Checklist-5 (PCL-5) and the PROMIS Anxiety scale; also, these three measures have been added to the parent study to allow for a replication test across samples (i.e. we will be able to perform the planned tests in a subset of patients with low back pain from the parent project who are taking opioids at baseline). Participants enrolled in the supplemental study will also additionally complete weekly assessments of their opioid use (as well as other mechanism variables) during the baseline, treatment, and immediate post-treatment phase. To facilitate recall for these, participants will be asked to have their medications physically available at assessments. Analgesic medication (both usual and rescue) data will be converted to standard equivalencies using the formulas developed at the UW Pain Relief Center (methadone for opioids, ibuprofen for NSAIDS, and phenobarbital for sedative-hypnotics).[26]

*For **Aim 1** of this supplemental study*, the primary moderator measures are: (1) the Coping Strategy Questionnaire, Pain Catastrophizing items; (2) the Pain-Related Cognitive Process Questionnaire, Non-Judging scale; and (3) ActiGraph assessed activity counts. Other moderators will also be examined in secondary analyses. The primary outcome will be baseline to post-treatment change in opioid use, as assessed in MMEs. The Aim 1 supplemental hypotheses will be tested via a series of three OGRS tests.[27,28] Indicator coding will be used and these tests will be interpreted in the context of point estimates and confidence intervals. Effect sizes will be calculated for any moderation main effects or interactions emerging that have confidence intervals that do not contain zero, and these effects will also be probed using the Johnson-Neyman boundary of significance to determine at what level of the moderator is outcome influenced. The Johnson-Neyman procedure eliminates the need to probe at a variety of arbitrary points along the moderator and defines regions of significance and regions of non-significance. In our pilot work we have successfully implemented this statistical approach in a sample of N=69 individuals with low back pain to detect moderator main and interaction effects to provide a preliminary test of the LA&E model in a trial comparing MM, CT and Mindfulness-Based Cognitive Therapy (MBCT). This sample size provided sufficient power ($\alpha \leq .05$) to identify: (1) an interaction effect for MM vs. MBCT ($b = .09$, $p < .05$, Confidence Interval [CI]: .003 to .175), such that people with low baseline catastrophizing showed greater improvement

in pain intensity when assigned to MBCT (*r* = -.36; within condition effect), with the boundary of significance identified as a Pain Catastrophizing Scale score of ≤16.35; (2) a further interaction effect for MM vs. MBCT (*b* = -.23, *p* = .05, CI: -.46 to .003), showing that higher baseline mindfulness was associated with greater improvement in pain intensity in MBCT (*r* = .40; within condition effect), with the boundary of significance identified as a Five Facet Mindfulness Questionnaire Observe Scale score of >15.03. Thus, based on these effects in our pilot work testing the LA&E predictions, we anticipate that the proposed sample size for this supplemental project of N=90 will be sufficient to detect medium to large effects (at the $\alpha < .05$ level). Hypotheses 1a-1c would be supported if an interaction effect emerges (significant at the $\alpha < .05$ level) and one or more of the within group effect sizes (of the moderator on the primary outcome) are medium or large.

*For **Aim 2** of this supplemental study*, the primary mediator measures are: (1) a Numerical Rating Scale assessing characteristic pain intensity (in the past week); (2) the PROMIS Depression scale; and (3) the PROMIS Anxiety scale. Additional secondary mediators, selected per the primary mechanisms examined in the parent study (e.g., catastrophizing, mindfulness, activity level), will also be explored in the supplemental project sub-sample. The association between treatment-related changes in the primary mechanisms on changes in outcome will be tested via three PROCESS tests with 5,000 bias-corrected bootstrap resamples.[29] The PROCESS bias-corrected bootstrap approach has been shown to consistently be the most powerful test of mediation (i.e., compared to the Sobel test, Baron and Kenny's approach) and is appropriate for small sample sizes.[29,30] We will examine the significance of each path to determine if treatment condition has a differential effect on the mediator and/or outcome (although treatment-related differences in outcome are not expected), and whether early change in the mechanism is associated with later change in outcome. In the instance of a possible specific vs. shared mechanism effect, post-hoc associations will be tested via correlations to identify estimates of effect sizes for descriptive purposes.

We applied this approach to the three active treatments in pilot data obtained in our RCT comparing CT, Hypnosis and Hypnotic-CT (within the subsample of participants who reported musculoskeletal pain who were prescribed opioids, N=18) to examine the relative statistical power achieved in that sample to detect medium to large effects for the analyses planned for this supplemental project. In two PROCESS models testing if early change in pain intensity or depression were specific vs. shared mechanisms in accounting for late treatment change in opioid use, results showed: (1) a non-significant effect of condition on outcome (path *c*) as well as on both mechanisms (path *a*); and (2) a significant effect of both mechanisms on the outcome (path *b*; *p*s < .01). Post-hoc correlations were then conducted for descriptive purposes. We found that early change in both pain intensity and depression were significantly associated with later change in opioid use across groups (*r*s = .58 and 68, respectively); on the other hand, early change in outcome was not significantly associated with later change in mechanism. Taken together, these results (1) provide support for early change in pain intensity and depression as underlying later reductions in opioid use, and (2) are consistent with a shared mechanisms account for the role of early change in pain intensity and depression as mechanisms driving decreased opioid use across the treatments studied in this pilot data. The proposed sample size and procedures of the supplemental project will afford the capacity to test these associations more definitively.

Overall, our pilot data indicate that if changes in outcome and mechanisms in the supplemental project are medium to large in nature, then the sample size of N=90 will be adequate to test the mediation hypotheses 2a and 2b. Support for Hypothesis 2a and the shared mechanisms conceptualization would be found in the instance of a non-significant effect

of condition on the mechanism variable, but significant ($\alpha \leq .05$) effect of the mechanism on outcome collapsed across groups. Support for Hypothesis 2b on the other hand would be found in the instance of a significant effect of condition on the mechanism, with change in the mechanism differentially associated with change in outcome across treatment conditions.

HUMAN PARTICIPANTS SECTION

E. Risk to Participants

E1. Human Participants Involvement and Characteristics

We plan to enroll up to 90 participants into the study. Our primary source of potential participants for this study is all individuals who have been seen as patients at either Harborview Medical Center (HMC) or the University of Washington Medical Center (UWMC), and who meet study eligibility criteria.

If needed and required, we will also recruit from other modalities. These other modalities include through flyers/brochures/advertisements in various clinics and hospital spaces, the UW Medicine Newsroom, clinician and participant referrals, social media/online recruitment, and nationally, if needed.

E2. Sources of Materials

Several sources of information will serve as data for the study, including medical record reviews, self-report assessments and interviews, ActiGraph activity data, and audio-recorded treatment sessions (to be used for supervision and determination of adherence and fidelity). The study design involves non-invasive procedures.

The data described will be collected solely for research purposes.

E3. Potential Risks

It is anticipated that participants, irrespective of treatment condition, will experience significantly more benefits than risks from participation in this study. Although the methods and interventions have limited participant risks, several safeguards will be implemented to reduce these.

E3a. General / Reaction to Assessments

Regarding research risks, participants may experience fatigue and/or boredom while completing the telephone/online assessments, EMA surveys, and/or the treatment sessions. Some participants may also experience mild anxiety, frustration, and/or stress while answering sensitive questions about depression, pain, and mood. As a result of answering questions about pain, some participants may focus more on their pain, which may lead to a temporary increase in pain intensity. Participants will be told that such phenomena associated with close self-monitoring are a part of the treatment approaches we are offering, and will be addressed as part of the interventions.

E3b. Stress / Discomfort Caused by Treatments

Our research team has had a great deal of experience with each of the treatments to be examined in this study, and each has minimal risks. The three types of treatment involve discussions about pain and related topics in a group setting that may make some individuals feel uncomfortable. Some participants may also experience mild anxiety, frustration, and/or

stress during the course of treatment should any topics or activities prove difficult for them. Some individuals learning cognitive restructuring of thoughts and beliefs or practicing mindfulness meditation may remember past experiences that are uncomfortable and/or cause distress, even after the session has ended. Regarding the mindfulness meditation training, some individuals may find the state of focused awareness uncomfortable, or may experience mild disorientation or grogginess during or after the session has ended due to the occasionally relaxing nature of this practice. Regarding the activation skills intervention, although clinicians will instruct participants engage only in safe and personally appropriate activities, there is a risk that participants may experience physical strain or injury when conducting activities with a physical component.

Should any participants experience these discomforts, the intervention leaders are clinicians with the expertise and clinical privileges needed to address these in appropriate clinical fashion in real time. Study investigators (Drs. Jensen, Ehde, and Friedly) are also available on site for additional consultation or support if needed. There is little chance of physical injury from the treatment procedures described above.

One potential risk is that participants may experience some distress when sharing personal information during the group telehealth intervention, although this is a relatively low risk event, because personal disclosure will not be specifically elicited. To reduce distress about public disclosure, the meaning of confidentiality will be explained at the outset of each session and group members will be asked to maintain the confidentiality of all session content. Participants will be explicitly instructed that revealing deeply personal information, by exploring the past or confiding in the group about personal information, is not considered part of the treatment protocol. Additionally, any participant expressing significant discomfort in the group treatment will be referred for alternative treatments. Participants may also feel uncomfortable because the sessions will be audio-recorded. Participants who choose to participate in the intervention will be advised at the time of informed consent that sessions will be audio recorded, so that they may self-select out of the study if recording is a barrier. Participants will be informed that the session recordings will be used only for treatment implementation monitoring and training purposes, and that no one outside the study staff will have access to the recordings.

E3c. Actigraphy Device

Participants may find it uncomfortable or inconvenient in general to wear a device like an ActiGraph both during the day and while sleeping. There is no risk of electrical shock while wearing the ActiGraph and it cannot track where participants are, record any verbal/audio, or track what behavior they are specifically doing. Participants may experience sweating or skin irritation while wearing the ActiGraph if they have sensitive skin.

E3d. Privacy and Confidentiality

Participants may also worry about the confidentiality of their responses during the assessments. There is a risk of invasion of privacy in that the research staff directly involved with data collection will need to keep participants' names, addresses (email and postal), and phone numbers for the duration of the study in order to contact them for the follow-up assessments. There is also a chance that a participant's identity and participation in the study may be discovered by an outside party given the group intervention dynamic. Given that this is a group intervention, participants within each group will know the first names and some information about other participants. However, participants will be encouraged to share only

their first names, and to disclose only that information that they are comfortable sharing and that pertains to pain and treatment.

E3e. Mental Health Issues / Suicidality

Although unlikely, it is possible that by participating in the study it may be discovered that a participant is suicidal or experiencing significant mental health issues. Please note that these conditions would also likely be detected in the course of usual care. The study suicide protocol will be implemented in the instance of a participant expressing suicidality.

E4. Protection Against Risk

E4a. General / Reaction to Assessments

Participants will be informed during the consent process and throughout the study they do not have to discuss any topics they do not wish to during treatment or the assessment periods. In addition, participants will be informed in the consent process they are free to stop any session, treatment, or assessment at any time. Participants are informed they may refuse to answer any questions that make them feel uncomfortable.

All study personnel who conduct the assessments will be qualified, trained, and closely supervised by study investigators. All participants will be clearly informed of their right to withdraw from the study at any point without adversely impacting their routine medical, psychiatric, or psychotherapeutic care.

All participants will be offered the opportunity to discuss any situations or experiences associated with the study procedures that they deem uncomfortable or adverse with the UW Co-PI, Dr. Jensen, who is a licensed clinical psychologist. Dr. Jensen is a trained psychologist who has experience assessing the level of distress of patients and proceeding accordingly whenever an adverse event should arise.

E4b. Stress / Discomfort Caused by Treatments

Researchers will take multiple steps to ensure and monitor the well-being of participants during treatment. Study investigators, led by Dr. Ehde, will offer ongoing, scheduled supervision and consultation with study clinicians, including routine assessment of any potential problems or adverse events.

For all treatment interventions, several steps will be taken to monitor the possibility of adverse events participants may experience as a result of the treatment interventions. First, during the recruitment process, research staff will clearly outline the physical components of the activation skills intervention. In doing so, staff will also instruct individuals who are concerned about the physical nature of the intervention to consult their physician before agreeing to participate. Additionally, staff will clearly outline the possible risks of discomfort and distress when changing thoughts and beliefs as it relates to the cognitive therapy intervention, as well as possible mild disorientation and grogginess as it relates to the mindfulness meditation intervention.

Second, clinicians will employ several protective measures when administering the treatment interventions. As it relates to the activation skills intervention, at the first treatment session clinicians will get to know the personal physical capabilities of each participant, allowing any future physical activity recommendations to be tailored to the individual. Further, before participants complete any assigned physical activities, the clinician will review the activity with the participant to ensure that it is reasonable and safe. Lastly, the clinician will routinely assess during the treatment phase whether participants are experiencing any adverse effects related to the activity skills intervention, and will (in conjunction with the study medical doctor, if needed) advise the participant whether they should stop or modify their activity, or recommend they seek guidance from their primary health care provider (if the event is significant but non-imminent) or urgent/emergency care (if the event is life-threatening or an urgent, acute medical issue). As it relates to the cognitive therapy and mindfulness meditation interventions, during each treatment session clinicians will routinely assess whether participants are experiencing any adverse effects related to the treatment interventions, and will (in conjunction with PI supervision, if needed) advise the participant whether they should stop or modify participation in mindfulness meditation or cognitive therapy treatment activities.

E4c. Actigraphy Device

Participants will be warned about possible irritation to the skin and general discomfort wearing the device during the informed consent session. If the participant says they cannot wear the ActiGraph due to skin irritation, researchers will provide the participant with a more comfortable way of wearing the ActiGraph on the wrist (e.g., using a softer material on the wrist strip).

E4d. Privacy and Confidentiality

We will take multiple steps to protect participants' privacy and confidentiality. All of the data collected from participants will be kept in strict confidence. No information that is linked to a research participant's identity will be provided to anyone outside of the study or regulatory entities responsible for oversight without permission from the participant.

Electronic Data

All study data collected for purposes of data analysis will be de-identified, labeled with a code number that is unique to each research participant, and maintained separate from any identifying information.

All electronic data collected via telephone, online, and Ecological Momentary Assessment (EMA) data will be encrypted and stored in a HIPAA- and IRB-compliant web-based system. These data will also be downloaded and saved in a limited access folder on the secure UW network drive.

The participant will send back the ActiGraph to study personnel in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Study personnel will download the data collected by the ActiGraph and link it to the participant's other data via their participant identification number. The data will be stored in the same limited access folder on the secure UW network drive as the other data used for data analysis purposes. Data may be downloaded from the ActiGraph only with the assistance of ActiGraph software that is

unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer).

An electronic Master List key code will be maintained that links the participants with their code number. This key code will be stored in a password-protected Microsoft Access database that does not contain any study data. This database will also reside in a limited access folder on the UW network drive. Only approved study personnel will have access to the Master List key code, participant identifying information, and de-identified study data. We will analyze and report participant data in aggregate form and no PHI will be entered into these analyses or reports.

One exception to the protocol of separating all study data from participant identifying information pertains to audio recordings generated for each treatment session. Specifically, the group treatment sessions will be audio recorded to make sure study clinicians are following study procedures. The study clinicians will notify participants before the start of the session that they will be recording the session. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be (1) reviewed by study personnel and used for assessing fidelity to treatment protocol by study clinicians, and (2) used for training purposes. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be participants' voices and if the study clinician or group members state participants' names during the discussion.

Another exception pertains to the audio recorded qualitative interviews collected after the conclusion of treatment. Specifically, unblinded research staff will use open-ended questions to interview participants about their experiences in the treatment program and collect study feedback, if any. Effective 2020, there will also be a question on COVID-19's impact during treatment. Research staff will notify participants before the start of the interview that they will be recording the interview. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be transcribed (by third party software) and reviewed by unblinded study personnel only and coded for themes that may highlight information about the program not captured by study outcome data. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be the participant's voice and if the staff member states the participant's name during the interview. No blinded staff members will have access to these qualitative interviews.

Additionally, another exception is the alerts sent to participants to complete the EMA surveys via notifications and/or email messages. Specifically, the alert may include the participant's identification number in the body of the notification/email, creating a crosswalk between the participant's identity and participant data. Please note, however, that the EMA data that will be collected will not be stored with any identifying information.

Finally, participants will be asked to complete a document outlining home practice completion. The document itself will not contain any identifying information, but since it will be on Google Drive, identifying information may be included (e.g., name or participant ID). The documents will then be downloaded from Google Drive and engagement in home practice data will be extracted and stored. The documents will be stored in a limited access folder on the secure UW network drive only accessible by unblinded research staff.

Hard Copy Data

Any hard copies of study forms will be stored on a secure, badge-protected floor in the Ninth and Jefferson Building. Any hard copy forms containing participant identifiers will be stored in locked filing cabinets in a locked cabinet separate from the de-identified study data.

E4e. Mental Health Issues / Suicidality

Although the study poses no serious risks to participants, participants may notify research personnel about pre-existing mental health issues that have not been previously identified. A suicide risk assessment protocol will be implemented by non-clinical staff (see below). It should be noted that risk of suicide is an exclusion criteria for this study, so we anticipate that the likelihood of suicide risk is low.

Suicide Risk Assessment Protocol: Non-Clinical Research Staff

A suicide risk assessment protocol will be implemented by non-clinical staff under the following condition:

If a participant mentions or alludes to thoughts, intentions, plans or behaviors related to self-directed violence (SDV) outside of the context of formal assessment.

Study staff (e.g., Research Coordinator, Research Assistant) are not licensed mental health providers. This protocol outlines specific steps that study staff will follow in order to ascertain whether a study investigator or study clinician who is supervised by a licensed mental health care provider needs to be contacted for follow-up assessment and/or triage. In the event that a study staff member perceives sufficient risk that further assessment is warranted, the study staff will alert an investigator or a study clinician who can assess risk. Because our research staff are not clinicians (i.e., they have no official clinical role), our plan primarily reflects the importance of *activating the procedures for suicide risk assessment and risk management/suicide prevention.*

Thus, in the event that the participant mentions thoughts, intentions, or plans related to harm to self, the research staff member will ask the participant some clarifying questions, such as: “Let me clarify, are you having any thoughts about harming yourself deliberately, or are you just thinking about dying or that you would be better off dead?” or “Let me clarify, are you having any thoughts about deliberately harming yourself?” If the participant endorses follow-up questions that suggest a possibility of risk for suicide, the research staff member will gather additional information about acute risk (i.e., presence of intent, plan, means for self-directed violence, protective factors such as presence of dependents).

In the course of this discussion, if the participant clarifies that while they are having thoughts about self-harm, they have no intent or plan, and if they volunteer reasons they would not harm themselves (e.g., having dependents, or religious beliefs that prevent suicide), then this will be considered a negative screen. Because suicide risk assessment for clinician is beyond the role of non-clinical research staff members, we propose a low threshold for a positive screen.

1. In the event of a negative screen, the research staff member will complete the interaction with the participant, and then alert Dr. Jensen, Dr. Ehde, or a study clinician within 24 hours to review the screen and determine if further action needs to be taken.

2. In the event of a positive screen over the telephone during an assessment (i.e., if the research staff member perceives that there is imminent risk of self-harm because the

participant has expressed information about intent, means, plans for self-harm) then the research staff member will:

a. Verify the contact information and location of the participant and thank them for their candor and advise the participant that they will be contacting a mental health provider to perform a further assessment. They will use the following script: “Thank you for being honest with your answer(s). To ensure that you are safe and getting any help you might need I am going to ask a mental health provider to speak with you more about this.” The research staff member will keep the participant on the phone while using another modality of communication (i.e., text, e-mail, pager) to reach Dr. Jensen, Dr. Ehde, or a study clinician who is supervised by Dr. Jensen or Dr. Ehde (who are both licensed, privileged, and credentialed) to do more in-depth assessment of risk.

b. Once a clinician contacts the participant they will follow best clinical practice for the assessment and management of suicide risk (see “Suicide Risk Reduction Protocol – Clinical Staff” below).

c. If a clinician is not available immediately and/or if the research staff member perceives imminent risk, they will encourage the participant to seek immediate evaluation at the nearest ER and/or to contact the National Suicide Prevention Lifeline (https://suicidepreventionlifeline.org/).

d. After directing the participant to the crisis line or ER, the research staff member will follow-up with Dr. Jensen or Dr. Ehde to determine if additional steps (e.g., calling 911) need to be taken. A study clinician will follow up with the participant within 24 hours.

e. Dr. Jensen, Dr. Ehde, or a study clinician who is supervised by a licensed health care provider will document actions taken. An AE report will also be filed if indicated.

3. In the event that a study staff member has reason to believe a participant is in grave danger (as would be the case extremely rarely, and only if they made explicit statements to this effect):

   a. The staff member could contact local police and request a well-being check.

Suicide Risk Assessment Protocol: Clinical Research Staff

The goal of this protocol is to ensure that reasonable steps are consistently taken by study clinicians and investigators to protect participant safety and welfare. The study clinicians will be credentialed and privileged providers at the UW or Masters-level or post-doctoral level clinicians under the supervision of a credentialed and privileged UW provider. Additionally, both Dr. Jensen and Dr. Ehde are credentialed, privileged, and licensed providers at the UW. Should there be any indication of risk for self-directed violence that arise during interactions with study staff, the study clinicians/investigators will follow the same specific procedures and policies that psychologists who are clinicians at UW follow for assessing and managing risk.

In instances where the clinician is concerned about safety/suicide risk in a study participant (i.e., if they state or allude to thoughts or plans of self-directed violence, mention recent self-directed violent behavior or behavior preparatory to self-directed violence during a study intervention session), or in instances where a study clinician/investigator is contacted by a

research staff member and asked to follow-up with a participant, the study clinicians/investigators will follow the same risk assessment and prevention protocol that is required of UW licensed psychologists.

F. Data Safety Monitoring

F1. Adverse Event & Unanticipated Problems Definitions

F1a. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a participant during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study. Staff will document any occurrence that meets this definition, is a new symptom/condition for the participant, and results in either self-treatment or treatment by a health care provider.

F1b. Unanticipated Problems (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

F1c. Serious Adverse Event (SAE)

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

- Results in death;

- Is life-threatening (places the participant at immediate risk of death from the event as it occurred);

- Results in inpatient hospitalization or prolongation of existing hospitalization;

- Results in a persistent or significant disability or incapacity; or

- Results in a congenital anomaly or birth defect.

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment,

the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

F2. Characteristics of an Adverse Event

F2a. Relationship to Study Procedures

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

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

F2b. Expectedness of SAEs

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

F2c. Severity of Event

The following scale will be used to grade adverse events:

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

F3. Reporting Procedures

F3a. Regulatory Event Documentation

All regulatory events, incidents, or problems involving risks to participants, including AEs, SAEs, and Unanticipated Problems (UP), will be documented in the REDCap electronic database that houses all study data. All regulatory events will share a common electronic form template. Two separate copies of the same form will exist, (1) one for events involving information that could unblind staff to a participant's treatment allocation, and (2) another for events without details that could unblind staff to a participant's treatment allocation. Only unblinded staff will have access to the form that outlines events with details that could unblind staff to a participant's treatment intervention. The form will be filled out for every regulatory event. A study clinician will review all events that are designated AEs or SAEs to assess severity and relationship to study procedures.

The Regulatory Event form will assess the following information for all three event types (AE, SAE, and UP):

- A brief description of the incident/problem.
- Dates corresponding to event onset, stop, and location.
- Whether or not the event was unexpected or unanticipated.
- Whether or not the event placed participants or others at greater risk of harm than was previously recognized.
- The degree to which the event was related to study procedures.
- Whether or not the study procedures were discontinued due to the event.
- The steps taken to remedy the event.
- The steps taken to report the event to the appropriate entities.
- (AE/SAE only) A ranking of the severity of the event according to section F2c.
- (AE/SAE only) The specific outcome of the event.
- (SAE only) The category of the SAE.

For reporting purposes, regulatory event documentation will be aggregated into central reports using REDCap's "Reports" functionality. The "Reports" functionality allows data to be pulled from the Regulatory Event forms and summarized in one central report. The content of these reports and the frequency in which they are distributed to regulatory bodies is outlined in sections F3b. and F3c.

F3b. AE Reporting

Research staff will generate reports summarizing all AEs for each participant using the REDCap "Report" feature outlined above in section F3a. The report will contain the participant's code number, date of AE, severity, attribution level to study, action taken, and outcome. These adverse events will be provided quarterly in this format to the DSMC, UW IRB, and NCCIH in accordance with requirements.

F3c. SAE/Unanticipated Problem Reporting

- Unanticipated fatal or life-threatening SAEs at least possibly related to study procedures will be reported immediately to the NCCIH Program Officer, Chair of the DSMC, and the UW IRB.

- Breaches of confidentiality or inappropriate access to protected health information will be reported to the NCCIH Program Officer, Chair of the DSMC, and the UW IRB within 24 hours.

- Other unanticipated SAEs or serious problems at least possibly related to study procedures will be reported to the NCCIH Program Officer and DSMC Chair within 5 days, and to the UW IRB within 10 days.

- Anticipated or unrelated SAEs will be reported to the DSMC and NCCIH Program Officer as part of the annual DSM report.

Research staff will record all SAEs and unanticipated problems using the Regulatory Event form outlined above in section F3a. These serious adverse events/problems will be summarized using the REDCap "Report" format and provided quarterly in this format to the DSMC, the UW IRB, and NCCIH in accordance with requirements.

The Chair of the DSMC will be contacted when an SAE/unanticipated problem is discovered to receive consultation on the matter. The Chair of the DSMC will use her discretion to determine whether the other DSMC members should also provide additional consultation.

F4. Data Quality and Safety Review Plan and Monitoring

F4a. Description of Plan for Data Quality and Management

Data collected by research staff will be entered directly into a database created in REDCap, a secure HIPAA-compliant web-based system. Web forms will be created to enhance functionality and proper data entry. The REDCap system also allows researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered (in instances where an e-signature is specified).

All group treatment sessions will be audio recorded to ensure compliance to treatment procedures. These recordings may also be used for training purposes. A portion of treatment sessions will be randomly selected to be reviewed by study researchers to ascertain fidelity to protocol. Study clinicians will receive feedback as needed if they diverge from protocol.

In addition, research study staff will review the study data in detail on a quarterly basis to detect any systematic issues with data collection and protocol compliance. Data types that will

be reviewed include participant accrual, status of enrolled participants, adherence data regarding study assessments and intervention, any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems.

Regarding protocol deviations, only participant study visits completed outside of the protocol-defined windows would be considered protocol deviations; non-completion of study components by participants would not result in protocol deviations. This was approved by the NCCIH PO on 5/25/2018.

F4b. Frequency of Data Review

The frequency of data review for this study differs according to the type of data and can be summarized in the following table:

Data type	Frequency of review	Reviewer
Participant accrual	Quarterly	Co-PIs, Chair of DSMC
Status of all enrolled participants	Quarterly	Co-PIs, Chair of DSMC
Participant adherence to study procedures	Quarterly	Co-PIs, Chair of DSMC
AEs	Quarterly	Co-PIs, Chair of DSMC
SAEs	Per occurrence	Co-PIs, Chair of DSMC, NCCIH, UW IRB
Unanticipated Serious Problems	Per occurrence	Co-PIs, Chair of DSMC, NCCIH, UW IRB

F4c. Participant Accrual and Compliance

Review of the rate of participant accrual and compliance with inclusion/exclusion criteria will occur monthly during the first six months of recruitment and then every three months to ensure that a sufficient number of participants are being enrolled to allow for an adequate test of the primary study hypotheses and that they meet eligibility criteria.

F4d. Measurement and Reporting of Participant Adherence to Treatment Protocol

Data on participant adherence to the study protocol will be collected monthly by research staff and reviewed quarterly by the PI and the Chair of the DSMC. Adherence of participants to both assessment completion and treatment will be evaluated by running queries to discern adherence rates. If adherence falls below the rate of 80% for EMA assessments or 85% for non-EMA pre- and post-treatment assessments, which might put at risk the ability to test the study's primary hypotheses, the Chair of the DSMC will suggest a conference call for study investigators to discuss methods for improving adherence.

F4e. Stopping Rules

This study will be stopped prior to its completion if: (1) one of the interventions is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that might warrant stopping the trial.

F4f. Designation of a Monitoring Committee

Name/Role	Credentials	Organization	Expertise
Mary Beth Brown / Chair	P.T., Ph.D.	UW	Physical Therapist, conducts research on exercise therapy in cardiopulmonary populations
Tracy Jirikowic	Ph.D., OTR/L, FAOTA	UW	Occupational Therapist, conducts health services research (including clinical trials) on individuals with disabilities
Katie Odem-Davis	Ph.D.	Independent Consultant	Biostatistician
Sean Rundell	P.T., Ph.D., D.P.T.	UW	Physical Therapist, conducts health services research with focus on low back pain

The Data Safety Monitoring Committee (DSMC) for this study is comprised of Drs. Brown, Jirikowic, Odem-Davis, and Rundell.

Dr. Brown is qualified to chair the DSMC because of her expertise in the area of exercise science research and randomized controlled trials. Dr. Jirikowic is qualified to review the patient safety data generated by this study because of her expertise in the area of rehabilitation research and randomized controlled trials. Dr. Rundell has considerable experience conducting health services research. Dr. Odem-Davis was selected given her expertise in biostatistics.

F4g. Safety Review Plan

Study researchers, including staff members and study clinicians who conduct the telephone assessments and facilitate the treatment groups, will collect safety information on an ongoing basis. By systematically monitoring for events, we will ensure that problems are detected immediately and addressed as indicated.

Treatment

Study clinicians will collect unsolicited information reported by participants during treatment sessions including, but not limited to, physical or psychological decline, or unexpected reactions to the treatment intervention.

Any AEs collected during treatment sessions will be recorded on the participant's REDCap Regulatory Events form created and completed during participation.

General

Research staff and study clinicians will collect unsolicited information reported by participants during study participation including suicidal thoughts or suicidal ideation (SI), increased alcohol/drug use, intentions to harm someone else, or psychological decline.

Any AEs collected during the course of the study will be recorded on the participant's REDCap Regulatory Events form created and completed during participation.

All information leading to an adverse event (AE), serious adverse event (SAE), or unanticipated problem (UP) will be reported per UW protocol/requirement, i.e., to UW IRB using

the approved UW IRB forms. All documentation collected, submitted, and approved will be stored in a regulatory e-binder located within a limited access folder on the study server. We do not plan to monitor charts for AEs.

Safety information collection will begin as soon as study recruitment begins. Safety information collection will end once the participant completes the final assessment, i.e., approximately six months following completion of the intervention.

Progress Report (Quarterly)

Research staff will generate three quarterly study reports per year that outline study progress including recruitment, retention/attrition, any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems for that particular quarter. This report will be provided to the Co-PIs and the Chair of the DSMC. The Chair of the DSMC may solicit input from the other DSMC members if she detects anything of concern (e.g., higher rates of AEs than anticipated). The Chair of the DSMC will generate a report only if there is anything of concern that will be supplied to the study PIs, the UW IRB, and NCCIH.

Annual Report

Study staff will generate an Annual Report during the last quarter of the year. The structure of the annual report will be identical to the three quarterly reports done earlier in the year; that is, it will follow the Study Report Outline (see below) with a general summary of what has occurred over the past year and most recent updates and progress since the third quarterly report. It will also include a list and summary of any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems; anything already reviewed in previous quarters by the DSMC Chair and Co-PIs will be clearly indicated in the report. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to all members of the DSMC. The DSMC along with the co-PIs will convene to review and discuss the report. The annual progress report will be forwarded to (1) the UW IRB and (2) NCCIH.

Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team will generate progress reports on a quarterly basis (three per year) for review by the Chair of the DSMC, as well as an annual report (during the final quarter of the year) to be reviewed by all DSMC members. There will be a total of four reports (three quarterly, one annual) per calendar year.

Study Report Outline

I. Table of Contents
II. Introduction
    a. Summary of Study Status and Issues or Problems
III. Study Administration
    a. Recruitment Status
        i. Overall Recruitment Status and Recruitment Source
        ii. Comparison of Targeted to Actual Enrollment
        iii. Reasons for Ineligibility
        iv. Reasons for Declination, Unable to Contact, Deferral
IV. Study Data Reports/Tables or Figures
    a. General Information
        i. Enrollment Status
        ii. Demographic/Baseline Data
        iii. Assessment Retention
        iv. Treatment Participation
        v. Treatment Fidelity
V. Safety Assessment
    a. SAEs
    b. Adverse Events
    c. Reportable Problems
    d. Protocol Deviations

Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

F5. Reporting Changes in Study Status

During the funding of this study, any action by the IRB, the DSMC, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Officer within 1 business day of notification.

G. Potential Benefits of Research to Participants and Others

Previous studies with the therapeutic skills taught in the planned study support their efficacy in reducing pain intensity and improving other pain-related outcomes. We anticipate based on this previous research that many of the participants will experience significant reductions in their daily pain intensity and opioid use and other benefits associated with the treatments. Participants in all three conditions will have the benefit of a caring and interested group leader, thus promoting therapeutic alliance, as well as interaction with other group members.

In our past research, many group members have expressed satisfaction from learning that there are other people with experiences similar to their own, and from receiving group treatment in a caring and nonjudgmental environment. Thus, participants in all three treatments will take away from the study new skills and knowledge regarding chronic pain and how to manage it, and – given previous results of RCTs for psychosocial interventions for chronic pain – should experience some degree of relief from pain and suffering and increases in their quality of life.

H. Publication of Research Findings

Any manuscript will be made available for review by the study sponsor prior to submission.

I. Importance of Knowledge to Be Gained

The findings from this study will provide clinically meaningful information that will have positive effects on the lives of patients with chronic pain who are at high risk for opioid misuse. The findings will provide important new information regarding for whom the three treatments studied are most beneficial for with respect to opioid use reduction. These moderation findings will inform the future development of patient-treatment matching algorithms. The results will also investigate the treatment mechanisms of the treatments studied, as well as those factors that underlie post-treatment relapse, maintenance, and continued gains following treatment. Results will elucidate the temporal sequence of lagged mechanism effects to determine rates of change in opioid use as a function of change in pain intensity and emotional distress. Results will also precisely inform relapse prevention interventions. Progress in the understanding of treatments has been hampered by the lack of mechanism studies, such as the one planned, to identify the mechanisms of treatment outcome and relapse. The current study will help address this significant gap.

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Appendix: Evaluation Timeline

Assessment	Screening	Enrollment	Pre-Treatment	Baseline Monitoring Period	Treatment & Treatment Monitoring Period	Post-Treatment Monitoring Period	Post-Treatment	3-Month Follow-up	6-Month Follow-up
Inclusion/Exclusion Criteria	X								
Informed Consent		X							
Baseline Data and Demographics		X							
Opioid Use MME (Re-Assessment of Study Eligibility)			X						
Opioid Use MME (Randomization Stratification)			X						
Opioid Use MME (Primary Outcome)			X	X	X	X	X	X	X
Secondary Outcomes			X	X	X	X	X	X	X
Primary Mechanisms			X	X	X	X	X	X	X
Secondary Mechanisms			X	X	X	X	X	X	X
Tertiary Outcomes			X				X	X	X
Tertiary Mechanisms			X				X	X	X
Moderators			X		X		X		
Treatment Homework Completion					X				
Participant Engagement					X				
Qualitative Outcomes							X		
Optional Assessments			X				X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X