Chronic Pain Skills Study Protocol

CHRONIC PAIN SKILLS STUDY

A randomized, 3-group parallel design, 240-subject clinical trial to test the efficacy and mechanisms of self-hypnosis and mindfulness meditation on chronic pain in Veterans.

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Contents

TOOL REVISION HISTORY

Version Number: 2.0
Version Date: 12-08-15
Summary of Revisions Made:

1. Eliminated reference of MED exclusion criterion for non-research participants; Changed exclusion criterion regarding reported average daily use of morphine equivalent dose (MED) from >100mg to >120mg MED;
2. Eliminated exclusion criterion regarding receipt of services from the VAPSHCS Pain Service;
3. Reference to revision in protocol regarding psychological screening assessment, specifically that the psychologist could complete a medical record review or use firsthand clinical experience to deem eligibility. The psychologist may call the subject if s/he does not feel s/he can make a definitive judgement regarding eligibility following the medical record review;
4. Reference to additional measures (PROMIS Global Health and StarTBack Screening Tool);
5. Minor revisions to Table 1 to include new measure;
6. Minor revisions to Table 4 to include new measures;
7. Minor revisions to Table 5 to include new measures, update and correct assessment schedule.

Version Number: 3.1
Version Date: 01-11-16
Summary of Revisions Made:

1. Eliminated reference to provision of VAPSHCS research brochure (no longer required);
2. Revised reference to amount of compensation for EEG assessments (from $50 to $100);
3. Eliminated reference to having subjects choose to complete the consent session and the pre-treatment EEG assessment on the same day at the IBIC (still possible, yet no longer offered to subjects).
4. Updated Study Team Roster;
5. Updated table showing research staff who are blind or unblind to assignment;
6. Update language regarding length of optional assessment;
7. Removed reference to scanning treatment case report forms via Clinical Documentations Unit;
8. Changed a typo ‘unblended’ to ‘unblinded.’

Version Number: 4.0
Version Date: 03-11-16
Summary of Revisions Made:

1. Updated description of psychologists who could conduct the psychological screening assessments.

Version Number: 5.0
Version Date: 04-20-16
Summary of Revisions Made:

1. Updated team roster;
2. Update address of secure clinical drives;
3. Reference to feedback regarding treatment modality;
4. Protocol change: open-end questions regarding treatment satisfaction and treatment modality administered by unblinded staff member;
5. Removed reference to ITHS as organization for Katherine Davis, now listed as independent consultant.

Version Number: 5.1
Version Date: 05-19-16
Summary of Revisions Made:

1. Added language that participants are limited to attend each intervention only once

Version Number: 6
Version Date: 06-24-2016
Summary of Revisions Made:

1. Added language that participants may experience discomfort (numbness, tingling, perceived loss of sensation) from sitting still for extended periods of time.

Version Number: 7.1
Version Date: 08-04-16
Summary of Revisions Made:

1. Updated protocol to reflect revision in open label phase procedures to minimize chance of unblinding.
2. Revised language regarding the consent process to reflect change to consent via telephone and postal mail.
3. Added language to define participation in a treatment study group as attending four or more treatment sessions for that particular group (e.g. mindfulness meditation).
4. Clarified that signing the repository consent form gives study researchers permission to include data from all study activities as described in the main study consent form, including the open label phase.
5. Updated study roster to reflect staff changes.
6. Updated study roster by changing personal email addresses to VA/UW addresses.

Version Number: 8
Version Date: 08-18-16
Summary of Revisions Made:

1. Updated study roster to reflect staff changes.
2. Updated protocol to reflect screening, enrollment, baseline data collection and randomization relative to onset of treatment intervention.
3. Updated protocol to allow study researchers to conduct the medical record review (MRR) screening component after receipt of a clinic consult and prior to the mailing of the letter of orientation
4. Updated protocol to reflect that pre-treatment assessments may be repeated if groups do not start within 4 weeks of completion of the assessments.
5. Updated protocol to reflect the addition of 3- and 6- month optional assessments.
6. Updated protocol to reflect open label screening process.
7. Updated protocol to reflect that the open label consent process can take place in person as well as by phone and postal mail.
8. Updated protocol to reflect data validation of exploratory treatment data.

Version Number: 9
Version Date: 11-21-16
Summary of Revisions Made:

1. Updated study protocol to reflect possibility of collecting less than four short assessments during each assessment period.
2. Updated roster to reflect new group leaders added to the study and also group leaders that were removed.
3. Eliminated examples provided for exclusion criterion regarding psychiatric and behavioral conditions with symptoms that are unstable and severe.
4. Emphasized that clinical discretion may be used to determine eligibility regarding mental health exclusion criteria.
5. Took out reference to attached CVs for DSMC members (accidental inclusion from original IRB application).

Version Number: 10
Version Date: 01-03-17
Summary of Revisions Made:

1. Added language indicating subjects will not be withdrawn from the study if they present unstable and/or severe symptoms related to a psychiatric condition following enrollment unless study researchers believe it is in the subject's best interest to be withdrawn.
2. Added language indicating subjects will not be withdrawn if deemed at high suicide risk following enrollment unless study researchers believe it would be in subject's best interest to be withdrawn

Version Number: 11
Version Date: 01-06-17
Summary of Revisions Made:

1. Added a sleep supplement component funded by the sponsor. The procedures for the sleep supplement will be treated as an optional sub-study, with subjects going through an additional informed consent process if interested in participating. The sleep sub-study consists of the following components:
    a) Self-report items administered via telephone during the main pre-treatment, 4 weeks, post-treatment, and 3 month assessment periods;
    b) Wearing an actigraph device measuring sleep and sleep quality during the main pre-treatment, post-treatment, and 3 month assessment periods;
    c) Completing a pencil-and-paper sleep/wake diary during the main pre-treatment, post-treatment, and 3 month assessment periods.

    Sleep sub-study subjects will have the opportunity to be compensated up to $150 if they participate fully in all three main time points.
2. Added reference to protocol where a blank medication list is sent to a subject in advance of the EEG assessment, along with a revised letter.
3. Eliminated use of term "proposed" relative to study, as the grant was in fact awarded.
4. Added PANAS positive affect subscale (10 items) as part of main phase measures.
5. Added PROMIS Psychosocial Illness Impact Positive measure as part of main phase measures.
6. Updated Blinded/Unblinded Research Staff list to reflect current group leaders.

Version Number: 12
Version Date: 03-12-17
Summary of Revisions Made:

1. Clarified language pertaining to the timing of the formal screening process.
2. Revised our procedures regarding the timing of the initial telephone call following the mailing of the approach letter to prospective subjects.
3. Clarified language pertaining to the credentialed providers who would be leading the groups. There are providers from a variety of disciplines who may lead groups.
4. Added the option of sending text reminders for participants who request this type of communication rather than a telephone call.
5. Added a reminder letter that would be mailed prior to follow-up assessments.

Version Number: 13
Version Date: 06-21-17
Summary of Revisions Made:

1. Revised wording of sex/gender as a demographic variable collected/ used for stratification in randomization from “sex” to “sex/gender” to be more accurate of data collected/used.
2. Revised wording to reflect actual intention of collecting sleep baseline data before treatment starts rather than prior to randomization.
3. Revised wording to reflect actual intention of administering the Modified Stanford Hypnotic Clinical Scale (SHCS) before treatment starts rather than prior to randomization.
4. Updated language to reflect that data collected as part of the sleep sub-study will be collected up to 7 days during each assessment period.
5. Update language to indicate clinicians will not have access to the crosswalk between study data and participants’ identities.
6. Deleted incorrect language making reference to the transcription of treatment data on to a new CRF with SUBID only; study sponsor gave study researchers permission not to transcribe data but rather have only electronic copies of the original forms saved on a secure clinical drive.
7. Add Regan Permito to the list of study staff members.
8. Remove Julie Bondzie, Kaitlyn Kadel, Emily Koelmel and Dustin Logan from study staff members.
9. Eliminated incorrect reference to staff not reviewing treatment data of non-research participants; staff may review the form to ensure no adverse events take place that would require clinical intervention.
10. Corrected language in Table 3 regarding timing of pre-treatment brain activity assessment.
11. Revised language to reflect that research staff ideally will attempt to collect each pain assessment a minimum of 24 hours between each assessment, but may collect each assessment no less than 22 hours between each assessment if necessary.
12. Removed incorrect reference to scheduling of treatment groups based on enrollment numbers.
13. Revised language regarding number of group leaders per treatment group.

14. Removed asterisk indicating exclusion criterion #5 is verified solely by medical record review given the redundant nature.
15. Corrected Table 5, assessment schedule, to indicate Theta, alpha, beta, and gamma bandwidth power are only recorded during the pre- and post-treatment assessment periods.
16. Corrected Table 5, assessment schedule, to indicate the Working Alliance Inventory, Group Climate Questionnaire, and Treatment Expectancies/Credibility are collected during treatment only as part of the two-week assessment period.
17. Added language indicating ineligible individuals will be provided any relevant clinical resources available in addition to the resource list.
18. Added language regarding possible risk of discomfort and distress upon hearing other Veterans discuss their pain or other problems in a group setting.
19. Added language regarding possible risk of discomfort and distress due to increased focus on pain problem during assessments/treatments.
20. Added language regarding protection against risk of discomfort/distress during treatment group settings.

Version Number: 14
Version Date: 10-23-17
Summary of Revisions Made:

1. Updated study roster to reflect current staff members.
2. Clarified language that main phase participants would be approached to participate in the Open label phase only after they have completed the 6-month f/u assessment.
3. Defined a "study completer" for the main phase of the study and the sub-study.
4. Added 6 items from the Neurobehavioral Status Inventory to the pre-,post-treatment and 3-month main phase assessments, and to the pre- and post-treatment Open label assessments.
5. Clarified language in D6o to state that we will track reasons for treatment withdrawal rather than reasons for missed treatment sessions.
6. Corrected language in D6x to state that participation in less than 50% (rather than less than 60%) of treatment sessions would be reported as a protocol deviation. Also clarified in section D6n that participation in less than 4 treatment sessions would be reported via Note-to-File.
7. Updated the potential risks of the EEG procedure to include the potential for temporary increase in pain and the potential for temporary increase in PTSD symptoms.
8. Clarified in section 3j that we would use the sponsor-recommended Note-to-File template rather than reporting via the VA template AND the sponsor template.
9. Added language to D6t to indicate that data could be shared with study investigators at UW via the secure data transfer method – SAFE.
10. Updated AE reporting in 3d to state that AEs related to the sleep sub-study will also be reported to the WSU IRB.

Version Number: 15
Version Date: 02-16-18
Summary of Revisions Made:

1. Added language that consent would be obtained using the UW EEG consent document prior to the EEG study procedure.

2. Added language that investigators expect 10% of the actigraphs from the sleep sub-study to not be returned due to loss/misplacement by the participant or loss in the mail. Participants would have the option of hand delivering the actigraph to a research staff member at either the Seattle or American Lake VA campus.
3. Added language that the EEGs are conducted at the UW IBIC and that informed consent would be obtained at IBIC prior to the EEG.
   Dr. Melissa Day was added to the roster
4. Dr. Pagulayan was removed as the DSM chair. Tracy Simpson was moved to DSM chair. Kendall Browne was added to the DSM committee.
5. Added language to describe measuring a participants head to ensure that the EEG nets would fit their head.

Version Number: 16
Version Date: 05-07-18
Summary of Revisions Made:

1. Clarified language that source documents will be stored at either the Seattle or American Lake division. Also clarified that the source documents will be transported between Seattle and American Lake sites.
2. Added Anne Arewasikporn and Kevin Yagle to team roster

Version Number: 17
Version Date: 07-17-18
Summary of Revisions Made:

1. Corrected Study Assessment Schedule. An X was inadvertently removed from Post-treatment for the working alliance and global climate measures, so the X was added back in.
2. Clarified that the Brain Wave Activity is an Optional study procedure (as it is written in the consent document and intended by study investigators.
3. Increased the enrollment number for the Sleep Sub-Study from 135 to 180.
4. Updated language to show that after cohort 9, new participants would be offered treatment materials (workbook and audio recordings) for the intervention that they were not randomized to in place of an invitation to participate in the open label phase.
5. Removed David Kearney from Blinded/Unblinded staff list on page 67.
6. Added Emily Stensland to the list of study staff members.
7. Defined lost to follow up and study completers for the main, open label and sleep study
8. Added language to show that optional assessments will stop once there is enough data to answer exploratory questions.
9. Added language that participants enrolled in the Sleep Sub-Study may be asked to complete the Pre-Tx assessment period again if they do not begin treatment within four weeks of completing the Pre-Tx assessment period.

Version Number: 18
Version Date: 10-30-18
Summary of Revisions Made:

1. Update study team roster and Blinded/Unblinded Research Staff table with added and removed group leaders

2. Added language that participants who were randomized in cohorts 1-9 and are eligible for the open label phase will be offered the option of either receiving treatment materials in the mail or enrolling in the open label phase.

Version Number: 19
Version Date: 03-11-19
Summary of Revisions Made:

1. Increased the enrollment number for the Sleep Sub-Study from 180 to 195.
2. Increased the enrollment number for the Main Study from 343 to 355.
3. Updated team roster and blinded/unblinded table.
4. Removed language that refers to future groups or cohorts for Non-research participants.
5. Clarified that the actigraph data will transmitted by WSU staff to VA staff electronically in de-identified form to be stored indefinitely on the secure VA server with the rest of the study data.
6. Clarified that data from the main phase of the study will be shared with WSU study investigators for the purposes of data analysis.
7. Removed references that de-identified data would be shared via the SAFE method.

Version Number: 20
Version Date: 05-28-19
Summary of Revisions Made:

1. Clarified that primary analysis will use an Intent to treat approach and not a per protocol approach.
2. Detailed approach to missing data.
3. Aim I will be tested using Analysis of CO-variance (ANCOVA), rather than Analysis of Variance (ANOVA) as originally and erroneously specified.
4. Removed reference to using repeated measures ANOVAs for the exploratory aim that looks at the longer-term effects of the two active treatments relative to the education control, added the use of a Generalized Estimating Equations (GEE) approach.
5. Removed reference to additional exploratory brain activity analyses using the LORETA method.
6. Added the use of PROCESS, a free downloadable add-on to SAS or SPSS to conduct the mediation and moderation analyses, as recommended by Hayes & Rockwood (2017).
7. The analytic procedures for the supplementary study differ slightly from those to be used in the parent study. Aim 1 of the parent study uses an ANCOVA to look at between-group changes in outcomes from pre to posttreatment. The power analyses for the parent study were based on estimated effects at posttreatment, not at the later follow-ups. In contrast, the sleep study supplement Aim 1 proposes to look at differences in outcome both at posttreatment and at 3 months posttreatment follow-up, using a technique that accounts for repeated measures within subjects. We did not change the proposed analyses for the sleep study, but simply are explaining here why the analyses look slightly different between the main study and the supplement. We have added some minor clarifying remarks in the updated protocol also (shown in track changes).
8. Updated study staff roster.
9. Added Group Comfort Questionaire.

Version Number: 21
Version Date: 02-19-20
Summary of Revisions Made:

1. Added language to serve as a reminder of why the exclusion criteria of >120mg MED was determined.

Version Number: 22
Version Date: 05-26-20
Summary of Revisions Made:

1. Added language stating that the crosswalk will be destroyed once the study is in data analysis and closed to enrollment and determined to do so by the study PIs.

Version Number: 23
Version Date: 06-30-20
Summary of Revisions Made:

1. Updated non-key study staff roster

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***<u>Please note</u>: unless prefaced by the subheader "Main study" or "Sub-study", each section pertains to both the main study <u>and</u> the sleep sub-study.**

PRÉCIS

Study Title: Chronic Pain Skills Study

Objectives: Main Study

The purpose of this randomized controlled trial is to evaluate the efficacy and mechanisms of self-hypnosis (HYP) and mindfulness meditation (MM) as treatments for chronic pain in a sample of 240 Veterans. Participants will be randomly assigned to 8 group sessions of (1) HYP, (2) MM, or (3) an education control condition (ED). Primary (characteristic pain intensity) and secondary outcomes will be assessed at pre-treatment, three times during treatment, post-treatment, and at 3- and 6-month follow-up. Potential treatment moderators and mediators will also be assessed. The study will address two aims.

Aim 1: Determine the efficacy of 8 sessions of group delivered HYP and MM training for reducing characteristic pain intensity in Veterans, relative to 8 sessions of ED. The hypothesis associated with Aim 1 is:

Hypothesis 1: Primary Study Hypothesis. Veterans receiving 8 sessions of HYP or MM training will report significantly greater pre- to post-treatment decreases in average pain intensity than Veterans receiving 8 sessions of ED.

Aim 2: Evaluate the moderation effects of brain states (as measured by EEG) on response to HYP and MM, relative to ED. The hypothesis associated with Aim 2 is:

Hypothesis 2: Brain State Moderating Hypothesis (Secondary). Pain reduction with HYP and MM will be significantly associated with different patterns of baseline brain activity. Specifically, participants who report the most pain reduction with HYP will evidence higher levels of global theta activity and lower levels of left frontal gamma activity at baseline. Participants who report

the most pain reduction with MM will evidence lower levels of alpha activity at baseline. Baseline brain activity will not be significantly associated with pain reduction following ED.

Sub-Study Title: Sleep and Pain in Veterans Sub-Study

Objectives: Sleep Sub-Study

The purpose of the sub-study is to examine how sleep relates to chronic pain within the context of the randomized controlled trial with a sample of up to ~~135~~ ~~180~~* 195** Veterans. Participants in the sub-study will wear an actigraph device and complete sleep/wake diaries to assess sleep quality and duration at pre-treatment, post-treatment, and at 3-month follow-up. The sub-study will address two aims.

*Due to a higher attrition rate than anticipated, we have increased the enrollment number from 135 to 180 to ensure the 117 completers needed.

**Enrollment number increased to allow for the recruitment of a full cohort in the final cohort of the study.

***Aim 1*: Determine the efficacy of 8 sessions of group delivered HYP and MM training for improving sleep quality and duration in Veterans, relative to 8 sessions of ED. The hypothesis associated with Aim 1 is:**

Hypothesis 1: Participants in the HYP and MM treatment groups will show improvements in self-reported sleep quality and in actigraphic sleep duration both immediately post-treatment and at 3-month follow-up, relative to the control group.

***Aim 2*: Evaluate the relationships between sleep quality, sleep duration and pain intensity. The hypothesis associated with Aim 2 is:**

Hypothesis 2: Changes in sleep quality and duration precede (and thus predict) subsequent changes in pain intensity. Secondarily, we will investigate whether associations are moderated by treatment group. We hypothesize that larger lagged effects will occur for the two treatment conditions, relative to the control condition.

Design and Outcomes

Main Study:

A randomized, 3-group parallel design, 240-subject clinical trial to test the efficacy and mechanisms of self-hypnosis (HYP) and mindfulness meditation (MM) on chronic pain in Veterans.

Sub-Study:

Sleep data collection (quality, duration) on up to ~~135~~ ~~180~~ 195 Veterans with chronic pain who are enrolled in the main study.

Interventions and Duration

Main Study:

Participants will be randomly assigned to 8 group sessions of (1) self-hypnosis (HYP), (2) mindfulness meditation (MM), or (3) an education control condition (ED). Treatment groups will meet once per week over an 8 week period. Each session will last for duration of about 90 minutes. Primary (characteristic pain intensity) and secondary outcomes will be assessed at pre-treatment, three times during treatment, post-treatment, and at 3- and 6-month follow-up. The total time involved in the study is approximately 20-23 hours over a 9-month period.

Once participants complete their involvement in the primary study (i.e., after they have received one of the treatments and completed their last follow-up assessment), they may be invited to attend either (or ultimately both, if they wish) of the other two group treatments. This is called the "open label" phase of the study.

Participants who attend treatment for the first time in cohort 10 and all subsequent cohorts will not be offered the open label phase given study researchers intend to stop running treatment groups by the time these participants will complete the main phase of the study. Instead, these participants will be offered the treatment materials for the treatment of their choice. The treatment materials (workbook and audio recordings) will be mailed via USPS.

Participants who were randomized in cohorts 1-9 and are eligible to participate in the open label phase for cohorts 11 or 12 will be offered the option of either receiving treatment materials in the mail for the treatment of their choice or enrolling in the open label phase depending on space availability.

Sub-Study:

All participants enrolled in the sleep sub-study will be asked to wear a wrist actigraph (Actiwatch 2, Philips Respironics, Bend, OR) for up to 7 consecutive days, up to 24 hours/day to collect objective sleep data at 3 time points: before treatment begins, immediately following the end of treatment, and 3 months following the end of treatment. During each one-week assessment period they will also be asked to complete a brief questionnaire each morning and evening, and fill out a sleep log that includes estimates of time to bed, time to sleep, time awake and out of bed, sleep quality, and daytime napping.

Sample Size and Population

Main Study:

We plan to enroll up to ~~343~~ 355** Veterans with moderate to severe chronic pain to achieve a sample size of 240 completers, with 80 completers in each of the treatment groups.

Enrolled participants who complete the required baseline components (cognitive assessment, hypnotic and relaxation exercise, baseline data and demographic form, and pre-treatment assessment period) will be randomized in stratified blocks to ensure that participants with each sex/gender and pain type (neuropathic, non-neuropathic, mixed or undetermined) have an equal chance of being randomized to one of the 3 conditions. Stratifying in this manner will ensure the groups are balanced to reduce variation in outcome that is associated with each stratification variable.

Sub-Study:

Recruitment will follow the protocol of the main study. We propose to recruit up to ~~135~~ ~~180*~~ 195** of the ~~343~~ 355** parent grant participants in order to ensure complete data from 117 participants, assuming a 15% drop-out rate. Based on our experience, we anticipate that at least 75% of the parent sample will elect to join the sleep study.

*Due to a higher attrition rate than anticipated, we have increased the enrollment number from 135 to 180 to ensure the 117 completers needed. A 13% attrition rate was determined based on the main study. The actual attrition rate for the sleep study is 27%.

** Enrollment number increased to allow for the recruitment of a full cohort in the final cohort of the study.

A. SPECIFIC AIMS

A1. Problem Statement

Main Study:

As many as 50% of male and 75% of female Veterans presenting to Primary Care report chronic pain [1-4], and reporting rates are even higher in specialty clinics.[5-7] Among Veterans returning from Iraq and Afghanistan, 82% report chronic pain,[8] and the prevalence of painful musculoskeletal, joint, and back problems tends to increase in the years following deployment.[9] Prevalent co-morbidities among Veterans, such as substance use disorders, sleep dysregulation, mood disorders, and Post Traumatic Stress Disorder (PTSD) can amplify the experience of pain and complicate treatment.[10-12] In Veterans, the presence of co-morbid pain and anxiety is associated with increased service utilization,[13] while co-morbid pain and substance use increases the risk of medication misuse.[14] Pain is also associated with greater depression and anxiety,[15] sleep dysregulation [12, 16], decreased quality of life,[17] and lower self-reported health.[18]

The most common treatments for chronic pain are analgesics.[19-21] However, chronic pain is multi-dimensional in nature and is therefore often refractory to these and other biomedical interventions.[22] Moreover, the most powerful analgesics – opioids – are associated with adverse side effects including sedation, constipation, and respiratory depression.
Opioids are potentially addictive, which can contribute to their misuse, addiction, and diversion (e.g., selling, hoarding or non-prescribed use).[23] Further, opioid analgesics typically engender tolerance effects. *In sum, there is a compelling need to identify additional effective treatments for Veterans with chronic pain, particularly ones that offer alternatives to pharmacologic agents.*

Sub-Study:

U.S. Veterans commit suicide at a rate of 22 per day.[24] Those receiving long-acting opioid and sedative co-prescriptions to manage pain and sleep are at much higher risk.[25, 26] Chronic pain and insomnia independently rank high as risk factors for suicidal ideation and suicide attempts.[27, 28] Greater understanding of how pain and sleep interact in chronic pain populations

is urgently needed in order to develop strategies to improve these distressing symptoms. Treating pain and sleep concurrently would seem to be a logical approach.[29] However, specific recommendations have not yet been proposed or translated into clinical practice. When treated concomitantly, pain and sleep treatments often include prescribing both sleep and pain medications, which can have deadly synergistic results.

The co-occurring pain-sleep problem has been called a "vicious cycle" and use of opioids, marijuana, alcohol, as well as illicit and prescribed drugs have been used in an attempt to find relief.[30]

There is a compelling, urgent need to address poorly managed pain and sleep, particularly for Veterans, using safe and effective treatment approaches.

A2. Specific Aims and Hypotheses

Main Study:

Several chronic pain self-management approaches have been developed that provide patients with a skill-set they can use – anywhere and anytime – to better manage pain and its effects on their lives. Importantly, these treatments encourage individuals to play an active role in their healthcare, rather than remain a passive recipient of biomedical interventions.

Two such skills-based self-management techniques that may contribute to better pain management and improvements in psychological functioning and sleep quality in Veterans are self-hypnosis (HYP) and mindfulness meditation (MM). Both HYP and MM are easily taught and learned, and therefore could be seamlessly incorporated into clinical practice in VA hospitals and clinics across the country. However, *at this point in time, little is known about the efficacy of HYP and MM interventions for chronic pain in Veteran populations, their effects on co-morbid conditions, and their biological and psychological mechanisms*. Such information is critical to the development of strategies to efficiently and cost-effectively maximize their efficacy and to ensure optimal implementation.

The purpose of this randomized controlled trial is to test the efficacy and mechanisms of HYP and MM on chronic pain in 240 Veterans. Participants will be randomly assigned to 8 group sessions of (1) HYP, (2) MM, or (3) an education control condition (ED). Primary (characteristic pain intensity) and secondary outcomes will be assessed at pre-treatment, three times during treatment, post-treatment, and at 3- and 6-month follow-up. Potential treatment moderators and mediators will also be assessed.

The study will address two aims.

Aim 1: Determine the efficacy of 8 sessions of group delivered HYP and MM training for reducing characteristic pain intensity in Veterans, relative to 8 sessions of ED. The hypothesis associated with Aim 1 is:

Hypothesis 1: *Primary Study Hypothesis*. Veterans receiving 8 sessions of HYP or MM training will report significantly greater pre- to post-treatment decreases in average pain intensity than Veterans receiving 8 sessions of ED.

<u>Aim 2</u>: Evaluate the moderation effects of brain states (as measured by EEG) on response to HYP and MM, relative to ED. The hypothesis associated with Aim 2 is:

Hypothesis 2: *Brain State Moderating Hypothesis (Secondary)*. Pain reduction with HYP and MM will be significantly associated with different patterns of baseline brain activity. Specifically, participants who report the most pain reduction with HYP will evidence higher levels of global theta activity and lower levels of left frontal gamma activity at baseline. Participants who report the most pain reduction with MM will evidence lower levels of alpha activity at baseline. Baseline brain activity will not be significantly associated with pain reduction following ED.

In addition to testing the above specific hypotheses, we will use the data obtained in this study to further explore (1) the effects of HYP and MM relative to each other and to the ED control condition on key co-morbid symptoms and conditions other than pain intensity; (2) the longer-term (up to 6 months) effects of HYP and MM, relative to ED; and (3) additional potential moderators (e.g., hypnotizability, treatment outcome expectancies, treatment motivation, demographic variables, pain type [neuropathic vs. nociceptive], cognitive functioning) and mediators (changes in EEG activity, pain acceptance, catastrophizing, mindfulness, therapeutic alliance, amount of skill practice between sessions) of treatment outcome.

<u>Sub-Study</u>:

A significant barrier to advancing science regarding pain and sleep is the lack of precise, objective sleep measurements.[31, 32] Chronic pain studies reporting on sleep typically rely on self-report,[31] which limits confidence in sleep-related findings due to report and recall bias.[33-36] The study will increase our understanding by adding wrist actigraphs – small, wrist-watch sized activity monitors worn on the wrist – to unobtrusively capture sleep/wake activity data in a trial of non-pharmacological pain interventions. Actigraphs are the technology standard for objective, naturalistic assessment of sleep.[37]

Duration of sleep has been linked to improvements in pain reports[38] while sleep restriction has been found to increase pain perception and decrease ability to disengage from pain.[32] Sleep deprivation reduces the pain threshold and alters levels of interleukins, suggesting an inflammatory response to sleep loss[39] which potentiates pain.[40] However, to what extent such potential mechanisms play a role in chronic pain, and whether or not sleep is a viable target for interventions to mitigate chronic pain, remains to be investigated.

The purpose of the sub-study is to examine how sleep relates to chronic pain within the context of the randomized controlled trial with a sample of up to ~~135~~ ~~180~~ 195 Veterans. Participants in the sub-study will wear an actigraph device and complete sleep/wake diaries to assess sleep quality and duration at pre-treatment, post-treatment, and at 3-month follow-up. The sub-study will address two aims.

<u>Aim 1</u>: Determine the efficacy of 8 sessions of group delivered HYP and MM training for improving sleep quality and duration in Veterans, relative to 8 sessions of ED. The hypothesis associated with Aim 1 is:

Hypothesis 1: Participants in the HYP and MM treatment groups will show improvements in self-reported sleep quality and in actigraphic sleep duration both immediately post-treatment and at 3-month follow-up, relative to the control group.

<u>Aim 2</u>: Evaluate the relationships between sleep quality, sleep duration and pain intensity. The hypothesis associated with Aim 2 is:

Hypothesis 2: Changes in sleep quality and duration precede (and thus predict) subsequent changes in pain intensity. Secondarily, we will investigate whether associations are moderated by treatment group. We hypothesize that larger lagged effects will occur for the two treatment conditions, relative to the control condition.

B. BACKGROUND AND SIGNIFICANCE

B1. Significance of Research

<u>Main Study</u>:

Results will determine if the preliminary evidence supporting the efficacy of HYP and MM in other populations generalizes to a heterogeneous sample of Veterans with chronic pain. The study findings will provide critical information regarding the mechanisms of HYP and MM, including potential moderators and mediators of each. If the primary study hypotheses are supported, the findings will provide the evidence needed to allow for greater access to treatments that would to reduce the pain and suffering in Veterans living with chronic pain.

<u>Sub-Study</u>:

We have a unique opportunity with this sub-study to leverage existing resources, collect high-quality, objective sleep data using wrist actigraphy, and combine expertise in pain and sleep science to disentangle the relationship of pain and sleep symptoms. The knowledge gained can be used to develop and test novel solutions for pain treatment that provide safe, effective alternatives to pharmacologic agents, and ultimately, reduce suffering of Veterans and others living with chronic pain.

B2. Relevance to VA Patient Care Mission

We will administer the treatments in group sessions (which are more efficient than individual sessions) across multiple clinic settings at VAPSHCS using credentialed providers (e.g. psychologists and nurse practitioners) already working in those clinics. The interventions will be offered as part of normally available clinic services, and integrated into the administrative and clinical infrastructure of these clinics. If, as we anticipate, the efficacy of these interventions is supported, *the system will already be in place in the VAPSHCS for the treatments to continue.* Moreover, the interventions will be extremely easy to extend to other VA clinics.

This strategy of designing the interventions in a way that provides for rapid dissemination and utilization in the event that the findings support the treatment(s) is another important innovation of the current study.

C. PRELIMINARY STUDIES

Our team has been conducting large, nationally funded randomized controlled trials (RCTs) on the efficacy of various treatments for chronic pain for over two decades, including clinical trials of hypnosis and meditation procedures, demonstrating that (1) we have the expertise to

conduct the study and (2) we have experience in recruiting and retaining the participants (including Veterans) needed for clinical trials.

Self-Hypnosis training studies. We have successfully completed three RCTs testing the efficacy of HYP training for reducing chronic daily pain in persons with MS,[41] SCI,[42] and low back pain (the latter study was in a sample of Veterans recruited from the Michael E. DeBakey VA Medical Center in Houston, Texas; Mark P. Jensen, Co-Investigator).

These studies demonstrate (1) that the HYP procedures we have developed are effective in at least three populations of individuals with chronic pain and (2) we have experience in the design, conduct, and successful completion of RCTs of CAM interventions. These studies also provide us with critical effect size information needed for the power analyses for testing the primary study hypothesis (i.e., differences between HYP and the education control condition) in the study.

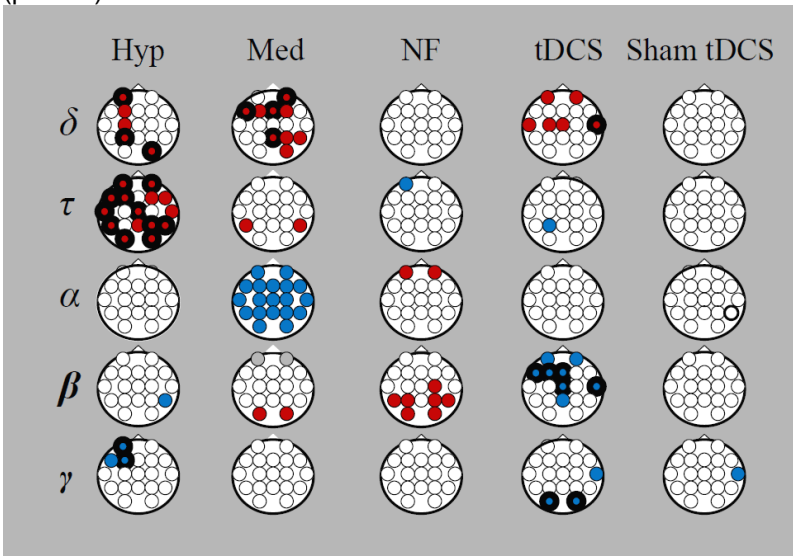
Mindfulness training studies. Recently we completed a pilot RCT investigating an adapted mindfulness-based cognitive therapy (MBCT) for pain protocol compared to a delayed treatment control (DT) for headache pain.

Results demonstrated large benefits for pain intensity (*d* = .80)[43] as well as for pain interference, pain acceptance, and catastrophizing (*d*s = 1.29, 1.22, and .94, respectively). Characteristics of treatment responders and non-responders in our pilot RCT on pain intensity were explored via mixed-methods analyses and showed a medium effect size difference (*d* =.64) in pain acceptance, suggesting that pain acceptance may be critical to the efficacy of MM for improving pain intensity. Pain acceptance is one of the mediators we propose to examine in this study.

Recruitment of Veterans into clinical trials. For the past 10 years, members of our research team have gained considerable experience recruiting Veterans from the VA Puget Sound Health Care System (VAPSHCS) into numerous studies, including RCTs. We have in place proven recruitment and retention methodologies. Collapsing across three recent studies, we were able to identify 355 eligible participants, enroll 203 (57% of those eligible) and retain 179 (88% of those enrolled). These studies are particularly pertinent to this study as they entailed similar participant burdens and recruitment challenges, and we recruited from the clinics proposed for inclusion in this study. In sum, we have extensive experience in successfully enrolling Veterans from the clinical settings of this project. Based on this experience, we estimate that over the 45 months of participant recruitment, we could potentially recruit up 650 (50% of those eligible) participants who meet the eligibility criteria for the current study, and retain as many as 572 (88%) of these in the trial. These numbers far exceed those needed for the current study (i.e., ~~343~~355 recruited, 240 retained).

EEG and pain study. We have recently completed a NIH-funded R21 pilot study to examine the effects of a single session of four pain treatments and a sham (placebo) intervention on pain and EEG. In this study, 30 individuals with SCI and chronic pain were given an EEG and measures of pain before and after a single session of HYP, a focused awareness meditation procedure, transcranial direct current stimulation (tDCS), neurofeedback to reinforce more alpha and less beta activity, and a sham tDCS control procedure.

Figure 1. Associations between baseline EEG and response to treatment. Red = moderate (> .30) positive association (more of this = more response); Blue = moderate (< -.30) negative association (less of this = more response); bold lines = significant (p < .05) association.



We found that (1) each of the active procedures influenced EEG activity in different ways, and that (2) EEG at baseline predicted treatment response. Our findings regarding baseline EEG as an outcome predictor are quite striking, especially those that predict pain reduction with HYP and meditation (see Figure 2). They indicate that *HYP and meditation operate via different mechanisms* (and that these differences can be assessed using spectral analysis of EEG data); that is, "different brains" respond to each treatment.

If these findings are replicated in future studies, they would provide strong support that not only do HYP and MM operate via different mechanisms, but that individuals who do not respond to one could very well respond to the other; therefore both treatments should be offered.

With respect to this latter finding, we found that patients who responded more to HYP had more theta activity overall and less left frontal gamma at baseline, while those who responded to meditation had less alpha at baseline (see Figure 2). Interestingly, these differences are consistent with our hypotheses about the mechanisms of HYP and mediation. That is, higher levels of theta are found in individuals who have more trait hypnotizability (tendency to respond to hypnotic suggestions in general).[44] This brain oscillation is associated with higher levels of focused attention[44-46] thought to be a critical aspect of hypnosis.[47] Moreover, there is growing evidence that individuals with more trait hypnotizability also respond to hypnosis and hypnotic suggestions by inhibiting activity in frontal regions involved in executive functioning,[48-50] consistent with our finding of decreased left-frontal gamma (see Figure 2).

With respect to the findings regarding pre-treatment alpha predicting response to meditation, we know that meditation increases alpha activity, so it is reasonable that those "lacking" in alpha activity would be those most likely to respond to meditation. Continued examination of the impact of HYP and meditation techniques on brain states – and the ability of brain states at baseline to predict treatment response– represents an exciting and innovative area of study for the field. Hence, we focus on this as our second study aim.

D. RESEARCH DESIGN AND METHODS

D1. Synopsis

Main Study:

The sample will include up to ~~343~~ 355 Veterans with chronic pain. Inclusion criteria include: (1) Veteran status (defined as prior service in the US Armed Forces and eligible to receive health care services through Veterans Health Affairs); (2) 18 years of age or older; (3) self-reported presence of chronic physical pain; (4) average pain intensity rating of ≥ 3 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week; (5) worst pain intensity rating of ≥ 5 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week; (6) duration of chronic pain 3 months or more; (7) Experiences pain at least 75% of the time in the past 3 months; (8) able to read, speak, and understand English. Exclusion criteria include: (9) severe cognitive impairment defined as two or more errors on the Six-Item Screener;[51] (10) Current or history of diagnosis of primary psychotic or major thought disorder as listed in participant's medical record or self-reported within the past five years; (11) Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported or noted in chart (within the past 5 years); (12) psychiatric or behavioral conditions in which symptoms were unstable or severe as listed in participant's medical record or self-reported within the past six months; (13) any behavioral issues as noted in the medical record that would indicate the participant may be inappropriate in a group setting; (14) presenting symptoms at time of screening that would interfere with participation, specifically active suicidal ideation with intent to harm oneself or active delusional or psychotic thinking; (15) Difficulties or limitations communicating over the telephone; (16) any planned life events that would interfere with participating in the key elements of the study; and (17) reported average daily use of >120mg morphine equivalent dose (MED).

Study participants who complete all baseline assessments will then be randomly assigned to eight group sessions of one of three manualized treatments: (1) pain education (ED), (2) self-hypnosis training (HYP), or (3) mindfulness meditation training (MM). Inclusion of the face-valid pain education condition will allow us to control for many of the non-specific effects of HYP and MM treatments, including time, therapist attention, and treatment outcome expectancy.[52, 53] Moreover, this condition is expected to be beneficial in ways that are not reflected in our outcome measures (e.g., improved knowledge/understanding of chronic pain, improved communication skills).

This RCT will examine the immediate post-treatment and long-term (3- and 6-months from end of treatment) efficacy and mechanisms of HYP and MM on average pain intensity (primary outcome), worst pain intensity, depression, anxiety, sleep disturbance, pain interference, medication use, post-traumatic stress, thoughts about pain, mindfulness and global satisfaction relative to the ED intervention designed to control for time, dose, attention, and other nonspecific therapeutic effects such as therapeutic alliance. Self-report data will be collected primarily via telephone excluding the cognitive assessment and hypnotic and relaxation exercise.

This RCT will also examine whether pain reduction with HYP and MM will be significantly associated with different patterns of baseline brain activity. Brain activity data will be collected

via electroencephalogram (EEG) once before and once after treatment to test the second aim of this study.

The study uses a 3-group parallel design. During their study participation, all participants will continue to receive their usual medical, psychiatric, and psychotherapeutic care. Participants will also be offered to participate in one or both treatments they did not receive following end of participation in the main phase.

Sub-Study:

The sample for the sub-study will include up to ~~135~~ ~~180~~ 195 Veterans with chronic pain who are enrolled in an existing 3-arm RCT examining the efficacy and mechanisms of two active treatments (mindfulness meditation and self-hypnosis training), relative to a pain education control condition. At the time of recruitment into the parent study, all participants will receive information on the supplemental sleep study and be invited to join. If they agree, after consenting to the parent study, a research staff member (trained by Dr. Wilson, the lead on the supplemental study) will explain the sleep study and review the eligibility criteria and consent form specific to this study. Use of wrist actigraphy will be demonstrated and the additional sleep data collection will be explained. Once consented, participants who have agreed to participate will have additional self-reported sleep data collected along with the original RCT's planned pre-treatment assessments. As a condition of the parent grant, study participants will then be randomly assigned to eight group sessions of one of three standardized treatment conditions.

All participants enrolled in the sleep study will be asked to wear a wrist actigraph (Actiwatch 2, Philips Respironics, Bend, OR) for up to 7 consecutive days, up to 24 hours/day to collect objective sleep data at 3 time points, following study enrollment. During that one-week period they will also be asked to complete a brief questionnaire each morning and evening, and fill out a sleep log that includes estimates of time to bed, time to sleep, time awake and out of bed, sleep quality, and daytime napping. Participants will also call in to a voice mail system daily for up to 7 days to report their sleep and wake times.

These data (sleep/wake diary, sleep calls) will help validate the actigraph objective sleep data, assure participant engagement with sleep data collection, and serve as additional covariate and mechanism variables to explain sleep findings more completely.

These additional sleep data (self-reported sleep data via telephone, objective actigraph data, sleep/wake diary, sleep calls) will be collected at time points that align with significant data collection time points from the parent grant: immediately pre-treatment, treatment mid-point at week 4 (self-report data via telephone only), post-treatment at week 8 for assessment of post-treatment effect, and again at month 3 for a long-term measurement.

Table 1. Study Design: Main Phase

Step	Data Collected	How Often/When
Cognitive Assessment	Cognitive functioning	Once following consent, before treatment begins
Relaxation and Hypnotic Exercise	Hypnotic responsivity	Once following consent, before treatment begins
Baseline Data and Demographic Form	Demographic and general health information, pain type	Once following consent, before treatment begins
Pre-Treatment Telephone Assessments	average pain intensity (primary outcome), worst pain intensity, depression, anxiety, sleep disturbance, pain interference, global health, medication use, post-traumatic stress, thoughts about pain, mindfulness, treatment motivation and expectancy, cognition	Once following consent, before treatment begins
Pre-Treatment EEG Brain Activity	Delta, theta, alpha, beta, and gamma power	Once following consent, before treatment begins

Randomization	No data collected	Once following completion of all baseline study procedures
Treatment	Homework completed between sessions, pain and comfort levels pre- and post-session, participant engagement as per clinician	Eight sessions avg. once per week
During Treatment Assessments	Average pain intensity (primary outcome), depression, anxiety, sleep disturbance, pain interference, global health, medication use, post-traumatic stress, thoughts about pain, mindfulness, group climate, therapeutic alliance,	After sessions 2, 4 and 6
Post-Treatment Telephone Assessment	average pain intensity (primary outcome), depression, anxiety, sleep disturbance, pain interference, global health, medication use, post-traumatic stress, thoughts about pain, mindfulness, global satisfaction, therapeutic alliance, treatment satisfaction, treatment modality and feedback, cognition	Once following end of treatment
Post-Treatment EEG Activity Assessment	Delta, theta, alpha, beta, and gamma power	Once following end of treatment
3 Month Telephone Assessments	Average pain intensity (primary outcome), depression, anxiety, sleep disturbance, pain interference, global health, medication use, post-traumatic stress, thoughts about pain, mindfulness and global satisfaction, cognition	Three months following end of treatment
6 Month Telephone Assessments	Average pain intensity (primary outcome), depression, anxiety, sleep disturbance, pain interference, global health, medication use, post-traumatic stress, thoughts about pain, mindfulness	Six months following end of treatment

Table 2. Study Design: Open Label Phase (for participants enrolled in cohorts 1-9)

Step	Data Collected	How Often/When
Pre-Treatment Telephone Assessments	Average pain intensity (primary outcome), depression, anxiety, sleep disturbance, pain interference, global health, post-traumatic stress, and medication use, cognition	After completion of 6 month assessment of main phase, before treatment begins
Treatment Intervention Selection	No data collected	Once following completion of pre-treatment assessments
Treatment	Homework completed between sessions, pain and comfort levels pre- and post-session, participant engagement as per clinician	Eight sessions avg. once per week

Post-Treatment Telephone Assessment	Average pain intensity (primary outcome), depression, anxiety, sleep disturbance, global health, pain interference, post-traumatic stress, medication use, global satisfaction, and treatment satisfaction, cognition	Once following end of treatment

Table 3. Study Design: Sleep Sub-Study

Step	Data Collected	How Often/When
Pre-Treatment Telephone Assessments	Two questions about how much the subject agrees with certain statements about his/her sleep, as well as two questions about how confident the subject is about carrying our certain sleep behaviors	Once following consent, before treatment begins
Pre-Treatment Actigraph Device and Sleep/Wake Diary	Sleep duration and quality (objective and self-report), wake/ sleep times (self-report), how the subject felt that day, any problems s/he experienced such as illness or discomfort, and basic activities s/he participated in like going to work, napping, drinking caffeinated beverages, etc. (self-report)	One-week period following consent, before treatment begins
4 Week Telephone Assessments	Two questions about how much the subject agrees with certain statements about his/her sleep, as well as two questions about how confident the subject is about carrying our certain sleep behaviors	One-week period following treatment session #4
Post-Treatment Telephone Assessment	Two questions about how much the subject agrees with certain statements about his/her sleep, as well as two questions about how confident the subject is about carrying our certain sleep behaviors	Once after the end of treatment
Post-Treatment Actigraph Device and Sleep/Wake Diary	Sleep duration and quality (objective and self-report), wake/ sleep times (self-report), how the subject felt that day, any problems s/he experienced such as illness or discomfort, and basic activities s/he participated in like going to work, napping, drinking caffeinated beverages, etc. (self-report)	One-week period following the end of treatment
3 Month Telephone Assessment	Two questions about how much the subject agrees with certain statements about his/her sleep, as well as two questions about how confident the subject is about carrying our certain sleep behaviors	Once three months after the end of treatment

3 Month Actigraph Device and Sleep/Wake Diary	Sleep duration and quality (objective and self-report), wake/ sleep times (self-report), how the subject felt that day, any problems s/he experienced such as illness or discomfort, and basic activities s/he participated in like going to work, napping, drinking caffeinated beverages, etc. (self-report)	One-week period three months after the end of treatment

D2. Study Timeline

Main Study:

We designed a five-year study plan and timeline for achieving short-term study objectives. There will be 36 months available to enroll up to 355 participants, with 240 participants projected to complete all study elements. Please note that the researchers received funding for 58 months instead of 60 months (i.e. five years), which is reflected in the timeline below.

Months 01-09 in Year 01 will be spent hiring staff, obtaining IRB and sponsor approval, finalizing treatment manuals, and creating databases. Subject enrollment will require 3.17 years (Months 10 through 48). Data collection and cleaning will be ongoing and will continue through Months 10-56. Months 53-58 will be devoted to data analysis and dissemination activities.

Sub-Study:

Months 01-05 in Year 01 of the supplement will be spent training Seattle-based personnel, finalizing data collection procedures, and securing IRB agreements and approvals between sites. Participant enrollment and data collection will require 1.5 years (Month 06 in Year 01 to Month 12 in Year 02).

	Start	End	Q1 09/01/14-11/30/14	Q2 12/01/14-2/28/15	Q3 03/01/15-05/31/15	Q4 06/01/15-06/30/15	Q1 07/01/15-09/30/15	Q2 10/01/15-12/31/15	Q3 01/01/16-3/31/16	Q4 04/01/16-06/30/16	Q1 07/01/16-09/30/16	Q2 10/01/16-12/31/16	Q3 01/01/17-3/31/17	Q4 04/01/17-06/30/17	Q1 07/01/17-09/30/17	Q2 10/01/17-12/31/17	Q3 01/01/18-3/31/18	Q4 04/01/18-06/30/18	Q1 07/01/18-09/30/18	Q2 10/01/18-12/31/18	Q3 01/01/19-3/31/19	Q4 04/01/19-06/30/19
Development (Months 1-9)	Sep-14	May-15																				
Prepare recruitment, enrollment, randomization and retention procedures																						
Implement meetings with investigators and staff from all sites																						
Obtain Veterans Affairs Puget Sound Health Care System (VAPSHCS) IRB approval including submission of application																						
Obtain approval by NCCIH																						
Construct and test databases for measures, session data, and tracking																						
Obtain University of Washington (UW) Institutional Review Board (IRB) approval including submission of application																						
Preparation (Months 1-9)	Sep-14	May-15																				
Hire research staff																						
Train research staff																						
Register with clinicaltrials.gov																						
Obtain Certificate of Confidentiality																						
Purchase supplies																						
Create and organize filing system																						
Open checking accounts, subject payments																						
Order participant workbooks																						
Accommodate Sponsor Site Visit																						

	Start	End	Q1 09/01/14-11/30/14	Q2 12/01/14-2/28/15	Q3 03/01/15-05/31/15	Q4 06/01/15-06/30/15	Q1 07/01/15-09/30/15	Q2 10/01/15-12/31/15	Q3 01/01/16-3/31/16	Q4 04/01/16-06/30/16	Q1 07/01/16-09/30/16	Q2 10/01/16-12/31/16	Q3 01/01/17-3/31/17	Q4 04/01/17-06/30/17	Q1 07/01/17-09/30/17	Q2 10/01/17-12/31/17	Q3 01/01/18-3/31/18	Q4 04/01/18-06/30/18	Q1 07/01/18-09/30/18	Q2 10/01/18-12/31/18	Q3 01/01/19-3/31/19	Q4 04/01/19-06/30/19
Participant Enrollment/ Data Acquisition (Months 10-56)	Jun-15	Apr-19																				
Enroll an average of approximately 8-9 participants per month (Months 10-48)						9	36	63	90	117	144	171	198	225	252	279	306	333	343			
Assign participants to treatment intervention							6	25	44	63	82	101	120	139	158	176	195	214	233	240		
Conduct treatment with participants							6	25	44	63	82	101	120	139	158	176	195	214	233	240		
Acquire pertinent data from enrolled participants																						
Provide ongoing supervision to research and clinical staff																						
Conduct weekly meetings with research staff to address enrollment																						
Operations and Maintenance (Months 10-56)	Apr-15	Apr-19																				
Submit annual reports to Sponsor																						
Submit IRB continuing review reports (annually)																						
Maintain personnel training files																						
Monitor and supervise staff to ensure adherence to procedures																						
Conduct regular meetings with clinical staff																						
Data and Safety Management (Months 10-56)	Jun-15	Apr-19																				
Conduct data entry																						
Conduct data checking/cleaning ongoing throughout																						
Review monthly progress reports (Co-PIs)																						
Review quarterly progress reports to (DSMC Chair and Co-PIs)																						
Review Data and Safety Management Annual Report (DSMC)																						
Publication/ Disseminaton (Months 9-58)	May-15	Jun-19																				
Attend annual scientific meetings to report on progress and findings																						
Prepare papers for publication (Months 53-58)																						

D3. Inter-Site Communication and Coordination

Main Study:

Routine communication and coordination between the investigators of the two study sites (UW and VAPSHCS) will occur primarily through via joint teleconferenced executive meetings. These meetings will be scheduled once every two weeks through month 7 in Year 1, and then on an as-needed basis during the publication/dissemination period. Research staff from both sites will also meet either in-person or via telephone with the research manager on a weekly basis to address recruitment and enrollment and general workload strategies. Additionally, the research manager will visit each site on a regular basis to monitor and review each site's study activities.

Sub-Study:

Routine communication and coordination between the investigators of the three study sites (UW, VAPSHCS, and WSU) will occur primarily through via joint teleconferenced executive meetings on an as-needed basis throughout the sub-study. Research staff from all three sites will also meet via telephone on a regular basis to address recruitment and enrollment and general workload strategies.

D4. Participant Recruitment and Feasibility

Veterans will be recruited from several clinics and service lines at VAPSHCS: the Rehabilitation Care Service (which includes the Polytrauma Network Site for the northwest four states, the Multiple Sclerosis Clinic/Center of Excellence, Prosthetic/Limb Loss Clinic, and Musculoskeletal Clinic), and the Spinal Cord Injury Service. Each of these clinics sees 200-500 new Veteran patients per year and carries an ongoing patient load of 200 – 400 patients. We will also recruit patients from Primary Care as needed, which carries an ongoing patient load of 19,000 patients per year. Last, Veterans may be referred to the study by clinicians in other service lines or from VA community-based outpatient clinics (CBOC) , but we will not actively recruit Veterans from other service lines.

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

D5. Participants

Main Study:

We propose to enroll up to ~~343~~ 355* participants in order to ensure complete data from 240 randomized participants, assuming a very conservative 30% drop-out rate (the dropout rate in our other studies has averaged 12%). We will monitor the dropout rate on an ongoing basis, and modify the number of participants recruited as needed to ensure a final sample of N = 240 study completers.

*Enrollment number increased to allow for the recruitment of a full cohort in the final cohort of the study.

A completer is someone who is enrolled, randomized and participated in at least one data assessment point following randomization.

If someone is enrolled and not a completer, they would be defined as either 1.) Enrolled, not randomized or 2.) Enrolled, randomized, did not provide any data after randomization

For Open Label: A completer is someone who is enrolled, selects treatment and participates in the post-treatment assessment point.

If someone is enrolled and not a completer, they would be defined as either 1.) Enrolled, did not select treatment or 2.) Enrolled, selected treatment, did not participate in the post-treatment assessment.

Sub-Study:

We propose to enroll up to up to ~~135~~ ~~180~~ 195 participants in the sub-study to ensure complete data from 117 randomized participants, assuming a 25 - 30% drop-out rate. We will monitor the dropout rate on an ongoing basis, and modify the number of participants recruited as needed to ensure a final sample of N = 117 sub-study completers.

A completer is someone who is enrolled, randomized and participated in at least one data assessment point following randomization.

If someone is enrolled and not a completer, they would be defined as either 1.) Enrolled, not randomized or 2.) Enrolled, randomized, did not provide any data after randomization

Eligibility Criteria

Inclusion criteria:

(1) Veteran status (defined as prior service in the US Armed Forces and eligible to receive health care services through Veterans Health Affairs);*
(2) 18 years of age or older; *
(3) Self-reported presence of chronic pain;**
(4) Average pain intensity rating of ≥ 3 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week; **
(5) Worst pain intensity rating of ≥ 5 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;**
(6) Duration of chronic pain 3 months or more; **
(7) Experiences pain at least 75% of the time in the past 3 months; Those who have a hard time answering this question will be asked the following question: "Which statement best describes your pain?"
    (a) Pain all the time, but the pain intensity varies;
    (b) Pain most of the time with only occasional periods of being pain-free;
    (c) Pain that comes and goes;
    (d) Occasional pain;

    Participants must report experiencing pain that matches one of the first two options;**
(8) Able to read, speak, and understand English.**

Exclusion criteria:

(1) severe cognitive impairment defined as two or more errors on the Six-Item Screener;[51] **
(2) Current or history of diagnosis of primary psychotic or major thought disorder as listed in participant's medical record or self-reported within the past five years;*
(3) Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported or noted in chart (within the past 5 years);*
(4) Psychiatric or behavioral conditions in which symptoms are unstable or severe as listed in participant's medical record or self-reported within the past six months;*
(5) Any behavioral issues as noted in the medical record that would indicate the participant may be inappropriate in a group setting;
(6) Presenting symptoms at time of screening that would interfere with participation, specifically active suicidal ideation with intent to harm oneself or active delusional or psychotic thinking;**
(7) Difficulties or limitations communicating over the telephone;**
(8) Any planned life events that would interfere with participating in the key elements of the study.**
(9) Reported average daily use of >120mg morphine equivalent dose (MED). ** (see notes below regarding the >120mg cut off

*also verified via medical record review in CPRS, as described below in section D6b.
**verified solely via self-report, as described below in section D6b; there is no medical record review component.

Veterans above 120 MED are typically better served by the Opioid Safety Program in which medication concerns are addressed first, typically through Pain Clinic taper, suboxone prescription, or even referral to the Addiction Treatment Center (ATC).

Per the VA/DoD Opioid Safety CPG (2017):
"The risk of prescription opioid overdose and overdose death exists even at low opioid dosage levels and increases as dosage increases. Significant risk (approximately 1.5 times) exists at a daily dosage range of 20 to <50 mg morphine equivalent daily dose (MEDD) and further increases (approximately 2.6 times) at a range of 50 to <100 mg MEDD compared to risk at <20 mg MEDD. Risk continues to increase at higher dosage ranges (≥100 mg MEDD)."

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. Moreover, age is one of the potential moderator variables we propose to study, so we will be better able to evaluate age effects with greater age variability in the sample.

D6. Procedures

D6a. Recruitment

Prospective participants will be identified via several mechanisms:

Chronic Pain Skills Program Consult

Any clinical provider at VA Puget Sound or an affiliated community-based outpatient clinic (CBOC) can refer a Veteran for participation. The consult will contain information about eligibility and research vs. non-research options.

We will offer regular in-services and study information to providers who staff the clinics/service lines described above so they will be familiar with the study and clinic inclusion and exclusion criteria and basic intervention components.

As part of this research study, researchers will develop a clinic (known as the 'Chronic Pain Skills Program') that offers the three types of group treatment to both research participants as well as non-research participants.

A provider may refer to the Chronic Pain Skills Program any Veteran with chronic pain the provider believes would benefit from learning pain management skills. The provider would make the referral by selecting the program from a menu in CPRS as a consult. There will be instructions on the consult that remind the referring provider of the eligibility criteria.

Research staff will monitor the incoming consults through automatic notifications. Staff will then review the medical records of each Veteran in CPRS. Research staff will contact ineligible patients to inform them of their ineligibility with the assistance of a script. Research staff will send a letter of orientation to all eligible Veterans who are referred to the program. The letter will be accompanied by a document explaining the difference between attending the program as a research participant versus a non-research participant.

Research participants, in addition to the attendance of treatment sessions, would (1) participate in all of the study assessments including the brain activity assessments, (2) be compensated for completion of these assessments, and (3) be randomized to one of the three interventions following informed consent. Non-research participants would simply participate in the treatment intervention of their choice (i.e. would not be randomized), and would not receive any compensation beyond travel reimbursement the VA may offer.

Veterans referred to the Chronic Pain Skills Program can contact research staff via telephone if interested in participating in the research. Research staff would also call Veterans in 1-2 weeks following the mailing if there is no response to make sure the Veteran received the letter. Research staff would use a script to inquire whether the Veteran is interested 1) in participating in the program at all, and 2) if yes, whether the Veterans would like to participate in the program as a research participant or non-research participant.

Research staff would initiate the study screening process using the research recruitment script and screening case report form if the Veteran is interested in participating in the program as a research participant. Research staff would initiate the non-research screening process using the non-research screening checklist and recruitment script.

The basic outcome of the screening for non-research participants will be stored electronically in aggregate form in de-identified form to help discern the feasibility of implementing this type of program in the future in VA medical centers. Research staff will inform eligible individuals of the three different group treatments if the Veteran wants to participate in the clinic as a non-research participant.

The research staff member would then convey both treatment group selection and preferred location (Seattle or American Lake Division) of this non-research participant either in person, via telephone or via PKI encrypted email to Dr. Williams. Dr. Williams would then add the participant to the appropriate clinic list.

Number of Contacts: Research staff would send one letter of orientation, leave up to three successive unanswered voicemails, and send a final letter indicating research staff will no longer be attempting to contact the participant unless notified otherwise before terminating attempts.

Provider Referral

a) Health care providers from the clinics/services listed above may also provide research staff members via CPRS or encrypted VA email the contact information of potential participants who expressed interest in participating in the research study following a discussion during a medical appointment. Staff would then review the medical records of the Veterans in CPRS. Research staff would contact ineligible patients to inform them of their ineligibility with the assistance of a script. Research staff would use a script to contact eligible Veterans via telephone to help describe the study in more detail. Research staff would initiate the study screening process if a Veteran 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 would leave up to three successive unanswered voicemails and then send a final letter indicating research staff will no longer be attempting to contact the Veteran unless notified otherwise before terminating attempts.

b) Providers can also refer Veterans to the study by providing the Veteran with a brochure and inviting them to follow-up independently. The Veteran would then contact research staff via telephone if interested in participating in the study.

Number of Contacts: Following initial contact by Veteran, research staff would leave up to three successive unanswered voicemails and then send a letter indicating research staff will no longer be attempting to contact the Veteran unless notified otherwise before terminating attempts.

c) In addition, CPRS records will be reviewed for Veterans with upcoming visits to certain clinics (e.g., various Rehabilitation Care Service clinics) where we expect a high rate of interest, relevance, and eligibility.
Specifically, staff would review the medical records in CPRS of these Veterans as per medical record screening protocol to determine initial eligibility (see detailed description below).

Research staff would contact a provider via encrypted email to inform them when a particular Veteran 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 Veteran. Ideally this would then result in scenario ‘a’ described above.

d) Finally, research staff will contact on a regular basis clinical providers within the clinics/service lines described above to inquire whether any recent patients seen by the providers who were not referred to the study may be a good fit for the study. The clinical

providers would then provide via encrypted email names of Veterans to research staff members who they deem might be a good fit. Staff would review the medical records in CPRS of these Veterans as per medical record screening protocol to determine initial eligibility (see detailed description of medical record screening below). Research staff will send eligible Veterans an approach letter along with an information sheet about the study if s/he is deemed eligible. The Veteran would then contact research staff via telephone if interested in participating in the study. Research staff would call Veterans in 1-2 weeks following the mailing if there is no response to make sure the participant received the letter. Research staff would use a script to inquire whether the Veteran is interested in participating in the research study or not.
Research staff would initiate the study self-report screening process if the Veteran 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 would send one approach letter, leave up to three successive unanswered voicemails, and then send a final letter indicating research staff will no longer be attempting to contact the Veteran unless notified otherwise before terminating attempts.

Select Medical Record Review

CPRS records will be reviewed for Veterans seen in several Rehabilitation Care Service (RCS), Spinal Cord Injury Service (SCI), and some primary care clinics up to three years prior to beginning recruitment. This strategy will be used to augment current provider and self-referrals, and will be done in reverse chronological order, month by month, until recruitment goals are met. Specifically, staff would review the medical records in CPRS of these Veterans as per medical record screening protocol to determine initial eligibility (see detailed description below). Research staff would send eligible Veterans an approach letter along with an information sheet about the study if s/he is deemed eligible. The Veteran would then contact research staff via telephone if interested in participating in the study.

Research staff would call Veterans in 1-2 weeks following the mailing if there is no response to make sure the Veteran received the letter. Research staff would use a script to inquire whether the Veteran is interested in participating in the research study or not. Research staff would initiate the study self-report screening process if the Veteran is interested in participating using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

Number of Attempts: Research staff would send one approach letter, leave three successive unanswered voicemails, and then send a final letter indicating research staff will no longer be attempting to contact the Veteran unless notified otherwise before terminating attempts.

Self-Referral

Flyers and brochures describing the study will be available throughout both VAPSHCS divisions. Interested Veterans would then contact research staff via telephone. Research staff would initiate the study self-report screening process if the Veteran 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).
Staff would review the medical records in CPRS of Veterans deemed initially eligible as per medical record screening protocol to determine final eligibility (see detailed description of medical record screening below). Research staff would contact ineligible Veterans to inform

them of their ineligibility with the assistance of a script. Research staff would begin scheduling the informed consent process with eligible Veterans.

Number of Contacts: Following initial contact by Veteran, research staff would leave up to three successive unanswered voicemails and then send a letter indicating research staff will no longer be attempting to contact the Veteran unless notified otherwise before terminating attempts.

The recruitment approaches described above will provide participants who are representative of the general Veteran population with chronic pain, and enhance the generalizability of the study results.

Please note that only research staff members will screen, consent or perform study procedures with potential participants.

D6b. Screening Procedures: Research Study Participants

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

Component 1: Medical Record Screening
Each potential participant's medical records in CPRS will be reviewed to confirm the following inclusion criteria:

- Veteran status (defined as prior service in the US Armed Forces and eligible to receive health care services through Veterans Health Affairs);
- 18 years of age or older.

In addition, each potential participant's medical records in CPRS will be reviewed to rule out the following exclusion criteria:

- Current or history of diagnosis of primary psychotic or major thought disorder as listed in participant's medical record or self-reported within the past five years;
- Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported or noted in chart (within the past 5 years);
- Psychiatric or behavioral conditions in which symptoms were unstable or severe as listed in participant's medical record or self-reported within the past six months;
- Any behavioral issues as noted in the medical record that would indicate the subject may be inappropriate in a group setting;

A staff member will record the findings of the medical record review using the screening case report form.

The medical record screening may be reviewed either before or after the self-report screening component depending on recruitment source.

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

Component 2: 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.

The self-report screening may take place either before or after the medical record review depending on recruitment source. Please note that several criteria will be confirmed twice by both initial steps (medical record and self-report screening).

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

- Self-reported presence of chronic pain;
- Average pain intensity rating of ≥ 3 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
- Worst pain intensity rating of ≥ 5 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
- Duration of chronic pain 3 months or more;
- Experiences pain at least 75% of the time in the past 3 months; Those who have a hard time answering this question will be asked the following question: "Which statement best describes your pain?"
  a) Pain all the time but the pain intensity varies;
  b) Pain most of the time with only occasional periods of being pain-free;
  c) Pain that comes and goes;
  d) Occasional pain.

  Subjects must report experiencing pain that matches one of the first two options.

An additional self-report inclusion criterion includes:

- Able to read, speak, and understand English.

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

- Current or history of diagnosis of primary psychotic or major thought disorder as self-reported within the past five years;
- Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported (within the past 5 years);
- Psychiatric or behavioral conditions in which symptoms were unstable or severe as self-reported within the past six months.

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

Additional self-report exclusion criteria include:

- Difficulties or limitations communicating over the telephone;
- Any planned life events that would interfere with participating in the key elements of the study.
- Reported average daily use of >120mg morphine equivalent dose (MED).

A staff member will record the findings of the self-report screening using the screening case report form.

Component 3: Psychological Screening Assessment

Once a prospective participant has been screened and deemed eligible to participate in the research study based on the self-report screening and medical record review, one of the study's credentialed VA psychologists will conduct a review of the subject's medical record or use firsthand clinical experience to discern whether a subject has experienced active suicidal ideation or delusional thoughts in the recent past, or if review of the chart provides sufficient information to make a clinically informed determination that risk is low or minimal.

The credentialed psychologist will call the subject if s/he does not feel s/he can make a definitive judgment regarding eligibility based on the medical record review. The psychologist will ask the participant some questions to assess the presence of active suicidal ideation or paranoid thoughts using an assessment sheet. Individuals who do have these types of thoughts will not be eligible for the study. Individuals will be referred to a mental health professional if he or she needs immediate attention following the study's suicide risk reduction protocol (described below).

A staff member will record the findings of the psychological screening assessment using the screening case report form.

Clinical discretion may be exercised as needed regarding this exclusion criterion.

Ineligible Veterans

Research staff will offer all ineligible Veterans a list of resources with information about treatment of pain (e.g. books, internet resources, etc.) and any relevant clinical resources available. 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.

In general, Veterans deemed ineligible for the study for reasons related to their appropriateness in group will also be ineligible for participation in the classes as a non-research participant.

However, Veterans deemed ineligible based on pain inclusion criteria may be offered the opportunity to participate in the Chronic Pain Skills Program as a non-research participant, i.e. only attend the treatment portion of the program without any research procedures involved, if space is available. The screening procedures for non-research participants including eligibility criteria are listed below.

Veterans who Decline

Research staff will collect basic demographic information using the demographic information form from all participants who are deemed eligible to participate (following self-report and medical record 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.

Veterans who decline but meet eligibility criteria will be offered the opportunity to participate in the Chronic Pain Skills Program as a non-research participant, i.e. only attend the treatment portion of the program without any research procedures involved, if space is available. The screening procedures for non-research participants including eligibility criteria are listed below.

Re-Screening

Research staff will re-screen participants (both via self-report and medical record review) 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 consent process:

(1) Self-reported presence of chronic pain;
(2) Average pain intensity rating of ≥ 3 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
(3) Worst pain intensity rating of ≥ 5 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
(4) Duration of chronic pain 3 months or more;
(5) Experiences pain at least 75% of the time in the past 3 months; those who have a hard time answering this question will be asked the following question: "Which statement best describes your pain?"

(a) Pain all the time but the pain intensity varies;
(b) Pain most of the time with only occasional periods of being pain-free;
(c) Pain that comes and goes;
(d) Occasional pain.

Participants must report experiencing pain that matches one of the first two options;

In addition, research staff will re-screen participants on the following mutable exclusion criteria if 3 months or more have elapsed between the initial screening and consent process:

(1) Current or history of diagnosis of primary psychotic or major thought disorder as listed in participant's medical record or self-reported within the past five years;
(2) Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported or noted in chart (within the past 5 years);
(3) Psychiatric or behavioral conditions in which symptoms were unstable or severe (within the past six months;
(4) Any behavioral issues as noted in the medical record that would indicate the subject may be inappropriate in a group setting;
(5) Reported average daily use of >120mg morphine equivalent dose (MED).

A staff member will record the findings of the re- screening using the re-screening case report form.

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

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

The recruitment outcome for each participant will be captured using a recruitment outcome case report form. The data collected via this case report form will be entered into a Microsoft Access database to help ensure accurate reporting of recruitment and enrollment efforts in future publications.

All participants who meet eligibility criteria following all three components of the screening procedures will then undergo the informed consent process if they wish to participate. Prospective participants will be sent directions on how to get to the VAPSHCS campuses (Seattle and American Lake) or the Integrated Brain Imaging Center (IBIC) at the University of Washington (UW) prior to the consent process. The directions will be accompanied by a cover letter and the study consent form.

The self-report screening and psychological assessment screening components may take place up to eight weeks prior to the start of the treatment groups for that particular cohort.

D6c. Screening Procedures: Non-Research Participants

All participants that either (1) decide to participate in the Chronic Pain Skills Program as a non-research participant or (2) are deemed ineligible to participate as a research participant based on pain inclusion criteria but would like to participate in the Program as a non-research participant will be screened by research staff to deem appropriateness for participating in the program as a non-research participant. Research staff would initiate the non-research screening process using the non-research screening script and case report form.

Inclusion Criteria (to be assessed via medical record and/or self-report screening components) for participation as a non-research participant include:

(1) Veteran status (defined as prior service in the US Armed Forces and eligible to receive health care services through Veterans Health Affairs);
(2) 18 years of age or older;
(3) Able to read, speak, and understand English.
(4) Self-reported presence of chronic pain;
(5) Duration of chronic pain 3 months or more;
(6) Chronic pain deemed bothersome by participant.

Exclusion Criteria (to be assessed via medical record and/or self-report screening components):

(1) severe cognitive impairment defined as two or more errors on the Six-Item Screener;[51]
(2) Current or history of diagnosis of primary psychotic or major thought disorder as listed in participant's medical record or self-reported within the past five years;
(3) Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD self-reported or noted in chart (within the past 5 years);
(4) Psychiatric or behavioral conditions in which symptoms were unstable or severe as listed in participant's medical record or self-reported within the past six months;
(5) Any behavioral issues as noted in the medical record that would indicate the subject may be inappropriate in a group setting;

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

The following inclusion criteria for research eligibility are <u>not</u> required for participation in the classes:

(1) average pain intensity rating of ≥ 3 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
(2) worst pain intensity rating of ≥ 5 on a 0-10 Numerical Rating Scale (NRS) of pain intensity in the last week;
(3) duration of chronic pain 3 months or more;

(4) Experiences pain at least 75% of the time in the past 3 months; Those who have a hard time answering this question will be asked the following question: "Which statement best describes your pain?"
(a) Pain all the time but the pain intensity varies;
(b) Pain most of the time with only occasional periods of being pain-free;
(c) Pain that comes and goes;
(d) Occasional pain;

Veterans with evidence of a potential mental health condition or those who have never been seen in Mental Health will need to participate in the same telephone psychological screening assessment described above. Specifically, research staff will arrange a time and date for the Veteran to participate in a telephone psychological screening assessment with a credentialed psychologist affiliated with the Chronic Pain Skills Program. The psychologist will ask the Veteran some questions to assess the presence of active suicidal ideation or paranoid thoughts using an assessment sheet. Individuals who do have these types of thoughts will be deemed inappropriate to participate in the program. Individuals will be referred to a mental health professional if he or she needs immediate attention following the study's suicide risk reduction protocol.

The basic outcome of the screening for non-research participants will be captured using the non-research participant recruitment outcome case report form and stored electronically in de-identified form to help discern the feasibility of implementing this type of program in the future in VA medical centers. Research staff will then describe each treatment group to non-research participants using a formalized script.

The research staff member would then convey both treatment group selection and preferred location (Seattle or American Lake Division) of this non-research participant either in person, via telephone or via PKI encrypted email to Drs. Williams. Drs. Williams would then add the participant to the appropriate clinic list.

Non-research participants are limited to participating in each treatment intervention only once. Participation is defined as attending four or more treatment sessions for that particular intervention. Non-research participants may attend each treatment intervention more than once if they in fact attend three or fewer sessions.

Non-research participants who attend treatment in cohort 12 will not be offered the option of participating in another treatment intervention given study researchers intend to stop running treatment groups after this cohort.

D6d. Consent Process

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 may take place at one of the following locations: (1) the VAPSHCS Seattle Campus; (2) VAPSHCS American Lake Campus or (3) IBIC at the UW.

The consent process will occur at a time deemed mutually feasible for the Veteran and staff member and coordinated on a case-by-case basis. The consent process will take place in a private location (e.g., a medical exam room or private conference room).

A research staff member will review each section of the informed consent form (ICF) approved by all regulatory institutions, 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 ICF and ask the research staff member questions about the ICF, 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 written informed consent and prior to enrollment in the study.

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 manager (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 in a subsequent visit.

Potential participants will be asked to repeat back understanding of this material as necessary. Individuals will not be permitted to participate if there is any question as to whether a person is able to provide informed consent.

The participant will then be asked to sign and date the ICF. Research staff will also date and sign the ICF. All participants will be offered a copy of the signed ICF for their records. A scanned copy of the consent form and an enrollment note template will be sent to the VAPSHCS Research Compliance Officer (RCO) as per VAPSHCS guidelines. In addition, a note of enrollment will be made in CPRS.

Research staff will also review a HIPAA authorization form with the participant that permits research staff to review in CPRS encounters of providers running the treatment groups to confirm attendance of said groups and extract data collected during treatment.

Finally, research staff will review with the participant a consent form for the data repository entitled “Rehabilitation Collaborative Repository”. By enrolling in this repository, the participant gives the researchers permission to retain their de-identified study (both main and open label phases) data indefinitely, combine data from this project with data from other projects, and conduct analyses/address scientific questions not described in this protocol. The participant will sign the separate repository consent form if they wish to participate in the repository. Participants may refuse to participate in the repository and still participate in the research study.

Research staff will file original copies of both the consent and HIPAA forms in Dr. Williams’ office, separate from data collected during screening and subsequent data collected during participation in the study.

Research staff will provide participants with staff business cards after the consent process. Participants will also be provided a response key to help answer questions asked during the telephone assessment periods.

Research staff will complete an enrollment case report form as well as documenting the consent process form for each enrolled subject that will be filed with study data.

D6e. Cognitive Assessment

Research staff will administer a battery of five neuropsychological measures assessing memory, information processing, and executive functioning. These measures, henceforth described as the cognitive assessment, take approximately 20-30 minutes to complete.

The cognitive assessment may be completed immediately following the consent process or at a later, mutually agreed upon time in person. Participants will be compensated $10 for completion of the cognitive assessment via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR), the nonprofit institute that works with the VA to conduct research.

D6f. Hypnotic and Relaxation Exercise

A research staff member will administer in person the Modified Stanford Hypnotic Clinical Scale (SHCS) to assess hypnotizability for all participants following enrollment but prior to the start of treatment. Research staff will read a brief introduction about the hypnosis scale before it is administered, as well as provide participants with a brochure about hypnosis published by the APA if the participant has reservations or additional questions about hypnosis. This measure takes approximately 15-20 minutes to complete.

Participants will be compensated $5 for completion of the hypnotic and relaxation exercise via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR), the nonprofit institute that works with the VA to conduct research.

D6g. Baseline Data and Demographic Form

A research staff member will then ask the participant to provide demographic data (age, sex/gender, marital status, income, education level, employment status) and deployment history (number and month of deployments, whether deployment involved hostile duty) for descriptive purposes. We will also ask participants their history of HYP, MM and ED treatment and practice, and the presence of history of military sexual trauma (using the 2-item clinical reminder screen by VHA) as trauma history has been associated with different pain experiences.

The baseline data and demographic form will take approximately 20-30 minutes to complete, and may be completed following enrollment either in person or over the telephone at a later time if more convenient for the participant. Participants will be compensated $10 for completion of the baseline data and demographic form via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR), the nonprofit institute that works with the VA to conduct research.

The informed consent process, including collection of data during the initial intake as outlined in our protocol, may take place up to six weeks prior to the start of the treatment groups for that particular cohort.

D6h. 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; and (6) 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 on at a specified contact number ensures a greater level of privacy for the participant.

The information may be completed following enrollment either in person or over the telephone at a later time if more convenient for the participant.

D6i. Preparation for Brain Wave Activity (Electroencephalogram or EEG) Assessment

Research staff may ensure that the EEG net (device worn on the head that holds the EEG electrodes) will fit a participant's head prior to the EEG assessment. Research staff will cut a piece of string that is about 70 cm long, make two marks 62 cm apart, leaving a little on either end to hold on to. Research staff will wrap the string around participants' head in a circular loop that includes the following landmarks: 1) the point between the eyebrows above the nose (the glabella); 2) the point farthest back on the back of the head (the occipital protuberance); and 3) the sides of the head even with the tops of the ears. If the head circumference is greater than 62 cm, the staff member will inform the participant that the EEG equipment would not accommodate them and therefore they would not be able to participate in this study procedure.

Time permitting, research staff will send a letter to each participant that provides simple instructions to ensure quality data is collected from the participant during the assessment, e.g. requesting the participant clean his/her hair the day of the assessment, not wear jewelry, refrain from as needed medications, etc.
In addition, the letter will instruct the participant to write down the name and dosage of medications they may use within 24 hours of the EEG assessment on an enclosed worksheet, and bring the completed worksheet to the appointment to serve as reference. The participant will be instructed not to write any identifying information on the worksheet. In addition, the participant will keep the worksheet after the appointment; research staff will not collect the worksheet.

Research staff will call the participant to remind him/her of the electroencephalogram or EEG assessment appointment, as well as provide simple instructions for the participant to ensure quality data is collected from the participant during the assessment, e.g. requesting the participant clean his/her hair the day of the assessment, not wear jewelry, refrain from as needed medications, etc. During this call research staff will use a script designed for this purpose.

Research staff will also call female participants the morning the EEG assessment is scheduled to determine if they are experiencing their menses or not. Research staff will use a telephone script designed for this purpose during the call. The EEG assessment will be re-scheduled if that is the case.

D6j. Brain Wave Activity (or EEG) Assessment

Brain wave activity will be assessed following enrollment by conducting a brain wave activity or EEG assessment. The brain wave activity assessment will take place at the Integrated Brain Imaging Center (IBIC) at the University of Washington main campus.

The IBIC is a research-dedicated technology center organized under the department of Radiology. EEG will be sampled with an electrode array using an electrode net dipped in a saline solution.

The research staff member, a UW IBIC employee with a Without Compensation (WOC) appointment at the VA, will obtain consent at the IBIC using the UW EEG consent document. They would then collect the EEG activity data, and ask the participant to remain as still as possible during portions of the assessment. The EEG technician will collect from the participant data regarding medication used within 24 hours of assessment. S/he will also ask the participant to rate the intensity of his or her pain just before the assessment (current pain), after a few minutes of the assessment (current pain and worst, least, and average pain over the past few minutes), and at the end of the EEG session (current pain, and worst, least, and average pain over the past few minutes), using 0-10 Numerical Rating Scales. Finally, the technician will ask the participant to think about their chronic pain in general or a particularly painful event for a period of two minutes. The technician will then ask the participant to rate his/her pain intensity, as well as answer some questions about how s/he thought about his/her pain during the two-minute period. The EEG technician then will ask each participant whether they experienced any negative effects they associate with study procedures to make certain all adverse events related to the study are recorded.

The entire brain wave activity assessment will take approximately 45-60 minutes to complete. Participants will be compensated $100 for completion of the brain wave activity assessment via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR). The check will be sent via USPS mail and accompanied by a payment cover letter.

The brain wave activity assessment must be administered at IBIC, and only after completion of the informed consent process. All other assessment activities may be administered at IBIC or a VA site. So, participants have some options around where they do their baseline assessments and in what combination.

Subjects will be asked to complete the same brain activity assessment following completion of treatment following the same procedures above.

The one difference will be, during the post-treatment assessment, participants will complete an additional 10-minute assessment portion in which they think about the skills they learned during the treatment sessions.

Participants will report the skills s/he used during this assessment portion, as well as general experience during this portion. Participants will be compensated $100 for completion of the brain wave activity assessment via a check written from the Seattle Institute for Biomedical and

Clinical Research (SIBCR). The check will be sent via USPS mail and accompanied by a payment cover letter.

Participants may still participate in the study if they decline to participate in the EEG assessments. The EEG assessment is optional.

D6k. Assessment: Pre-Treatment and General Overview

Subjective reports of pain intensity vary over time, and to most accurately measure pain intensity (our primary outcome), it is most valid to assess multiple times and take an average. Hence, we have developed a method of assessment that will seek to obtain up to four telephone assessments over a period of one week or 7 days. In addition, research staff will seek to administer these assessments ideally with a minimum of 24 hours between each assessment. Given scheduling confilicts, research staff may collect each assessment no less than 22 hours between each assessment if necessary.

During *each* telephone contact, research staff will ask participants, at minimum, to rate their current, average, worst and least pain intensity over the past 24 hours, as well as their average pain intensity over the past week.

In addition, if possible, research staff will ask the participant to rate their current, average, worst and least pain intensity over the past week during the final telephone contact. These assessments will be referred to as “short assessments.” The primary outcome will be an average of all of the 24-hour ratings (range=1-4 ratings) of average pain intensity obtained over a period of one week during each assessment period.

In addition, sometime during this assessment period researchers will ask questions regarding pain interference, depression, anxiety, sleep disturbance, post-traumatic stress disorder (PTSD) symptoms, medication use, medical services utilization, thoughts about pain and treatment motivation. This latter set of questions will only be asked once during the assessment period, and will be referred to as “the long assessment.”

Research staff will give participants the option to: 1) complete the long assessment during one of the four short telephone assessments described above; or 2) spread the long assessment across several days during the assessment period.
The entire long assessment or portions thereof may fall up to two days outside the 7-day period for the four short assessments. The entire time required to answer questions during the assessment period is 45-60 minutes.

Research staff may complete additional short assessments per assessment period with the participant if research staff is unable to complete up to four assessments within a span of one week. For example if a participant completes short assessment #1 on 11/1, Short assessment #2 on 11/6, short assessment #3 and long assessment on 11/08, and short assessment #4 on 11/10, research staff would attempt to complete one more short assessment by 11/13 and discard the data from short assessment #1 so that all short assessments are completed in a period of seven days (11/6-11/13). Participants will not be compensated additionally for completing these assessments. Participants may refuse to complete additional assessments and will remain in the study regardless.

In addition, the entire assessment period (up to 4 short assessments and the long assessment within a period of one week) may be repeated if the treatment groups the participant has been assigned to does not start within four weeks of completing the original pre-treatment assessment period. Participants will be compensated for completing this additional assessment period.

The assessment period described above will be completed prior to initiating treatment, and then after completion of treatment sessions #2, 4 and 6 and 8 (i.e. post-treatment), and 3 and 6 months following the end of treatment for a total of seven times. These assessment periods that occur following the start of treatment will also include questions about group climate, therapeutic alliance with the group clinician, treatment satisfaction, feedback about the treatment modality, and overall improvement since the participant began the pain program. The open-ended questions regarding treatment satisfaction and feedback on treatment modality will be collected by an unblinded staff member. Group Comfort Questions will be administered by an unblinded staff member at any time after session 8 (final group session). This assessment is optional. The window is from post-treatment until the participant is disenrolled.

Staff will send via USPS mail a reminder letter prior to the 3- and 6-month assessment periods.

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 via USPS mail.

Participants will be compensated $25 for the completion of each assessment period via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR). The check will be sent via USPS mail and accompanied by a payment cover letter.

The pre-treatment assessment period may take place up to four weeks prior to the start of the treatment groups for that particular cohort.

D6l. Randomization

Enrolled participants who complete the required baseline components (cognitive assessment, hypnotic and relaxation exercise, baseline data form, and pre-treatment assessment period) will be randomized in stratified blocks to ensure that participants with each sex/gender and pain type (neuropathic, non-neuropathic, mixed or undetermined) have an equal chance of being randomized to one of the 3 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/gender or type of pain.

Assignment to one of the 3 groups will be accomplished with a Microsoft Excel spreadsheet with random numbers created by the research manager with the guidance of the biostatistician. Only a research staff member who does not have access to study data during subject enrollment will conduct the randomization procedures. This randomization assignment will be entered into a password-protected database located on a VA secure drive. Research staff will complete a randomization case report form for each randomized subject that will be filed with study data.

The staff randomizing subjects will convey assignment to Dr. Williams via email with only a code number used i.e. no identifying information to identify the participant. Dr. Williams will then update the master list of participants, both research and non-research, of the clinic portion of the program.

Subjects will be sent a letter that outlines the schedule of treatment sessions they will attend.

Research staff will re-screen participants on approved mutable eligibility criteria (e.g. pain intensity, frequency, etc.) if 6 months or more has elapsed between the consent process and randomization.

Randomization may take place up to four weeks prior to the start of the treatment groups for that particular cohort.

D6m. Treatment Scheduling: Research and Non-Research Participants

Cohorts of study treatment groups will be offered beginning every four months. In each 4-month period, there will be two class options for each condition, one based in Seattle and one at American Lake. Thus, there will be six classes offered per four month period, or a total of 18 classes per year.

Trained instructors will commit to offering three groups per year: one of each treatment type. This will reduce the potential for therapist bias in on the outcomes. Up to 15 participants can be enrolled in each group treatment class.

Dr. Williams will maintain lists of group assignments (for both research and non-research participants) and coordinate the scheduling of group class appointments.
Both Dr. Turner and the unblinded research staff member responsible for randomization will have access to this information and be available to provide back-up if Dr. Williams is absent or preoccupied.

As aforementioned, the research staff conducting randomization procedures will alert Dr. Williams that a research participant has been randomized.

Research staff will also alert Dr. Williams of non-research participants who are eligible to participate, and of their intervention preference. These master schedule/lists will not contain any study data or links to study data (i.e., no subject identification numbers). Rather the lists will only include the participant's name, CPRS ID, tract of participation in the program (i.e. research or non-research participant), and general status in the program (on hold, active, pending). These master lists will be stored on a secure VA drive in a password-protected file. It will contain the minimal amount of information necessary to manage properly treatment group scheduling.

D6n. Treatment

In all three treatment conditions, intervention appointments will be scheduled in regular group clinics at the VA facility (American Lake or Seattle). This means that treatment sessions will appear on the Veterans' lists of regular clinical appointments. Although the appointments are scheduled for 90 minutes, in practice they will last 60-80 minutes, with a 10 minute time cushion built in to allow for participants who may have mobility limitations to arrive, settle, and then vacate the group rooms without hurrying.

The reason that there is variation in the amount of time planned for each group (60-80 minutes) is that some of the sessions may require more time than others; for example, the first session will take more time than the others because it will include time for introductions and reviewing the format of the treatment, as well as for answering questions about treatment. Some groups may have participants with mobility limitations who require a little longer than others to get physically settled into the room, some may require a 5-10 minute break during the session, and some groups- especially those with higher numbers of participants- may require a little more time than others to ensure each participant has an opportunity to actively participate and discuss.

Group clinicians will be asked to report how much time was spent in each group so we can control for possible differences in this variable between treatment conditions.

The group sessions will be conducted by VAPSHCS providers who have undergone a formal two-day training process that prepares clinicians to conduct each of the three treatment interventions in a group setting.

Providers will be licensed/credentialed/privileged allied health professionals at the VAPSHCS. Providers will represent a variety of disciplines, including but not exclusive to the following: Ph.D. licensed Psychologists, Pre-doctoral Clinical Psychology Interns (i.e., who are in their final year of a doctoral degree program and supervised by a licensed Clinical Psychologist) and Psychology Post-doctoral F(who have completed a Ph.D.), Occupational Therapists (MOTR/L), Speech-Language Pathologists (MS CCC-SLP), Social Workers (LICSW), Recreational Therapists (RT), Physical Therapists (PT, DPT), or Nurses (RN). Each provider will participate in a two-day training, which will cover group instruction for mindfulness meditation, self-hypnosis and pain education.

All study clinicians will also be given regular feedback by Drs. Jensen and/or Williams on their performance. In addition, ongoing consultation will be offered to providers leading mindfulness meditation and self-hypnosis interventions by Drs. Jensen and Day to ensure that any questions that in real time can be answered.

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

Additional participants will be scheduled for the groups until they reach the maximum size of fifteen. Providers 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 increase engagement in the treatment. Participants will be asked to record the extent of engagement in these activities using a form provided to them by the clinician. We realize that adherence to interventions assigned outside of treatment sessions may influence study outcomes so will utilize data collected by the clinicians 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.

Education (ED) condition. The pain education control condition will include 8 informational 90-minute group sessions that are compelling and informative, but are designed not to be effective for pain reduction, our primary outcome measure.

However, it is expected that participants in this treatment condition will experience improvement in other outcomes, such as coping skills, knowledge, and reduced distress. Hence, we describe this in our ICF as one of three treatment conditions, rather than as an inert control condition. Participants in this condition will be given pre-recorded audio recordings of the content of the sessions to listen to, to control for the between-session practice that will be encouraged in the HYP and MM groups (see below). We have used this condition successfully in past and current trials. Participants have rated it as helpful and credible, yet have not shown changes in pain intensity.[52, 53] Thus, it will control for non-specific factors related to the active interventions, including therapist attention, participation in a group, and time, but will not impact the primary outcome measure (pain intensity).

HYP condition. In the HYP condition, each group session will be highly structured. Group sessions will begin with a review and discussion of the home practice assignments and goals for the session. The facilitator will perform a standard hypnotic short induction followed by therapeutic suggestions, including post-hypnotic suggestions.

Participants will relax in a comfortable position with their eyes closed and will simply listen to the clinician read a standardized hypnotic script that will include an induction followed by suggestions for decreased pain and improvement in co-morbid symptoms (e.g., improved mood and optimism, relaxation, sleep quality). Sessions will also include discussion post-exercise. The sessions will end with recommendations for home practice. Participants will be given pre-recorded recordings of the hypnotic inductions and suggestions provided in each session and encouraged to practice self-hypnosis (first, using recordings, but over time and as they gain more confidence, on their own without the recordings), and time will be devoted to problem solving around any difficulties with self-hypnosis practice. We have a great deal of experience with this intervention.[41, 42, 54]

MM condition. The MM group interventions will teach participants Vipassana meditation, which is the specific form of MM typically implemented in mindfulness research. The emphasis is placed upon developing focused attention on an object of awareness, such as the breath. This focus is then expanded to include a more open, non-judgmental monitoring of any sensory, emotional, or cognitive events. As with the HYP intervention, a standard script will be read by the clinician to the participants, who 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, as with HYP, on their own without recordings). Time will also be devoted to problem solving around any difficulties with MM practice.

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.
The researchers will submit a modification request to both the VAPSHCS and UW IRBs should there be any change to study procedures or a substantive change in content based on new information that becomes available during the course of the study.

Attendance Records

Group leaders (clinicians) will be given an attendance record of the anticipated participants in their group and will be responsible for ensuring scheduling and other clinical matters are managed once the groups start. The attendance record will only include a participant's name and CPRS ID. The clinician will record the subject's absence or presence for each session on the record. Completed attendance records will be uploaded and stored on a limited access folder on the secure VA network drive. Only Dr. Williams, Dr. Turner, and the unblind staff member responsible for randomization will have access to these forms. The hard copies of these attendance records will be destroyed once they are uploaded to the drive at the end of each treatment group.

Participation in less than 4 treatment sessions will be considered a protocol deviation. A Note-to-file will be drafted at the end of each cohort to report research participants that completed less than 4 treatment sessions.

Data Collected during Treatment Sessions

Participants will complete and hand in a form regarding their completion of tasks or "homework" assigned by the clinician from the previous session.

In addition, participants will complete and hand in forms before and after each session that include questions regarding pain intensity and comfort level, as well as questions about what the participants have found helpful or non-helpful about the treatment.

Finally, study clinicians will complete a form each session that captures information regarding the perceived engagement of each participant in that particular session. All of these forms will be labeled with a subject's name.

Information will be gathered during the group interventions as per standard of care procedures that all attendees will do regardless of their participation in the study. The clinicians running the groups will not have access to the crosswalk between study data and participants' identities.

Following each session, per usual care the clinician will enter a progress note in CPRS for each participant, indicating attendance or absence for that particular session. The note will also include the length of the group session, as well as basic content covered during the session.

Information gathered during the group sessions (e.g., homework logs, pre- and post-class pain ratings, patient engagement) will be used for clinical supervision and treatment planning. This clinical information will be scanned and stored on a secure drive (PUG_Services (\\RO1PUGHSM03.r01.med.va.gov\RCS\Psychology\SKILLS CLINICAL GROUPS) within the Rehabilitation Care Service. Access to this drive will be limited to clinicians who are running the classes and their clinical supervisor, and unblinded staff members.

Unblinded staff members will extract these data associated with the main RCT as well as with the open-label phase (since all group participants will be completing the forms regardless of study status). These staff members will have access to this secure limited-access drive, and to the cross walk linking names/study IDs. These two staff members would identify the veterans who are study subjects and access the PDFs of the scanned information in this clinical drive, and enter the data directly into a secure database with the participant's code number (study id).

In this way, we leverage existing clinical data to 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 engaged in research activities, and there is no additional burden to the subjects.

The staff member will enter the data labeled with only the participant's code number into a password-protected database separate from all non-treatment study data. The staff member will not enter the data collected from non-research participants.

Audio Recordings

All group treatment sessions will be audio recorded to ensure compliance to treatment procedures. 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.

The study clinicians will notify participants before the start of the session that s/he will be recording the session, and all participants in the group (including non-research participants) will be asked to complete requisite consent forms to record voice. The audio recordings will be collected using a VA approved encrypted device.

The recordings will be stored on a secure server at the VA (V:\Chronic Pain Skills group\Fidelity Recordings). 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 group members state participants' names during the discussion.

Treatment Intervention Discontinuation

A participant will be withdrawn from the treatment intervention if s/he (1) engages in behavior that is disruptive to the group, and/or (2) engages 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 during treatment at (2, 4 and 6 weeks), post-treatment, 3-month and 6-month follow-up in order to allow for complete data for the planned intent-to-treat analyses. Participants will receive payment for the time it takes to provide outcome data at each assessment point.

D6o. Study design enhancements: Missed sessions and study retention strategies

We will monitor session attendance and session dates to track attendance. We will also track treatment withdrawal and the reason for withdrawal via the 'Treatment Withdrawal Form'. We will then enter the data into the unblinded Treatment Database.

We will make efforts to deliver the full treatment to every participant, but we expect some variation in treatment delivery dose as well as treatment drop-out. Reasons for attrition will be assessed for enrolled participants who withdraw from treatment.

We will use a number of strategies to maximize study retention. For example, treatment sessions will be offered at different times, on a recurrent basis, giving study participants a great deal of flexibility for scheduling.

Data collection staff will be taught listening skills and encouraged to be warm in all interactions in order to enhance rapport. Also, the Co-PIs will receive weekly reports from the staff so that the study investigators can discuss recruitment and retention during the weekly research meetings.

Finally, participants will receive remuneration for completion of the following study components:

Baseline components (hypnotic and relaxation exercise, cognitive assessment, baseline data and demographic form-$25 total);
Each of the seven assessment points ($25 each, $175 total);
Brain wave activity or EEG assessments ($100 per assessment, $200 total).

In addition, we plan to offer a $50 bonus for participants who complete all seven of the telephone assessments (up to $450 total). We have successfully used these and other strategies in our past trials, with a retention rate of 80% to 92% across similar studies. [41, 42, 53]

Replacement Check Protocol

VA research staff will send participants with a check that is outstanding 180 days after issuance a letter 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
- Instructs the participant to sign the reissuance form and send it back to research staff in the included self-addressed envelope.

Research staff will then forward the signed and completed letter to SIBCR, who will then issue a new check to participants. 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 again if requested by participants.

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

D6p. Optional Assessments

Pre- and Post-Treatment Assessment Periods:

For the pre-treatment and post-treatment telephone assessment periods, research staff will use a script to invite participants upon completing the assessment period to participate in an optional assessment consisting of two measures developed by study researchers. The optional assessment should take approximately 25-30 minutes to complete, and consists of questions about how participants feel when they feel pain or think about their pain problem, and how participants respond to their pain.

The collection of Optional assessments will stop once there is enough data to answer exploratory questions.

3- and 6-Month Assessment Periods:

In addition, research staff will invite research participants to participate in an additional optional telephone assessment after they complete the 3- and 6-month assessment periods. This optional assessment should take approximately 10-15 minutes to complete and will include questions about activity management, flourishing, and sense of humor.

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

The collection of Optional assessments will stop once there is enough data to answer exploratory questions.

D6q. Study Completion: Main Phase

Research staff will complete a study completion form when either a) a subject completes the 6 month assessment period, or b) withdraws or is withdrawn from the study. Subjects who complete the 6 month assessment period will be sent a cover letter along with their final remuneration with language indicating completion of the main phase. Subjects who fail to complete the 6 month assessment period will be sent a letter informing the subject that his/her participation in the main phase has ended.

Research staff will also note dis-enrollment in CPRS as per VAPSHCS regulatory protocol.

D6r. Open Label Phase (see updates below for cohorts after 9)

Following the completion of the main phase of the study (i.e. completion of 6-month assessment period, research staff will invite participants to complete in one or both of the treatment groups they did not attend during participation in the main phase if deemed eligible. Specifically, research staff would conduct a simple review of a subjects' medical record using a case report form to detect the presence or absence of a behavioral or suicide risk flag in CPRS. In addition, staff will answer two items regarding any observed behaviors that may make a subject for a poor candidate for the open label phase. Participants are limited to participating in each treatment intervention only once. Participation is defined as attending four or more treatment sessions for that particular intervention. Participants may attend each treatment intervention more than once if they in fact attend three or fewer sessions. Participants would only participate in one treatment group at a time.

Following the completion of the 6 month assessment period, the blinded assessor will inquire briefly into the subject's interest in participating in the open label phase of the study. If the subject is interested, the blinded research staff will inform the subject that an unblinded research staff member will call to give him/her more information about the open label phase.

An unblinded research staff member will then call the subject to describe the open label phase in more detail, including dates and times for particular interventions (e.g. mindfulness meditation) at each division. If the subject is still interested in participating, the unblinded research staff member will inform the subject that staff will call him/her to schedule the consent process. An unblinded research staff member will conduct the scheduling process to avoid unblinding blinded assessors.

Updated Open Label study procedures after cohort 9.

Participants who attend treatment for the first time in cohort 10 and all subsequent cohorts will not be offered the open label phase given study researchers intend to stop running treatment groups by the time these participants will complete the main phase of the study. Instead, these participants will be offered the treatment materials for the treatment of their choice. The treatment materials (workbook and audio recordings) will be mailed via USPS.

Participants who were randomized in cohorts 1-9 and are eligible to participate in the open label phase for cohorts 11 or 12 will be offered the option of either receiving treatment materials in the mail for the treatment of their choice or enrolling in the open label phase depending on space availability.

Consent Session (for cohorts 1-9)

Research staff will participate in and obtain informed consent from research participants prior to commencement of any further study procedures for the open label phase. The informed consent process may take place either via telephone and postal mail, or in person. The consent process will occur at a time deemed mutually feasible for the Veteran and staff member and coordinated on a case-by-case basis.

A research staff member will review each section of the informed consent form (ICF) approved by all regulatory institutions, 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 ICF and ask the research staff member questions about the ICF, 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 written informed consent and prior to enrollment in the study.

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 manager (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 later time.

Potential participants will be asked to repeat back understanding of this material as necessary.

Individuals will not be permitted to participate if there is any question as to whether a person is able to provide informed consent. The participant will then be asked to sign and date the ICF. Research staff will also date and sign the ICF. All participants will be offered a copy of the signed ICF for their records.

A scanned copy of the consent form will be sent to the VAPSHCS Research Compliance Officer (RCO) as per VAPSHCS guidelines.

In addition, a note of enrollment will be made in CPRS. Research staff will also review a HIPAA authorization form with the participant that permits research staff to review in CPRS encounters of clinicians running the treatment groups to confirm attendance of said groups and extract data collected during treatment.

Research staff will file original copies of both the consent and HIPAA forms in the Dr. Williams' office, separate from data collected during both the main and open label phases of the study.

Research staff will provide participants with staff business cards after the consent process. Participants will also be provided a response key to help answer questions asked during the telephone assessment periods.

Informed Consent Process via Telephone and Postal Mail

A blinded staff member would arrange a time to conduct the informed consent process via telephone if the individual is interested in participating via the recruitment script. The research staff member will then send a self-addressed, stamped envelope along with two copies of the approved consent form, the approved HIPAA authorization form, and a new cover letter. The approach letter will specify that, although individuals may review the forms in advance, they should not complete the forms until they have reviewed the forms with research staff at the scheduled informed consent session via telephone.

Informed Consent Process in Person

The informed consent process may take place at one of the following locations: (1) the VAPSHCS Seattle Campus; (2) VAPSHCS American Lake Campus or (3) IBIC at the UW. The consent process will occur at a time deemed mutually feasible for the Veteran and staff member and coordinated on a case-by-case basis. The consent process will take place in a private location (e.g., a medical exam room or private conference room).

<u>Open Label Phase Assessments (for cohorts 1-9)</u>

Research participants enrolled in the open label phase will complete telephone assessments twice with research staff: once before treatment, and once after treatment has ended. Each assessment will consist of questions regarding pain intensity, post-traumatic stress disorder, depression, anxiety, sleep disturbance, pain interference, and medication use. The post-treatment assessment will also include questions about treatment satisfaction and overall improvement since the participant began the open label phase. The entire time required to answer questions during the assessment is about 15-20 minutes.

Research participants will be compensated $10 for the completion of each assessment period via a check written from the Seattle Institute for Biomedical and Clinical Research (SIBCR). The check will be sent via USPS mail and accompanied by a payment cover letter.

<u>Treatment (for cohorts 1-9)</u>

An unblinded research staff member will notify Dr. Williams when an open label participant has completed the pre-treatment assessment, and inform her of the participant's intervention preference. This process will help avoid unblinding blinded assessors. Dr. Williams will add the participant to the clinic list described in section D6m. above. Treatment procedures for open label phase participants will be the exact same as described in section D6n. above

Research staff will complete an open label phase study completion case report form once the participant has completed participation in the open label phase. Research staff will also note dis-enrollment in CPRS as per VAPSHCS regulatory protocol.

D6s. Sleep Sub-Study

Recruitment

During the recruitment process for the main phase of the study, all prospective research participants will be informed briefly about the possibility of participating in the sleep "sub-study" following enrollment into the main phase via a research recruitment script.

Following completion of the informed consent process for the main phase, research staff members will inform prospective participants about the opportunity to participate in the sub-study with the assistance of a talking points script. All participants who enroll in the main phase of the study will be eligible to participate in the sub-study. Subsequently there is no separate screening process for the sub-study. Participants will only be approached about participating in the sub-study at the time of enrollment in the main phase; participants who have been enrolled and participated in a previous cohort may not participate.

Informed Consent Process

All participants interested in participating in the sub-study will participate in a separate informed consent process specific to the sub-study following enrollment into the main study. The informed consent process for the sub-study may take place at one of the following locations: (1) the VAPSHCS Seattle Campus; (2) VAPSHCS American Lake Campus or (3) IBIC at the UW. The consent process will occur at a time deemed mutually feasible for the Veteran and staff member and coordinated on a case-by-case basis. The consent process will take place in a private location (e.g., a medical exam room or private conference room).

A research staff member will review each section of the informed consent form (ICF) approved by all regulatory institutions, 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 ICF and ask the research staff member questions about the ICF, their rights as human participants, and participation in the sub-study. Potential participants will be fully informed of all risks and benefits prior to giving their written informed consent and prior to enrollment in the sub-study.

If during the course of this contact the potential participant has questions that cannot be addressed by research staff, Dr. Williams or the research manager (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 in a subsequent visit.

Potential participants will be asked to repeat back understanding of this material as necessary. Individuals will not be permitted to participate if there is any question as to whether s/he is able to provide informed consent.

The participant will then be asked to sign and date the ICF. Research staff will also date and sign the ICF. All participants will be offered a copy of the signed ICF for their records.

A scanned copy of the consent form and an enrollment note template will be sent to the VAPSHCS Research Compliance Officer (RCO) as per VAPSHCS guidelines. In addition, a note of enrollment will be made in CPRS.

Research staff will file the original copy of the consent form in Dr. Williams' office, separate from data collected during screening and subsequent data collected during participation in the study.

Participants will also be provided a revised response key to help answer questions asked during the telephone assessment periods for the sub-study.

Research staff will complete a sub-study specific enrollment case report form that will be filed with study data. In addition, research staff will complete a revised "documenting the consent process" form for each enrolled participant that will be filed with the signed consent form.

Telephone Assessment

A research staff member will ask each participant two questions about how much the participant agrees with certain statements about his/her sleep, as well as two questions about how confident the participant is about carrying our certain sleep behaviors. These questions will be asked during the pre-treatment assessment period, 4-week assessment period, post-treatment assessment period, and the assessment period that takes place 3 months following the end of treatment. The questions will take about 5 minutes to complete. The pre-treatment assessment period may be repeated if the participant does not start treatment within four weeks of completing the original pre-treatment assessment period.

Sleep/Wake Diary

Three times during his/her participation in the sub-study, we will ask the participant to keep what we call a sleep/wake diary: once following enrollment but prior to the start of treatment, once following the end of treatment, and once three months following the end of treatment. The sleep/wake diary will either be given to the participant in person or sent via postal mail. If sent via postal mail, the sleep/wake diary will be accompanied by a cover letter. Research participants will complete the sleep diary using pen and paper. The participant will complete a diary entry twice a day (morning and night) for up to seven days. In the morning, the participant would answer basic questions about his/her sleep during the previous night, including time the participant thinks s/he fell asleep, the quality of his/her sleep, and any other experiences that might have affected his/her sleep. In the evening, the participant will answer questions about how the participant felt that day, any problems s/he experienced such as illness or discomfort, and basic activities s/he participated in like going to work, napping, drinking caffeinated beverages, etc.

Also, the participant will be instructed to call a toll free number twice a day to report when s/he woke up in the morning, and when s/he is going to sleep in the evening. The number will be housed at the VAPSHCS, and only accessible to study staff. If a voicemail is left by the participant: staff will delete the voicemail after research staff record the data provided using the case report form.

Participants will be advised to leave his/her study ID only without any identifiers. These instructions will be given to the participant either in person or via postal mail.

Finally, the participant will be instructed to send back the completed sleep diary to WSU study researchers at the Spokane Sleep and Performance Research Center in a provided self-addressed stamped envelope along with the actigraph device (see description below). WSU research staff will use the sleep diary as a reference only for the data downloaded from the actigraph device; no data from the sleep diary will be entered into a database at that time.

Study investigators expect that 10% of the actigraphs will not be returned by study participants due to them being misplaced or lost in the mailing process. The actigraphs and sleep diaries do not contain any identifiers, so there would not be a risk of privacy breach. Participants would have the option of hand delivering the actigraph to study staff if they are on Seattle or American Lake VA campus.

WSU research staff will then send the completed sleep diaries in de-identified form to VAPSHCS staff via postal mail, who will then enter the data into the secure database.

The original hard copies will be filed at the VAPSHCS in a locked office separate from participant identifiers.

The sleep diary will take approximately two hours to complete over the 7-day period.

The pre-treatment assessment period may be repeated if the participant does not start treatment within four weeks of completing the original pre-treatment assessment period.

Actigraphy Device

Three times during his/her participation in the sub-study, we will ask the participant to wear a sleep monitor device called an Actigraph: once following enrollment but prior to the start of treatment, once following the end of treatment, and once three months following the end of treatment. The participant would wear the actigraph (Actiwatch , Philips Respironics, Bend, OR) like a wrist watch on his/her non-dominant arm. There is no risk of electric shock with this device. The device will measure how long the participant sleeps, as well as the overall quality of his/her sleep. The participant will wear the actigraph for up to seven days during the same period s/he is completing the sleep diary except for when the participant is participating in activities that might get the actigraph wet like swimming, showering, or bathing.

The participant will be instructed to send back the actigraph to WSU study researchers in a provided self-addressed stamped envelope at the end of the assessment period along with the sleep diary. The actigraph device will not be labeled with any identifying information. WSU research staff will download the data collected by the actigraph device. The data will be stored on a secure WSU server in de-identified form indefinitely. Data may be downloaded from the Actigraph only with the assistance of Actigraph software unavailable to the general population. The actigraph data will transmitted by WSU staff to VA staff electronically in de-identified form to be stored indefinitely on the secure VA server with the rest of the study data.

In addition, WSU research staff will complete a data cover page that records basic information regarding receipt of the actigraph, date data was downloaded, any comments regarding the data, etc. WSU research staff will then send the data cover page along with the daily diary of each participant to VAPSHCS research via postal mail in de-identified form. VAPSHCS will enter the data recorded on the actigraph data cover page into the secure database. The original hard copies will be filed at the VAPSHCS in a locked office separate from participant identifiers.

The sleep data temporarily stored on the actigraphy device will be deleted once the data are downloaded by the WSU study researchers.

Participants may be asked to wear the actigraph again for pre-treatment if the participant does not start treatment within four weeks of completing the original pre-treatment assessment period. Participants will be compensated for completing this additional assessment period.

Compensation

A participant will be compensated $40 each time s/he returns the actigraph device via postal mail. An additional $30 will be provided as compensation at the end of the study if a participant completes 100% of the sleep diaries and actigraph data collection.
A partial payment of $15 will be given if less than 100% of sleep diaries or actigraph data collection is completed. Compensation will be by check, which will be sent via postal mail along with a cover letter by the SIBCR: one version for pre-treatment and post-treatment, and one version for the three-month assessment period indicating the participant has completed the sleep sub-study.

Sub-Study Completion

Research staff will complete a sub-study completion form when a participant a) withdraws or is withdrawn from the sleep sub-study; b) completes the three month assessment periodor c) does not complete the three month assessment period.
Research staff will send a letter explaining the participant is no longer enrolled in the sleep sub-study if s/he fails to complete the three month assessment period.

Table 3. Participant Involvement

Procedure	Number of Visits or Assessments	How Often / When	Time Required for Participants	Compensation
Cognitive Assessment	One in-person session at VA Seattle or American Lake Divisions) or Integrated Brain Imaging Center (IBIC) at the UW	Once, following informed consent process; before treatment begins	About 20-30 minutes	$10
Hypnotic and Relaxation Exercise	One in-person session at VA Seattle or American Lake Divisions) or Integrated Brain Imaging Center (IBIC) at the UW	Once, following informed consent process; before treatment begins	About 15-20 minutes	$5
Baseline Data and Demographic Form	One session either (1) at VA Seattle or American Lake Divisions or Integrated Brain Imaging Center (IBIC) at the UW OR (2) via telephone	Once, following informed consent process; before treatment begins	About 20-30 minutes	$10

Procedure	Number of Visits or Assessments	How Often / When	Time Required for Participants	Compensation
Pre-Treatment Telephone Assessment Period	Up to 4 telephone assessments conducted within a one-week period	Once, following informed consent process; before treatment begins	About 45-60 minutes total	$25
Pre-Treatment Brain Activity Assessment	One in-person assessment at the UW Integrated Brain Imaging Center (IBIC) at the UW	Once following informed consent process, before treatment begins	About 45-60 minutes	$100
Pre-Treatment Sleep Sub-Study Procedures	Wear actigraph on wrist, complete sleep/wake diary twice a day, call in wake/bedtimes twice in a day during a one-week period	Once, following informed consent process; before treatment begins	2 hours for sleep/wake diary, continuous for actigraph device	$40
During Treatment Telephone Assessment Periods	Up to 4 telephone assessments conducted within a one-week period	Following sessions 2, 4 and 6	45-60 minutes per assessment period, 2.25-3.0 hours total	$25 per assessment period, $75 total
Treatment	8 group treatment sessions that takes place at the VAPSHCS Seattle or American Lake Campus	Average of once per week for eight weeks	up to 12 hours total	$0
Post-Treatment Telephone Assessment Period	Up to 4 telephone assessments conducted within a one-week period	Once following end of treatment	About 45-60 minutes total	$25
Post-Treatment Brain Activity Assessment	One in-person assessment at the UW Integrated Brain Imaging Center (IBIC) at the UW	Once following end of treatment	About 45-60 minutes	$100

Post-Treatment Sleep Sub-Study Procedures	Wear actigraph on wrist, complete sleep/wake diary twice a day, call in wake/bedtimes twice in a day during a one-week period	Once following end of treatment	2 hours for sleep/wake diary, continuous for actigraph device	$40
3 Month Telephone Assessments	Up to 4 telephone assessments conducted within a one-week period	Three months following end of treatment	About 45-60 minutes total	$25
3 Month Sleep Sub-Study Procedures	Wear actigraph on wrist, complete sleep/wake diary twice a day, call in wake/bedtimes twice in a day during a one-week period	Three months following end of treatment	2 hours for sleep/wake diary, continuous for actigraph device	$40, plus $15-30 bonus as applicable
6 Month Telephone Assessments	Up to 4 telephone assessments conducted within a one-week period	Six months following end of treatment	About 45-60 minutes total	$25
Bonus Payment: All telephone assessments completed	All seven telephone assessment periods are completed	Over 9-month period (see timeline listed above)	Totaling about 5-7 hours total over a 9-month period	$50
Open Label Phase Study (cohorts 1-9)	Two telephone assessments, 8 treatment sessions	Following completion of the main phase of the study	About 13 hours over a 3-month period (assessments and treatment sessions included)	$10 per assessment completed

D6t. Study Data

Main Study:

The following is a list and description of the data measures included in the study. We list the demographic and descriptive information we propose to collect from the study participants in the next paragraph. The primary outcome, secondary outcome, covariates (variables to control for in planned analyses if needed), and mechanism (mediator and moderator) variables for this study are listed in Table 4 (page 33).
Details regarding a subset of the key measures are provided below. All outcome measures will be administered by research staff members blind to group allocation.

Data will be shared with UW study investigators for the purposes of data analysis. All data will be de-identified and linked only by a participant ID code. All data sharing will be done in accordance with the collaborating institutional human participants' committees.

Data will be shared with WSU study investigators for the purposes of data analysis. All data will be de-identified and linked only by a participant ID code. All data sharing will be done in accordance with the collaborating institutional human participants' committees.

Study investigators will destroy the crosswalk which connects study participants to their study data once it is deemed no longer necessary. Based on information that we received regarding RCS 10-1, the crosswalk is considered a temporary document. The study will no longer need the crosswalk once the study is in data analysis and the PIs determine that the crosswalk is no longer needed. Destroying the crosswalk will further protect study participants.

Descriptive/Demographic variables. All participants will be asked to provide demographic data (age, sex/gender, marital status, income, education level, employment status) and deployment history (number and month of deployments, whether deployment involved hostile duty) for descriptive purposes.

We will also ask about their history of HYP,MM and ED treatment and practice, and the presence of history of military sexual trauma (using the 2-item clinical reminder screen by VHA) as trauma history has been associated with different pain experiences. We will also ask questions regarding substance dependence as well as co-morbid conditions.

Primary outcome variable: Average daily pain intensity. Average pain intensity will be assessed via telephone interviews using a 0-10 numerical rating scale (NRS) of average pain in the past 24 hours, up to four times within a 1-week period at each assessment point. The mean of these ratings will be used as the primary outcome measure of average daily pain intensity. Psychometric theory and research support composite pain measures as more reliable, valid, and sensitive to treatment effects than single ratings.[55, 56] The 0-10 NRS has demonstrated its validity as a measure of pain intensity through its strong association with other pain measures as well as its ability to detect changes in pain with pain treatment.[57] A consensus panel has also recommended the 0-10 as a core outcome measure of pain intensity in clinical trials of pain treatments.[58]

Covariates. All participants will be asked to maintain the same level(s) of analgesic intake and not seek additional pain treatments throughout participation. For example, if they are taking two ibuprofen/day for pain management, they will be asked to maintain this same dose throughout the study. This will help limit the potential confounding effect of changes in pain treatment on outcome. However, for ethical reasons, we will not require participants to maintain the same analgesics or to not receive additional treatments as a condition of the study. Medication use will be assessed via self-report including prescription medications, illicit substances (e.g., cannabis, alcohol; we will have in place a Federal Certificate of Confidentiality, so that all information provided can remain confidential), and non-prescribed medications (e.g., over-the-counter). To facilitate recall for these, we will ask participants to have their medications physically available at the time of assessment.

To ensure similar levels of medical services utilization and pain treatment between groups, we will ask participants to report any professional care for pain and analgesic use at each assessment point. Research consistently supports the validity of recall for medically related variables such as medical number of health care visits [59, 60] and these can also be verified in the medical record to ensure reliable reporting. Analgesic medication 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). This procedure

will provide data for both usual and rescue analgesics.[61] Note that medication use is also being proposed as a secondary outcome measure.

Table 4. Primary, secondary, co-variate, and mechanism variables.

Variable Type	Domain	Measure
Primary outcome	Average daily pain intensity	Average of up to 4, 0-10 recall NRS of average pain intensity
Secondary outcomes	Worst daily pain intensity	Average of up to 4, 0-10 recall NRS of worst pain intensity
	Depression	PROMIS Depression SF[62]
	Anxiety	PROMIS Anxiety SF[62], suppl. questions
	Sleep Disturbance	PROMIS Sleep Disturbance SF[62], suppl. questions
	Pain interference	PROMIS Pain Interference SF[62]
	PTSD Symptoms	PTSD Checklist-Civilian version [63]
	Medication use	participant report (see text)
	Global improv.	5-point Likert scale [58]
	Tx. Satisfaction	PGATS[64]
	Global Health	Single Item, SF-36 PROMIS Global Health v1.1.[65]
	Positive Affect	PANAS Positive Subscale[66]
	Positive Psychosocial Outcomes	PROMIS Psychosocial Illness Impact-Positive[67, 68]
Co-variates	Med serv utilization	# visits in the last week (during Tx) or last month (all others)
	Medication use	participant report
Mediators: Biological	Change in EEG	Theta, alpha, beta, and gamma bandwidth power
Mediators: Psychological	Pain acceptance	Chronic Pain Acceptance Ques. [69]
	Catastrophizing	Pain Catastrophizing Scale [70]
	Mindfulness	Five Facet Mindfulness Questionnaire- Short Form[71]
	Therapeutic Alliance	Working Alliance-Short Form [72]
	Motivational Systems	BIS/BAS[73]
	Happiness	Subjective Happiness Scale[74]
	Practice	Self-report of between-session skill practice
Moderators	Baseline EEG	Theta, alpha, beta, and gamma power
	Hypnotizability	Stanford Clin Hypno Scale [75-77]
	Tx outcm expec	Treatment Eff Scale [78-80]
	Tx motivation	5-point Likert scale
	Age, sex/gender, race/ethnicity	Demographic questionnaire
	Pain type	LANSS[81] and PainDETECT[82]
	5 cog functioning domains	RAVLT, SDMT, Digit Spain, Trail Making A&B, WRAT 4
	Functional Comorbidity	Functional Comorbidity Index (FCI)[83]
	Back Pain	STarTback[84]

Brain state will be assessed using standard practices for ensuring valid and reliable EEG measures (e.g., careful training and supervision of research assistants in Brain wave activity assessment procedures, checking impedance of all sites, not assessing women during menses, instructing participants to avoid muscle activity during the assessment). EEG will be recorded

with a dense array (128 electrodes) using an electrode cap. EEG analysis will be from a weighted average reference montage. During each assessment, EEG will be collected at a sample rate of 500 Hz over at least 10 minutes of an eyes-closed condition.

To ensure that participants do not sleep during the assessments, we will monitor participant alertness and include occasional verbal reminders to stay awake.

The primary EEG analysis will measure ratios of theta (4-7.5 Hz), alpha (8-12 Hz), beta (12-32 Hz), and gamma (38-42 Hz) frequency ranges over the whole brain from artifact free segments. Power ratios will be computed for each individual bandwidth (e.g., delta/total power). The final EEG measures will consist of composite scores of EEG activity averaged from 60 sec epochs (after excluding epochs with artifacts).

Table 5. Study Assessment Schedule, Main Phase

Measures	Screening	Pre-Treatment	Treatment	During Treatment	Post-Treatment	3 Month	6 Month
6-Item Screener[51]	X						
Stanford Clin Hypno Scale [75-77]		X					
Treatment Expectancies/Credibility[78-80]		X		X*			
Treatment Motivation		X					
Demographic Information		X					
LANSS[81] and PainDETECT[82]		X					
SDMT, Digit Span, RAVLT, Trail Making, WRAT		X					
Deployment History		X					
History Sexual Trauma		X					
Use of HYP or MM in the past		X					
Substance Dependence or Abuse(WHO ASSIST)[85]		X				X	X
Two- Item Conjoint Screening (TICS)[86]		X				X	X
Functional Co-Morbidity[83]		X					
StarT Back Screening Tool[84]		X					
Average of up to 4, 0-10 recall NRS of average pain intensity		X		X	X	X	X
Average of up to 4, 0-10 recall NRS of worst pain intensity		X		X	X	X	X
PROMIS Depression SF[62]		X		X	X	X	X
PROMIS Anxiety SF[62]		X		X	X	X	X
Depression, Anxiety, Stress Scales 21-item (DASS-21)		X					
Unvalidated Sleep Questions		X					
PROMIS Sleep Disturbance SF[62]		X		X	X	X	X
PROMIS Pain Interference SF[62]		X		X	X	X	X
PROMIS Global Health[65]		X		X	X	X	X
PTSD Checklist-Civilian version [63]		X		X	X	X	X
Medication Use		X		X	X	X	X
Medical Services Utilization		X			X	X	X
Theta, alpha, beta, and gamma bandwidth power		X			X		
Chronic Pain Acceptance Ques. [69]		X		X	X	X	X
Pain Catastrophizing Scale [70]		X		X	X	X	X
Five Facet Mindfulness Questionnaire- Short Form		X		X	X	X	X
Subjective Happiness Scale[74]		X		X	X	X	X
BIS/BAS[73]		X		X	X	X	X
Working Alliance-Short Form [72]				X*	X		
Self-report of between-session skill practice			X	X	X	X	X
Pain intensity, comfort, pre- and post- treatment session			X				
Group Climate Measure[87]				X*	X		
Participant Engagement, Treatment			X				
Treatment Satisfaction(PGATS)[64], Tx Modality					X		
Global Improvement[58]					X		
Situational Catastrophizing Questionnaire[88]		X			X		
Relaxation Experience- Brief Scale					X		
PANAS Positive Affect Subscale[66]		X			X	X	X
PROMIS Psychosocial Illness Impact Positive[67]		X			X	X	X
Neurobehavioral Status Inventory		X			X	X	
Group Comfort Questions					X**		

*Administered during the treatment phase of the study only at the two-week assessment timepoint.
** Administered anytime after session 8 (final group session). Late measure: Administered only to Cohorts 11,12. Measure is optional.

Sub-Study:
We will pair sleep data with the data (demographic, descriptive, outcome, covariate, mechanism, etc.) that are collected as part of the main study.

Primary outcome variable: Sleep Quality and Duration.

Three times during his/her participation in the sub-study, we will ask the participant to wear the actigraph (Actiwatch , Philips Respironics, Bend, OR) like a wrist watch on his/her non-dominant arm. The device will measure how long the participant sleeps, as well as the overall quality of his/her sleep.

In addition, we will ask the participant to keep what we call a sleep diary while wearing the actigraph, as well as call a toll free number twice a day to report when s/he woke up in the morning, and when s/he is going to sleep in the evening. These data will be used to validate the objective sleep data collected by the actigraph.

Mediator variable: Sleep Self-Efficacy

In addition to the mediators already examined within the main study, sleep self-efficacy will be explored using a 4-item Sleep Self-Efficacy and Control Scale.[89] This measurement is relevant with regard to whether the adoption of new skills increases participants' confidence that they can self-manage their sleep habits.[89] Gains in self-efficacy have been linked to significant reductions in chronic disease burden, affective symptoms and disability[90, 91] and are relevant to future planned work to maximize the effects of sleep and pain self-management.

Additional covariate and mechanism variables will be captured to explain sleep findings more completely. Routine and "as required" (PRN) medications for each participant will be recorded on the 7-day sleep log to aid in understanding how sleep or pain medicines relate to sleep measurements.

D6u. Treatment Fidelity Monitoring

Main Study:

We will take a number of steps to ensure that the treatment protocols are delivered uniformly. First, all treatments will be provided by clinicians who will be trained and supervised by the study investigators with a great deal of experience in providing such interventions. Second, all of the study clinicians will be provided with detailed treatment manuals. Third, adherence and fidelity will be monitored using audio recordings of the treatment sessions. The study investigators will review a random selection of these recordings throughout the study to ensure that procedures are followed. Corrective feedback will be provided to all clinicians regarding their adherence to the established protocols.

D6v. Data Collection and Management

Main Study and Sub-Study:

Data will be collected at the Seattle and American Lake divisions of the VAPSHCS, and the Integrated Brain Imaging Center (IBIC) at the University of Washington. The UW Principal Investigator (PI; Dr. Mark Jensen) and the research manager will be located at the University of Washington, whereas the VA PI (Dr. Rhonda Williams) and VA coordinator will be located at the Seattle VAPSHCS division. Data will be obtained from participants either via telephone or in person in an outpatient setting using the approved study case report forms.

Trained study personnel will conduct the screening interview either in person or via telephone at the VAPSHCS using a structured format in which the interviewer asks questions from a script and also notes the answers on a case report form. The same case report form will be used to guide the medical record review to ensure that the same historical information is gathered and coded for all participants.

The self-report assessments and psychological and cognitive assessment consist of standardized protocols with specific/scripted questions and scoring systems that quantify answers. All study personnel from all study sites who will be gathering data from these sources will be trained by the PI regarding the collection of data and will have professional education and training as required by these instruments.

Data will be de-identified and labeled with a code number that is unique to each participant in the study. The participant code numbers will consist of an arbitrary number consecutively numbered in order of screening/medical record review/approach (e.g., 1001, 1002, etc.). All hard copy data will be stored in locked filing cabinets in locked rooms at the VAPSHCS, while all electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. Study researchers will maintain a key code that links that study participants with their coded identifier. This key code will be stored separately from all other study data. Any materials with protected health information (e.g., Informed Consents) will be stored in separate locked filing cabinets from de-identified, coded materials to ensure the security of participant privacy. Special multilevel data security programs have been written into the network operating system to ensure that only authorized research personnel have access to the Center Network. A computer log is maintained of all system login attempts.

A database will be developed using Microsoft Access by the UW team. Once created, the database will be tested, any flaws fixed, and then the final version will be uploaded to the VA secure network drive. This database will be supported throughout the study by the UW study team.

Two separate study support persons will enter data from the hard copy forms into the database to ensure accuracy of data entry. All data entry discrepancies between these two data entries will be solved locally by the research manager.

‘Hard copy source documents will be stored at either the American Lake or Seattle VA site. If source documents need to be transported from one site to the other, they will be transported by a research staff member via VA shuttle transportation. The source documents will have only the 4-digit sub ID to identify subjects. The source documents will not contain PII. The source documents will be transported using either a standard briefcase or a packing box. All data entry will take place within five business days of collection.’

In addition, any source documents completed at the UW site will be sent using a delivery service that provides shipment tracking and delivery confirmation (e.g., Federal Express) to the VAPSHCS Seattle division site. Only approved study personnel will be able to access the databases and digital audio files.

All study data will be recorded directly on the CRFs except for the following data:

1) Inclusion and exclusion criteria extracted from Veterans' medical records during the screening process;
2) data collected during treatment that will be extracted from participants' medical records; and
3) brain wave activity data collected during the EEG assessment.
4) Sleep quality and duration data from the actigraphy device (sub-study only).

Sub-Study Only:

Sleep/Wake Diary

The participant will send back the completed sleep/wake diary to WSU study researchers at the Spokane Sleep and Performance Research Center in a provided self-addressed stamped envelope along with the actigraph device. WSU research staff will use the sleep diary as a reference only for the data downloaded from the actigraph device; no data from the sleep diary will be entered into a database at that time. WSU research staff will then send the completed sleep diaries in de-identified form to VAPSHCS staff via postal mail, who will then enter the data into the secure database with all other main study data. The original hard copies will be filed at the VAPSHCS in a locked office separate from participant identifiers.

Also, the participant will be instructed to call a toll free number twice a day to report when s/he woke up in the morning, and when s/he is going to sleep in the evening. The number will be housed at the VAPSHCS, and only accessible to study staff. If a voicemail is left by the participant: staff will delete the voicemail after research staff record the data provided using the case report form. Participants will be advised to leave his/her study ID only without any identifiers. These instructions will be given to the participant either in person or via postal mail.

Actigraphy Device

The participant will be instructed to send back the actigraph to WSU study researchers in a provided self-addressed stamped envelope at the end of the three data periods along with the sleep diary. WSU research staff will download the data collected by the actigraph device. The data will be stored on a secure WSU server in de-identified form indefinitely. Data may be downloaded from the Actigraph only with the assistance of Actigraph software unavailable to the general population.

WSU research staff will send the aforementioned Actigraph data cover page along with the daily diary of each participant to VAPSHCS research via postal mail in de-identified form. VAPSHCS will enter the data recorded on the actigraph data cover page into the secure database with the main study data. The original hard copies will be filed at the VAPSHCS in a locked office separate from participant identifiers.

WSU research staff will not have access to any identifying information of research participants collected and stored by VAPSHCS research staff.

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.

Study Researcher	**Blinded/Unblinded and Reason**	**When Blinded**
Mark P. Jensen, Ph.D.	Blinded (will oversee data fidelity)	Blind during data collection phase of study.
Rhonda M. Williams, Ph.D.	Unblinded (Dr. Williams will be responsible for group roster collection and addressing clinical issues)	N/A
Marcia Ciol, Ph.D.	Blinded (will help manage outcome data)	Entire study.
Dawn M. Ehde, Ph.D.	Blinded (no opportunity for unblinding)	Entire study.
Kevin Gertz, M.P.A.	Blinded (will help manage outcome data)	Blind during data collection phase of study.
Shahin Hakimian, M.D.	Blinded (no opportunity for unblinding)	Entire study.
Dave Patterson, Ph.D.	Blinded (no opportunity for unblinding)	Entire study.
Melissa Day	Blinded (no opportunity for unblinding)	Entire study.
Aaron Turner, Ph.D.	Unblinded (Dr. Turner will serve as back up for Dr. Williams for group roster collection and addressing clinical issues.)	N/A
Carrie Kincaid, B.A.	Unblinded (Assist with coordination of collection and entry of treatment data, assist w treatment fidelity)	N/A
Alisha McCall, B.A.	Blinded (will collect outcome data)	Blind during data collection phase of study.
Genevra Vanhoozer, B.A.	Blinded (will collect outcome data)	Blind during data collection phase of study.
Derek Anderson, Ph.D.	Unblinded (will be leading treatment groups)	N/A
Jenny Bambara, Ph.D.	Unblinded (will be leading treatment groups)	N/A

Megan Miller, Ph.D.	Unblinded (will be leading treatment groups)	N/A
Moriah Brier, MA	Unblinded (will be leading treatment groups)	N/A
Sarah Noonan, Ph.D.	Unblinded (will be leading treatment groups)	N/A
Kaitlin Harding, MS	Unblinded (will be leading treatment groups)	N/A

WSU Sub-Study Researchers

Study Researcher	Blinded/Unblinded and Reason	When Blinded
Marian Wilson, Ph.D.	Blinded (no opportunity for unblinding)	N/A
Hans van Dongen, Ph.D.	Blinded (no opportunity for unblinding)	N/A
Kimberly Honn, Ph.D.	Blinded (no opportunity for unblinding)	N/A
Devon Grant, Ph.D.	Blinded (no opportunity for unblinding)	N/A
Julie Erwin	Blinded (no opportunity for unblinding)	N/A
Lillian Skeily	Blinded (no opportunity for unblinding)	N/A

D6x. Statistical Analyses

Main Study:

Addressing Aim 1 by testing Hypothesis 1.General Approach to Analyses.
For the primary analyses addressing Aim 1, we will use an intent-to-treat (ITT) approach, which analyzes all participants who were randomized in their respective assigned treatment, regardless of how much they actually received of that treatment.

Missing Data. Analyses to identify potential patterns in missing outcome data will be conducted to determine if they are missing at random ("ignorable"). Missingness at random is

not testable, but we can look at the variables that were observed in groups with and without missing outcomes data. No association between observed variables and the group (missing vs. no missing) will be considered an indication that the data are missing at random. In addition, we will look at the reported reasons for missing values when available. If we can assume data are missing at random, we will use multiple imputation procedures. If there appear to be non-random missing outcomes data, we will use two methods designed to account for this: Heckman's selection models and pattern-mixture models, both of which model the joint distribution of the outcome and the missing mechanism. In the case of non-ignorable missing data, we will use both methods as a sensitivity analysis. If less than 5% of the data is missing and we can assume ignorable missing data, the following analysis will be performed.

Hypothesis 1 states that Veterans randomly assigned to receive eight group sessions of HYP or MM will report significantly greater pre- to post-treatment decreases in average pain than Veterans receiving eight sessions of ED. The response variable will be change in average pain intensity score from pre- to post-treatment (Pre-treatment score – Post-treatment score). This response variable will be analyzed using an analysis of covariance (ANCOVA) with treatment condition (HYP, MM, ED) as the explanatory variable and the baseline pain as a covariate.

Support for Hypothesis 1 would emerge if a significant treatment main effect is present after adjusting for the baseline covariate, and subsequent post-hoc analyses indicate larger baseline to post-treatment decreases in pain intensity in the HYP and MM conditions, relative to the ED condition. The overall significance level for the test of the null hypothesis that all three treatments have equal effect will be set to 0.05.

Although we anticipate that HYP and MM will have similar effects on the primary outcome variable, these analyses will also allow us to compare the relative effects of HYP and MM with each other, as part of the exploratory aims/analyses.

Pairwise comparisons of the treatment groups will be performed using Tukey method (see for example, Analysis of Messy Data Volume 1: Designed Experiments, Second Edition, by GA Milliken and DE Johnson. 2009, chapter 3).

Addressing Aim 2 by testing Hypothesis 2. Hypothesis 2 states that baseline EEG activity will predict differential response to HYP and MM, such that those participants who have higher baseline levels of global theta, and lower baseline levels of left frontal gamma will respond to HYP, while participants with lower baseline levels of global alpha will respond to MM. We will test for this moderator using a linear regression analysis, with pre- to post-treatment change in pain intensity as the response (criterion) variable.
Treatment Condition, absolute power of baseline theta, alpha, and (left frontal) gamma, and terms representing the interaction between treatment condition and each EEG bandwidth will be the explanatory variables. Significant Treatment Condition X Theta, Alpha, and Gamma interactions, with higher coefficients for baseline theta and lower coefficients for baseline gamma in the HYP group, and lower coefficient for baseline alpha in the MM group would support Hypothesis 2.

Additional exploratory analyses. In addition to testing the two study hypotheses, we propose a series of exploratory analyses (explained below) to take full advantage of the data collected to better understand the effects and potential mechanisms of HYP and MM. However, because these analyses are exploratory, we will report them as such. Any statistically

significant findings will be viewed as providing support for further, more definitive, testing in the future.

Effects of HYP and MM on secondary outcomes. To examine the potential effects of HYP and MM, relative to ED, on co-morbid conditions, we will repeat the ANCOVA analyses planned to test Hypothesis 1 for the secondary outcome variables (assessing pre- to post-treatment decreases in depression, anxiety, sleep disturbance, pain interference, PTSD symptoms) as the response variables, controlling for the respective baseline measures of these secondary outcomes. The response variable will be change in each outcome measure score from pre- to post-treatment (Pre-treatment score – Post-treatment score). This response variable will be analyzed using an analysis of covariance (ANCOVA) with treatment condition (HYP, MM, ED) as the explanatory variable and the corresponding baseline value for each secondary outcome measure as a covariate.

Perceived global improvement is a secondary outcome measure but unlike the other secondary outcome measures it was not measured at baseline, hence a slightly different approach will be used for this secondary outcome measure. Instead of a change score, we will simply use ANOVA to compare perceived global improvement with treatment condition as the independent variable.

To assess the effect of each treatment on post-treatment ratings of global satisfaction(which has only 5 categories), we will use an ordinal polytomous logistic regression. Because we anticipate that *both* HYP and MM will have significant beneficial effects on outcomes, we do not anticipate large differences between these two interventions in the outcome measures. However, we think that it would be important to estimate differences in outcome between the two active treatments for descriptive purposes. To do so, we will perform pairwise post-hoc tests to compare the means of the three groups.

We will report both the p-value and effect sizes for the tests between the two conditions (HYP and MM) on outcomes. While the study was not powered to simultaneously test for the primary and secondary outcomes, it is reasonable to assume that the sample size of 80 participants per condition (determined to adequately power the primary hypotheses) will allow for reliable estimates of the effect sizes for secondary outcomes as well.

Longer-term effects of HYP and MM, relative to ED.

As part of our exploratory aims, we plan to assess the extent to which change in pain intensity, the primary outcome, is maintained at 3 and 6 months post-treamtent, and to see if longer term changes in pain intensity differ between HYP and MM compared to ED. To assess this, we propose to use a Generalized Estimating Equations (GEE) approach, which accounts for the correlated nature of the data due to multiple observations of the same person over time. Response variables over time will be the change from pre-treatment to post-treatment, and pre-treatment to 3- and 6- months follow-ups, with intervention group and follow-up time as the main factors of interest (including a Group X Time interaction), and the pre-treatment value as the covariate. For the correlation matrix, we will assume an unstructured format, since there was no a priori reason to use a more structured matrix format. We will repeat these analyses for the secondary outcome measures mentioned above.

Mediation analyses.

The goal of mediation analyses is to examine whether group assignment (determined by randomization at baseline) impacts the change in pain intensity (primary outcome) from baseline to post-treatment through indirect effects on the hypothesized mediators (measured midway

between baseline and post-treatment). Our potential mediators have been identified a priori and are shown in the table of measures (Table 4).

To evaluate the association between intervention type, potential mediating factors, and change in pain intensity, we will first run models with individual mediators to get unadjusted estimates and to estimate the degree of confuouding in subsequent multivariate models. Per Hayes & Rockwood's 2017 recommendations, we will test multiple mediators in the same model, to more accurately reflect our theoretical understanding of parallel biological and psychological mediating processes, and to facilitate comparison of the size of indirect effects through different mediators. Mediators to be included in the model include change in EEG composite scores for theta, alpha, beta, and gamma bandwidths, pain acceptance, catastrophizing, mindfulness, therapeutic alliance, and skill practice. Also per the recommendations of Hayes and Rockwood (2017), we will compute bootstrap confidence intervals for the indirect effects. All mediation analyses will be done using PROCESS, a free downloadable add-on available for SPSS and SAS (the analysis packages we will use for the study's data analysis). PROCESS includes the computational code to generate a primary estimate for the mediation model which represents the indirect, or mediated effect, and allows for inclusion of moderator variables.

Our study is longitudinal and, in addition to posttreatment assessments, we have collected data at 3- and 6-months post-treatment on outcomes and all other variables (mediators and moderators). While the approach used in the PROCESS software can be somewhat adapted for longitudinal analysis, the most appropriate analysis would be longitudinal structural equations models, particularly latent growth models (e.g., Goldsmith et al. 2018). These models require specialized software such as AMOS or LISREL and are beyond the scope of our exploratory aims. If we are able to access such statistical resources in the future, however, we would like to leverage this dataset for these exploratory purposes.

Additional moderator analyses. As in any study, we are interested in exploring whether the treatments have different effects at different levels of other variables, that is, if there are interactions between treatments and those variables (which then would be called moderators). In our study, we have 16 potential moderators (e.g., demographic variables, baseline beta activity, etc., see Table 4). Given the large number of potential moderators and their interactions with treatment, it would not be adequately statistically powerful nor easily interpretable to include all of them in a single model at once. On the other hand, 16 models with a single potential moderator would not give a realistic picture of how the moderation effects were acting in the population of interest. To address these concerns, we propose to first assess the correlations between the potential moderators. If two or more potential moderators are highly correlated, we are unlikely to enter them in the same model (due to collinearity) and if necessary will choose one of them (based on what is know about the variable, such as how reliable it is) to continue as a candidate.

This process might reduce the number of potential moderators in a way that uses both empirical support (correlations) and integrates our theoretical knowledge about the variables. Once the potential moderators have been winnowed to a smaller number, we will construct the models gradually, by including potential moderators and their interaction with treatment in a forward fashion (in the order of statistical signifcance). Hayes and Rockwood (2017) recommend use of the macro PROCESS for this, which writes the SPSS syntax for a specified model. Statistically significant Treatment Condition X Moderator interactions would suggest that the impact of the moderator variable on outcome differs as a function of treatment condition. In the absence of interaction, statistically significant main effects for the potential moderators would suggest that they might be associated with the outcome. Given the very large number of exploratory moderator analyses proposed, we will be very cautious in interpreting the results, and will use

these analyses only as a way of identifying potential moderators to examine more closely in future research.

The moderation/mediation analyses described above are exploratory in nature. As a result we will not implement a multiplicity adjustment for these analyses. Study researchers will ensure that publications report all the analysis results and specify the total number of exploratory analyses that were conducted.

Sub-Study:

We will pair sleep data with the demographic and descriptive information as well as the pain outcomes that are collected as part of the main study. All data will be de-identified and linked only by a participant ID code and all data sharing will be done in accordance with the collaborating institutional human participants' committees.

For aim 1 of this supplemental study, the primary outcome measures are (1) self-reported sleep quality (subjective sleep assessment on the continuum from "good" to "poor" sleep), and (2) actigraphic sleep duration (the total amount of sleep per 24 hours measured objectively with wrist actigraphy). Secondary outcomes include self-reported and actigraphy-based sleep timing and continuity.

For the statistical analyses in support of aim 1, we will compare sleep quality and duration in self-hypnosis and mindfulness meditation treatment groups as measured by self-report and through wrist actigraphy from pre-treatment to immediate post-treatment, and at 3-month follow-up, relative to sleep quality and duration at the same time points in the education control group. *We hypothesize that participants in the two treatment groups will show improvements in self-reported sleep quality and in actigraphic sleep duration both immediately post-treatment and at 3-month follow-up, relative to the control group.* We will test this hypothesis, for each of the two primary outcome measures, by means of mixed-effects analysis of variance (ANOVA), where a random effect will be placed on the intercept, and the hypothesis tested with planned contrasts between conditions, at each time point, embedded in the mixed-effects ANOVA framework.[92] Secondary analyses will use additional key demographic variables (age, sex/gender, race/ethnicity, medications) as covariates.

For aim 2 of this supplemental study, the primary outcome measures will be paired with the primary pain outcome from the parent grant as measured with a 0–10 numeric pain intensity scale.[41]

As a secondary sleep outcome, for this aim we will add the PROMIS Sleep Disturbance Short Form, which is already being administered as a self-report measure of sleep quality within the parent project. This will allow us to evaluate the level of congruence between the parent grant and the subsample studied in the supplement.

For the statistical analyses in support of aim 2, we will determine whether changes in self-reported sleep quality and in actigraphic sleep duration in the hypnosis and mindfulness meditation treatment groups and the control group *precede* changes in pain, or vice versa, from pre-treatment to mid-treatment to immediate post-treatment to 3-month follow-up. Specifically, we will evaluate the association between early treatment changes in self-reported sleep quality (from pre-treatment to mid-treatment) and late treatment changes in pain (from mid-treatment to post-treatment), and vice versa.

We will also evaluate the association between treatment-related changes in objective sleep duration (from pre-treatment to post-treatment) and post-treatment changes in pain (from post-treatment to 3-month follow-up), and vice versa. *We hypothesize that changes in sleep quality and duration precede (and thus predict) subsequent changes in pain intensity*. Secondarily, we will investigate whether associations are moderated by treatment group*. We hypothesize that larger lagged effects will occur for the two treatment conditions, relative to the control condition.* Our hypothesis testing for aim 2 will be based on cross-lagged regression analysis.[103, 104]

Additional covariate and mechanism variables will be captured to explain sleep findings more completely. Routine and "as required" (PRN) medications for each participant will be recorded on the 7-day sleep log to aid in understanding how sleep or pain medicines relate to sleep measurements. Sleep data will be analyzed for relationships with data already collected within the parent grant, including depression scores and self-report of new self-hypnosis and mindfulness meditation skills practiced. In addition to the mediators already examined within the parent grant, sleep self-efficacy will be explored using a 4-item Sleep Self-Efficacy and Control Scale.[89] These mediator variables will be related to the sleep outcomes (not the pain outcomes as those are already analyzed for covariates in the parent grant) by including them as covariates in mixed-effects ANOVA, controlling for condition and time point. These will be exploratory analyses where type II error is more problematic than type I error; therefore no type I error threshold correction is envisioned. Mediator analysis results will be explicitly reported as exploratory.

D6y. *Missing Data*

Analyses to identify potential patterns in missing outcome data will be conducted to determine if they are missing at random ("ignorable"). Missingness at random is not testable, but we can look at the variables that were observed in both, group with missing and without missing outcomes data. No association between observed variables and the group (missing vs. no missing) will be considered an indication that the data is missing at random. In addition, we will also look at the reported reasons for missing values (when available). If we can assume missing at random data, we will use multiple imputation procedures. Currently, two methods are used when the data is considered not missing at random: Heckman's selection models and pattern-mixture models, both of which model the joint distribution of the outcome and the missing mechanism. In the case of non-ignorable missing data, we will use both methods as a sensitivity analysis. If less than 5% of the data is missing and we can assume ignoble missing data, the following analysis will be performed.

D6z. Power Analyses

We performed power analyses, reported below, to ensure that the study had more than adequate power to test the hypothesis related to the effects of the treatments on the primary outcome (average pain intensity).

Power to test the primary study hypothesis. The primary study outcome variable is change in average pain intensity, as represented by the difference between the baseline and post-treatment average pain intensity measures.
We have used this measure successfully in numerous previous trials.[41, 42, 52, 105, 106] Anticipated effects for HYP are based on the changes observed in our previous HYP trials using the 0-10 NRS measure, plus our pilot study of HYP for low back pain treatment, reported in the

'Preliminary findings' section.

Anticipated effect sizes for MM are based on published studies of the effects of treatments that involve mindfulness that used 0-10 NRS measures.

Assuming a decrease in pain score of 0.3 points for the education group, 0.8, 1 and 1.4 for the HYP, and 0.6, 0.8 and 1 for MM, we calculated the sample size to find differences between pre-post treatment difference scores, with an alpha of 0.05, power of 0.80, and varying the standard deviation (SD) from 0.15 to 1 (to cover values observed) when using an ANOVA. Sample sizes of 80 completers per condition (total = 240) will have at least 80% power, even at the largest standard deviation.

Power for secondary and exploratory analyses.

The sample size calculations above take into consideration only the primary hypothesis of interest (that different treatment have different effects in changing pain intensity), which is the most important result this study can provide for the person affected with chronic pain. However, the sample size of this study is relatively large and will provide extremely useful and important information regarding secondary outcomes, mediators and moderators associated with pain intensity and EEG. The results will form the basis for continuing research not only to find treatments that are efficacious, but also to hypothesize mechanisms of action, which will be crucial in designing future studies.

Power Calculations (Sub-Study)

We focus our power calculations on the most innovative aspect of the supplemental study, that is, the objective measurement of sleep by means of wrist actigraphy in the context of non-pharmacological pain treatments.

We base our power calculation on a previous study that is informative of the statistical power found in sleep duration data from wrist actigraphy as collected in naturalistic repeated-measures settings. In this previous study, 24 regional airline pilots participated in a two-day flight simulator study.[107] In the day before the study, they flew into the airport where the flight simulator center was located, and that night they planned their sleep naturalistically. As the pilots discovered that the workload during the study was high, they extended their sleep in the night between the two study days in order to recuperate. As measured by wrist actigraphy (same type as will be used in the supplement), the sleep duration in the night prior to the second study day was significantly greater than the sleep duration in the night prior to the first study day, by a difference of 1.35 hours (t_{23}=3.97, P<0.001). The correlation of sleep duration between nights was ρ=0.122. Relevant for our power calculation is also the systematic between-subjects standard deviation, which was SD=26.3 minutes.

In aim 1 of the supplemental study, we will use wrist actigraphy to compare sleep pre-treatment to immediately post-treatment (8 weeks) and to 3-month follow-up, relative to sleep at the same time points in the control group. Thus, we will make two repeated-measures comparisons: pre-treatment to post-treatment in the intervention group relative to the control group, and pre-treatment to 3-month follow-up in the intervention group relative to the control group. Because each of these two comparisons defines an interaction effect, which is inherently low on statistical power, we set the a-priori type I error threshold to α=0.1.[108] However, because we will do two comparisons using the same pre-treatment data, we must also control for multiple comparisons. Therefore, after applying Bonferroni correction, we end up with a type I error threshold of α=0.05.

To make use of the statistical power conferred by systematic between-subjects variability,[102] we will employ mixed-effects ANOVA to implement the test (which then again takes the form of an interaction effect).
For power calculation purposes this is relevant in that the standard deviation of interest is therefore the systematic between-subjects standard deviation provided above (which, in a comparison between independent samples, serves as the estimated pooled standard deviation).

Also, as we expect that treatment will improve sleep and we will only consider the effect beneficial if it involves extension of sleep duration, one-sided testing will be used. We will consider a mean increase in sleep duration of M=15 minutes or more to be clinically relevant.[109] Thus, we seek to demonstrate an effect size of Cohen's $d=M/SD$=15/26.3=0.57. To achieve 80% statistical power at a type I error threshold of α=0.05, we will need to study 39 participants per group (nQuery 7.0, Elashoff, 2007). Thus, we will need to study 39 participants in each of the two treatment groups and 39 participants in the control group. As such, our target sample size for the supplemental study is N=117.

For aim 2 of the supplemental study, with 39 subjects in each treatment group we will have the ability to investigate the relationship between actigraphically measured sleep duration and pain outcomes from the parent project. For each of the two intervention groups, we will first use a regression model on subjective pain with sleep duration as the covariate of interest, and our objective will be to test the regression coefficient for this covariate against zero (two-tailed). With 39 subjects, we will have 80% statistical power, at a type I error threshold of α=0.05, to detect a relationship between sleep duration and subjective pain if this relationship explains at least 17.5% of the variance (nQuery 7.0, Elashoff, 2007).

We will then apply an autoregressive cross-lagged model to investigate the cross-lagged relationship between actigraphically measured sleep duration and pain outcomes from the parent project. For each of the two intervention groups, we will use an autoregressive regression model on sleep duration with subjective pain as the covariate of interest, and our objective will be to test the regression coefficient for this covariate against zero (two-tailed). We will account for the variance in sleep duration at the post-intervention and follow-up time points that is explained by sleep duration at the respective immediately preceding time point, ρ^2, where the estimated value for ρ is drawn from our previous data set described above (ρ=0.122). With 39 subjects, we will have 80% statistical power, at a type I error threshold of α=0.05, to detect a cross-lagged relationship between sleep duration and subjective pain at the immediately preceding time point if this relationship explains at least 17.3% of the variance (nQuery 7.0, Elashoff, 2007).

HUMAN PARTICIPANTS SECTION

1. Risk to Participants

1a. Human Participants Involvement and Characteristics

We plan to enroll up to ~~343~~ 355 participants into the study. Male and female participants 18 years of age or older who have chronic pain will be approached to participate in the study. Participants will be recruited from clinics at the Seattle and American Lake Campuses of VAPSHCS, as well as community-based outpatient clinics (CBOC).

Veterans will be recruited from several clinics and service lines at VAPSHCS: the Rehabilitation Care Service (which includes the Polytrauma Network Site for the northwest four

states, the Multiple Sclerosis Clinic/Center of Excellence, Prosthetic/Limb Loss Clinic, and Musculoskeletal Clinic), and the Spinal Cord Injury Service. Each of these clinics sees 200-500 new Veteran patients per year and carries an ongoing patient load of 200 – 400 patients. We will also recruit patients from Primary Care as needed, which carries an ongoing patient load of 19,000 patients per year.

Participants will also be recruited from VA community-based outpatient clinics (CBOC).

1b. Sources of Materials

Several sources of information will serve as data for the study, including medical record reviews, self-report assessments, cognitive tests, brain activity assessments, 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 other than the data collected during the group treatment sessions will be collected solely for research purposes. Participants will be informed that data collected before and after treatment sessions, i.e. data regarding homework practice, pain intensity and comfort before and after each treatment session, and participant engagement as per the study clinician, will be reported in their medical record, as clinically indicated. Research participation will not influence any part of a patient's medical treatment.

E1c. Potential Risks

General/Reaction to Assessments

Regarding research risks, participants may experience fatigue and/or boredom while completing the telephone assessments, cognitive assessment and the treatment sessions. Some participants may also experience mild anxiety, frustration, and/or stress while answering questions about depression, anxiety and PTSD symptoms. As result of answering questions regarding pain and other symptoms, participants may experience a temporary increase in intensity and/or distress of symptoms.

Some participants may also experience mild anxiety, frustration, and/or stress if the cognitive assessment proves difficult for them, and/or during the course of treatment.

Brain Wave Activity Assessments

Some participants may find sitting still for up to one hour (including prep time, adjustment period and actual assessment) and/or wearing an electrode net on their head to be uncomfortable during the EEG assessment**.** Some participatns may also find a temporary increase in their overall pain. Some particpants may find the EEG assessment, including questions asked during the EEG, may cause a temporary increase in PTSD symptoms.

Treatment

The three types of treatment involve discussions and/or exercises about pain and related topics in a group setting that may make some individuals feel uncomfortable. In addition, some individuals may find it uncomfortable or distressing to hear other Veterans discuss their pain or other problems in a group setting. As result of group discussions or exercises, participants may focus more on their pain, which may lead to a temporary increase in pain intensity and/or

distress regarding their pain problem. Some individuals may also experience discomfort (numbness, tingling, perceived loss of sensation) from sitting still for extended periods of time.

Regarding the self-hypnosis training, some individuals may find the state of deep relaxation associated with hypnosis uncomfortable. Also, some individuals under hypnosis may remember past experiences that are uncomfortable and/or cause distress, even after the session has ended. In addition, some individuals under hypnosis or practicing mindfulness may also experience mild disorientation or grogginess during or after the session has ended. No stress or discomfort is anticipated to be associated with the education control intervention, and there is little chance of physical injury from the treatment procedures described above.

Sub-Study: Sleep/Wake Diary

Participants may experience fatigue and/or boredom while completing the sleep/wake diary. Some participants may also experience mild anxiety, frustration, and/or stress while answering questions about sleep and activities during the day.

Sub-Study: 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 or what they are doing. Participants may experience sweating or skin irritation while wearing the actigraph if they have sensitive skin.

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, 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.

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.

2. Protection Against Risk

General/Reaction to Assessments

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

All study personnel who conduct the assessments and treatment interventions will be qualified, trained, and closely supervised by the Co-PIs.

Participants will be provided with emergency contact numbers. 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 VA Co-PI, Dr. Williams, who is a licensed clinical psychologist.

Dr. Williams is a trained psychologist who has experience assessing the level of distress of patients and proceeding accordingly whenever an adverse event should arise.

Brain Wave Activity Assessments

All research staff will be trained to conduct the brain wave activity or EEG assessments and treatment procedures in a safe manner. Participants will be told they can stop any EEG assessment at any time if they feel uncomfortable.

The research staff member conducting the assessment will ask each participant following completion of the assessment whether they experienced any negative effects during the assessment they associate with the study procedures.

Treatment

Researchers will take multiple steps to ensure and monitor the well-being of participants during treatment. These include the following: 1) participants will be asked to complete a form after each treatment session that asks participants (research and non-research) if they found anything unhelpful about the treatment session. Any reporting of a possible adverse event will be reported to Dr. Williams. Should such events be identified, they will follow institutional protocols for ensuring appropriate management; 2) the Co-PIs will offer ongoing supervision and consultation with study clinicians including routine assessment of any potential problems or adverse events; 3) as needed supervision and consultation will be available for clinicians by investigator staff.

Group leaders will take steps to ensure groups are as comfortable as possible by facilitating relevant discussion, limiting side conversations, and addressing concerns that are raised. Group leaders may ask participants to talk more or less to ensure that everyone has an opportunity to participate and the conversation is productive and positive.

Sub-Study: Sleep/Wake Diary

Participants will be informed during the consent process and throughout the sub-study that they may refuse to answer any questions that make them feel uncomfortable while completing the sleep/wake diary. In addition, participants will be informed in the consent process that they are free to stop any study-related procedures at any time.

Sub-Study: Actigraphy Device

Participants will be warned about possible irritation to the skin and general discomfort wearing the device during the informed consent session. Participants will be informed in the consent process that they are free to stop any study-related procedures at any time.

F1d. Privacy and Confidentiality

We will take multiple steps to protect participants' privacy and confidentiality. All data collected for the study will be de-identified, labeled with a code number that is unique to each participant in the study, and maintained separate from any identifying information.
All of the data collected from participants, both research and non-research, 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 without permission from the participant.

As mentioned above, all data collected outside of the treatment sessions will be de-identified, labeled with a code number that is unique to each research participant, and maintained separate from any identifying information. All hard copy study data collected outside of the treatment sessions will be stored in locked filing cabinets in locked rooms at the VAPSHCS. Hard copy forms containing participant identifiers (consent form, HIPAA authorization form, personal data sheet) will be stored in locked filing cabinets in the Dr. Williams' office which is locked at all times, i.e. not in the same location as the study data.

All electronic de-identified data collected outside of the treatment sessions will be stored in password-protected databases in a limited access folder on the secure VA network drive. One exception to this protocol is the raw EEG data collected from participants, which will be stored without identifiers on the HIPAA compliant NAS II drive at the UWMC. Another exception is the sleep data collected by the actigraph device worn by participants in the sleep sub-study, which will be stored without identifiers on a secure drive at the WSU Spokane Sleep and Performance Research Center. WSU research staff will not have access to any identifying information of research participants collected and stored by VAPSHCS research staff.

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 database that does not contain any study data. This database will also reside in a limited access folder on the secure VA 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 subject 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 s/he will be recording the session. The audio recordings will be collected using a VA approved encrypted device that will be stored in a locked filing cabinet when not in use.
The recordings will be uploaded and stored in a limited access folder on the secure VA network drive. Each individual recording will be erased from the audio recorder once it has been uploaded to the drive. 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 participant identifying information. The only identifying information that will be contained the in recordings will be participants' voices and if the study clinician or group members state participants' names during the discussion.

Another exception pertains to data collected during the treatment sessions. Gathering these data is an integrated part of the clinical care provided to both research and non-research participants in the intervention groups. These data will be used by the clinicians in real time as part of clinical care, and include information about homework practice, changes in symptoms

that occur within and between sessions, and any subjective participant concerns. Following each session, per usual care the clinician will enter a progress note in CPRS for each participant, indicating attendance or absence for that particular session. The note will also include the length of the group session, as well as basic content covered during the session. In addition, all case report forms completed by treatment participants will be scanned and stored on a secure drive (PUG_Services (\\RO1PUGHSM03.r01.med.va.gov\RCS\Psychology\SKILLS CLINICAL GROUPS) within the Rehabilitation Care Service.

Access to this drive will be limited to clinicians who are running the classes, their clinical supervisor and unblinded research staff.

F1e. 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 by other VA providers. Therefore, participants will be referred to the VA's Mental Health Division for further assessment and/or treatment if a previously undiagnosed psychiatric disorder is identified. We will inform participants of this procedure as part of the informed consent process and participants must agree to this procedure to be eligible to participate in the study. This ensures that we can adequately manage any pre-existing clinical issues that become apparent through participant evaluation. For ethical reasons a subject will not be withdrawn from the study if they present unstable and/or severe symptoms related to a psychiatric condition following enrollment unless study researchers believe it is in the subject's best interest to be withdrawn.

It should be noted that risk of suicide (defined as being on the suicide high risk list, recent self-directed violent behavior) is an exclusion criteria for this study, so we anticipate that the likelihood of suicide risk is low. For ethical reasons a subject will not be withdrawn from the study if deemed a high suicide risk following enrollment, however, unless study researchers believe it is in the subject's best interest to be withdrawn.

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) is not licensed mental health providers. This protocol outlines specific steps that study staff will follow to cursorily assess risk. Their main responsibility will be to ascertain whether a clinician (study investigator or study clinician) 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 within the VA), our plan primarily reflects the importance of activating the hospital procedures for suicide risk assessment and risk management/suicide prevention.

For participants who are currently ***at the VA for an outpatient appointment*** non-clinical research staff will ask the participant some clarifying questions, such as "Let me clarify, are you having any thoughts about harming yourself deliberately?" If "no," no further action required. If "yes," then the research staff member will advise the participant that they will request some additional mental health assessment. They will use the following script: "Thank you for being honest with your answer. 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 not leave the Veteran unattended until they have either escorted the Veteran to a provider who will assess risk or a provider has arrived to assess risk.
The research staff member will contact a study clinician, study investigator with clinical privileges, the Veteran's established mental health provider, or another VAPSHCS psychologist (who may not be affiliated with the study) and ask them to assess the individual in person if possible.

If they cannot assess the participant in person, they may have the option of facilitating this assessment over the telephone (i.e., the clinician would call in to the office where the research staff member and the participant are present. All information gathered prior to the clinician's assessment will be relayed to the professional provider by the research staff member. VA protocol for assessment and management of at-risk patients will be followed by the assessing clinician. All information for at risk patients will be documented in an AE/SAE or other required documentation for IRB purposes, as well as flagged (if needed) in CPRS.

If the Veteran is currently admitted to the VAPSHCS as an INPATIENT, and the research staff member has determined that the participant has had thoughts of harming themselves deliberately, they will bypass the process of tracking down a psychologist to do the assessment, and immediately inform the patient's nurse of their concern, and request appropriate monitoring until a more in-depth assessment can be made.

The research staff member will ask the RN to alert participant's attending physician and any mental health staff assigned to the unit where the participant is currently admitted, appraise them of the situation, and request that the providers initiate risk assessment and management as indicated on their unit (i.e., consult Psychiatry on call for assessment, or the psychology staff on the unit, as indicated). The Psychiatry Consultation and Liaison service is on-site 24/7 and can provide thorough suicide assessment, monitoring, and treatment as indicated.

(1) For Veterans who are NOT physically on VA premises (i.e., when risk is noted via telephone) the suicide risk assessment protocol would include these steps:

    a. 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 more just thinking about dying or that you would be better off dead?" "Let me clarify, are you having any thoughts about harming yourself deliberately?" If the subject endorses follow-up questions that suggest risk of 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 Veteran 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. In the event of a negative screen, the research staff member will complete the interaction with the Veteran, and then alert Dr. Williams, Dr. Turner 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 Veteran and will thank them for their candor and advise the Veteran that they will be contacting a mental health provider to do further assessment. They will use the following script: “Thank you for being honest with your answer. 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 Veteran on the phone while using another modality of communication (i.e., text, e-mail, pager) to reach Dr. Williams, Dr. Turner or a study clinician who is licensed, privileged, and credentialed to do more in-depth assessment of risk.

b. Once a psychologist contacts the Veteran they will follow VA policies for the assessment and management of suicide risk. (see “Suicide Risk Reduction Protocol-Clinical Staff” below).

(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 research staff could contact local police and request a well-being check.

If a clinician is not available immediately and/or if the research staff member perceives imminent risk:

b. They will encourage the participant to either to contact the Veteran’s crisis line (800-273-8255, available 24/7, staffed by VA mental health providers who have access to the Veterans’ medical records and can coordinate care at the Veteran’s local facility)
c. Or to seek immediate evaluation at the nearest ER. Project staff will have a list of facilities available for reference. Participants who are enrolled in the study are also given a list of referrals at the time of consent. If there is another person present with the Veteran the research staff person may ask to talk with that person about their concerns and problem solve ways to facilitate getting the Veteran to an ER. The research staff member can also contact the crisis responders (from the suicide prevention team) for support/guidance.
d. After directing the participant to the crisis line or ER, the research staff member will follow-up with the Crisis Team and Dr. Williams (Dr. Turner if Dr. Williams is not available) to determine if additional steps (e.g., calling 911) need to be taken. A study clinician will follow up with the Veteran within 24 hours.
e. Dr. Williams, Dr. Turner or a study clinician will document actions taken in the participant’s medical record and alert their medical providers via co-signature within 24 hours of the event. An AE report will also be filed if indicated.

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.

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 Veteran safety and welfare.

It should be noted that risk of suicide (defined as being on the suicide high risk list, recent self-directed violent behavior) is an exclusion criteria for this study, so we anticipate that the likelihood of suicide risk is low.

The study clinicians will be credentialed and privileged providers at VA Puget Sound Health Care System providers. Additionally, both Dr. Williams and Turner are credentialed and privileged providers at VA Puget Sound Health Care System providers. Should there be any indication of risk for self-directed violence during interactions with study staff, the study clinicians/investigators will follow the same specific procedures and policies that psychologists who are clinicians (LIPs) at VAPSHCS 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 Veteran, the study clinicians/investigators will follow the same risk assessment and prevention protocol that is required of VA licensed psychologists.

The two relevant documents that explain the requisite assessment and safety planning protocols and policies policy are “MEMORANDUM TX-74, VA PUGET SOUND HEALTH CARE SYSTEM, DATE: April 2013”, and “PE-16 Suicide Risk Screening and Assessment, revised Feb. 2013.” If these documents are updated during the course of the study, we will follow the updated instructions.

In brief, the VA policy requires that a standardized assessment of risk be performed, and, if indicated, the clinician/investigator generate a plan for acute risk reduction (i.e., if the Veteran is evaluated to be at moderate or greater acute risk of self-harm).

This assessment follows a standardized template and must be documented in the Veteran’s medical record (CPRS) using the specified note titles and templates outlined in the attached policy guidelines, and the Veteran’s MH provider (if they have one) must be alerted via co-signature. If the Veteran does not have an identified mental health provider, Dr. Williams will place a consult to Mental Health (MH) to ensure that the Veteran receives appropriate care.

Study clinicians and investigators who are required to assess risk will be instructed on how to access the Suicide Prevention Coordinators at each study site (American Lake and Seattle Divisions). Suicide Prevention Coordinators can provide consultation and also assist with coordinating care and managing acute risk.

Other potential steps that may be taken to manage acute risk include (but are not limited to): referral to the nearest emergency room, calling 911 and activating civilian resources to ensure safety, contacting the Veteran’s Mental Health provider, referring the Veteran to the Veteran’s Help Line or other resource provided on a list at the time of study enrollment, or contacting a friend or family member of the Veteran and asking for their assistance in enhancing the Veteran’s safety. In the event that any of the above steps are required to ensure safety, study confidentiality may be violated; this is outlined in the ICF.

Furthermore, documentation of any self-directed violent intentions or plan, as well as behaviors will be noted within their CPRS medical record, and an AE/SAE/ Unanticipated Adverse Problem will be documented and sent to the VA Institutional Review Board according to the study protocol and guidelines.

3. Data Safety Monitoring

3a. Adverse Event and Serious Problem Information: Definition

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject 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. Staff will document any occurrence that meets this definition, is a new symptom/condition for the subject, and results in either self-treatment or treatment by a health care provider.

Serious Adverse Event (SAE)

A serious adverse event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

As per the VHA Handbook 1058.01 (4.w), an AE is also considered serious when medical, surgical, behavioral, social or other intervention is needed to prevent such an outcome.

Serious Problem

A serious problem is a problem in human research that may be reasonably regarded as [VHA Handbook 1058.01 (4.y)]:

1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or

2) Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.

3b. Classification of AE Severity

AEs will be labeled according to severity, which is based on their impact on the participant. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being." Please note that a severe AE and an SAE are distinct terms. A subject could experience a severe AE that does not meet the above-listed definition of an SAE; alternatively, a subject could experience a moderate AE that meets the SAE definition.

All AEs and SAEs that affect clinic patients, i.e. non-research participants, within the clinic context will be addressed by licensed providers conducting the treatment interventions as per VA guidelines.

3c. AE Attribution Scale

A "related AE" in VA research is an AE or problem that may reasonably be regarded as caused by, or probably caused by, the research procedures [VHA Handbook 1058.01 (4.r)] AEs will be categorized according to the likelihood that they are related to the study intervention according to VAPSHCS IRB protocol. Specifically, they will be labeled probably not related, possibly related, and probably related to the study intervention.

3d. AE Reporting and Follow-up

Each participant will have an adverse events form created and completed during participation. Each AE will be recorded on this particular form that records the subject's code number, date of AE, severity, attribution level to study, action taken and outcome.

In addition, research staff will record all AEs using a standard VAPSHCS approved Adverse Event Reporting Log that records the subject's code number, date of AE, severity, attribution level to study, action taken and outcome.

These adverse events will be provided annually in this format to the DSMC, both the VAPSHCS and UW IRBs and NCCIH in accordance with requirements. If the event is related to the sleep sub-study, it will also be reported to the WSU IRB.

3e. SAE Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the chair of the DSMC, both the VAPSHCS and UW IRBs and NCCIH in accordance with requirements. If the event is related to the sleep sub-study, it will also be reported to the WSU IRB.

- Unanticipated fatal or life-threatening SAEs related to study procedures will be reported immediately to the VA HRPP (orally), NCCIH Program Officer, chair of the DSMC and the UW and VAPSHCS IRBs.
- Other serious and unanticipated SAEs related to study procedures will be reported to the NCCIH Program Official, DSMC chair and to the VAPSHCS IRB 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. These SAEs will also be reported to the VAPSHCS IRB as part of the annual VAPSHCS IRB status report. The UW IRB does not require reporting SAEs that are not related to study procedures.

Research staff will record all SAEs using a standard form that records the subject's code number, date of SAE, severity, attribution level to study, action taken and outcome. These adverse events will be provided annually in this format to the DSMC, both the VAPSHCS and UW IRBs and NCCIH in accordance with requirements.

The Chair of the DSMC will be contacted when an SAE 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.

3f. Data Quality Assurance and Monitoring

Description of Plan for Data Quality and Management

The research manager and study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification will take place in the form of double-data entry. Specifically, two separate study staff members will enter data from the hard copy forms into the database to ensure accuracy of data entry. Visual Basic for Applications (VBA) code inserted in the Microsoft Access database will verify the 2nd entry against the 1st entry. Any discrepancies between the two entries will cause a warning window to open informing the data operator that a discrepancy has been detected.

All data entry discrepancies between these two data entries will be solved by the staff member completing the 2nd portion of double entry.

Exploratory data collected during the treatment sessions will be singly entered into the Treatment Database. For quality control, a second unblinded staff member will review 10% of the treatment data at the completion of the study. If there is more than a 5% error rate, then Investigators will be notified to determine a plan of action which may include implementing a 2nd entry verification.

All group treatment sessions will be audio recorded to ensure compliance to treatment procedures. 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.

Data types that will be reviewed include subject accrual, status of enrolled subjects, adherence data regarding study assessments and intervention, any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs and unanticipated problems. The results of these systematic reviews will be sent to the DSMC members on a quarterly basis.

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the first six months of recruitment and then every 3 months to ensure that a sufficient number of participants are being enrolled to allow for an adequate test of the primary study hypothesis and that they meet eligibility criteria.

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
Subject accrual	Quarterly	Co-PIs, DSMC
Status of all enrolled subjects	Quarterly	Co-PIs, DSMC
Adherence data, assessments and intervention	Quarterly	Co-PIs, DSMC

Data type	Frequency of review	Reviewer
AEs	Quarterly	Co-PIs, DSMC
Study-Related SAEs	Per occurrence	Co-PIs, DSMC, NCCIH, UW and VAPSHCS IRBs
Unanticipated Serious Problems	Per occurrence	Co-PIs, DSMC, NCCIH, UW and VAPSHCS IRBs

3g. Subject Accrual and Compliance

Measurement and Reporting of Subject Accrual, Compliance With Inclusion/Exclusion Criteria

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the first six months of recruitment and then every 3 months to ensure that a sufficient number of participants are being enrolled to allow for an adequate test of the primary study hypothesis and that they meet eligibility criteria.

Measurement and Reporting of Participant Adherence to Treatment Protocol

Data on adherence to the treatment protocol will be collected monthly by research staff and reviewed quarterly by the PI, the DSMC statistician, 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 suggested rate of 75%, which might put at risk the ability to test the study's primary hypothesis, the chair of the DSMC will suggest a conference call for study investigators to discuss methods for improving adherence.

3h. Study Discontinuation

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.

3i. Designation of a Monitoring Committee

Name/Role*	Credentials	Organization	Expertise
Katherine Davis	**Ph.D.**	**Independent Consultant**	**Biostatistician**
Kendall Browne	**Ph.D.**	**VAPSHCS**	**Staff Psychologist**
Tracy Simpson	**Ph.D.**	**VAPSHCS**	**Clinical Psychologist, Behavioral Interventions/Clinical Trials**

The Data Safety Monitoring Committee (DSMC) for this study is comprised of Drs. Simpson (chair), Browne and Davis. Dr. Davis, an independent consultant, has no professional or personal connection with the co- PIs.

Although Dr. Simpson is employed at the VAPSHCS, she does not collaborate with any of the research team members in a research or clinical capacity on a regular basis. Likewise, although Dr. Browne is employed at the VAPSHCS, she does not collaborate with the Co-PIs in a research or clinical capacity on a regular basis.

Drs. Simpson and Browne are qualified to review the patient safety data generated by this study because of their unique expertise in the area of randomized controlled trials (RCT) examining the efficacy of psychological interventions in Veteran populations. Dr. Davis was selected given his/her expertise in biostatistics.

3j. Methods and Timing for Assessing Recording, and Analyzing Safety Parameters

Monitoring Subject Safety and Study Compliance

Study researchers including staff members and study clinicians who conduct the telephone assessments, brain wave activity assessments, cognitive 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.

Brain Wave Activity Assessments

The research staff member conducting the assessment will ask each participant following completion of the assessment whether they experienced any negative effects during the assessment they associate with the study procedures. The response to this question will be captured using the EEG Assessment Recording Sheets.

Treatment

The study clinicians moderating the group treatment sessions will disperse forms after each treatment session that asks each participant what they found helpful or unhelpful about the treatment session. We believe these questions will allow participants to express any events that may be adverse and possibly related to study procedures.

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.

All information leading to an adverse event (AE), serious adverse event (SAE), or unanticipated problem will be reported per VA protocol/requirement, i.e., to VAPSHCS IRB using the approved VA IRB forms. Reports will be submitted within the designated required time frame (5 business days). In addition, staff members will use templates provided by the study sponsor to capture specific data pertaining to AEs, SAEs, or unanticipated problems. All documentation collected, submitted, and approved will be stored in a regulatory binder located within the locked study offices. We do not plan to monitor charts for AEs.

Study researchers will document any protocol deviations or events that may jeopardize the integrity of the study in a 'Note-to-File' using the sponsor template for this purpose.

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

Progress Report (Monthly and Quarterly)

Each month research staff will generate a study report that outlines 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 month. This report will be provided to the Co-PIs. The Co-PIs may solicit input from the chair of the DSMC if they detect anything of concern.

Each quarter research staff will generate the same study report that outlines 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 if there is anything of concern that will be supplied to the study PIs, VAPSHCS and UW IRBs and NCCIH.

Annual Report

Study staff will also generate an Annual Report that will include a list and summary of any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs and unanticipated problems. 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 VAPSHCS IRB, (2) the UW IRB and (3) NCCIH.

3k. Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team will generate progress reports on a quarterly basis for review by the Chair of the DSMC, as well as an annual report to be reviewed by all DSMC members.

Study Report Outline for Progress Reports

I. Table of Contents
II. Introduction
    A. Summary of Study Status and Issues or Problems
III. Study Administration
    A. Recruitment Status
        i. Enrollment by Month/Quarter
        ii. Comparison of Targeted to Actual Enrollment
    B. Retention Status
        i. Overall Subject Status
        ii. Individual Subject Status
IV. Study Data Reports/Tables or Figures
    A. General Information
        i. Enrollment

ii. Demographic/Baseline Data
iii. Subject Status

B. Safety Assessment
i. Treatment Duration for All Subjects
ii. AE Data
a. Overall Listing
b. Specific Symptom Listing
c. SAE Listing
d. Subject Deaths

Study Report Outline for Annual Reports

I. Table of Contents
II. Introduction
A. Summary of Study Status and Issues or Problems
B. Report Preparation Procedures
III. Study Description
A. Project Organization Chart, Personnel
B. Brief Statement of Purpose of Trial
C. Projected Timetable and Schedule
IV. Study Administration
A. Recruitment Status
i. Enrollment by Year/Month
ii. Comparison of Targeted to Actual Enrollment
B. Retention Status
i. Overall Subject Status
ii. Individual Subject Status
V. Study Data Reports/Tables or Figures
A. General Information
i. Enrollment
ii. Demographic/Baseline Data
iii. Subject Status
B. Safety Assessment
i. Treatment Duration for All Subjects
ii. AE Data
a. Overall Listing
b. Specific Symptom Listing
c. SAE Listing
d. Subject Deaths

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

3l. Reporting Changes in Study Status

During the funding of this study, any action by an 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 Official within 1 business day of notification.

4. Potential Benefits of Research to Participants and Others

Previous studies with the two treatments (HYP and MM) that will be examined support their efficacy reducing pain. We anticipate based on this previous research that many of the participants will experience significant reductions in their daily pain and other benefits

associated with the treatments. Although we do not anticipate that the education control condition will result in any improvements in the outcome variables studied, previous participants report high levels of satisfaction with this condition, and report that they find the information useful.

To increase the chances that those participants assigned to the control condition will get the most benefits possible out of their participation, they will all be invited to receive one of the two active treatments (their choice) after they complete their final follow-up assessment.
In addition, we anticipate that some of the participants who are initially randomized to one of the active treatments will not benefit from that treatment, and that this may be related to their baseline EEG. Thus, even those who received one of the active treatments will be invited to participate in the other treatment they did not receive.

This will not only maximize the chances that they will obtain pain relief from participation in the study, but will allow us to determine what percentage of participants who do not respond to one of the active treatments respond to the other. Thus, every study participant will have the opportunity to receive at least one of the active treatments being studied.

Sub-Study:
We do not anticipate participants will experience significant reductions in their daily pain or improvement in their sleep quality as a result of participating in the sub-study.

I. Publication of Research Findings

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

J. Importance of Knowledge to Be Gained

Main Study:
The findings from this study will provide important new information that will have positive effects on the lives of Veterans with chronic pain. First, if one or both of the treatments (HYP or MM) is found to be effective, as we anticipate will be the case given previous research and the findings from our pilot work, Veterans with chronic pain will have another effective treatment option for helping them better manage pain.

Second, the findings will provide important new information regarding treatment mechanisms (mediators and moderators) of the treatments studied.

As pointed out by Kazdin,[110, 111] progress in our understanding of treatments has been hampered by the lack of mechanism studies, such as this study, to identify the mechanisms and predictors of treatment outcome. The current study will help address this significant gap.

Sub-Study:

The findings from the sub-study will provide important new information that will inform future treatment and research aimed to improve the lives of Veterans and others living with chronic pain. First, if one or both of the treatments are found to be helpful regarding sleep, Veterans and other individuals with chronic pain will have another effective treatment option for helping them better manage sleep disturbances. Second, the findings will provide new information regarding treatment mechanisms (mediators and moderators) and the interplay between pain and sleep. If our new evidence supports that a focus on sleep will improve pain, future studies – including clinical trials that evaluate non-pharmacological sleep interventions – can build on this work. Presently, sleep is not yet regarded as a primary outcome measurement in chronic pain research,[41] nor is sleep consistently addressed in chronic pain clinical treatment. Our findings can advance the field in an innovative way and, potentially, change the way sleep and pain symptoms are studied and clinically managed.

Poor sleep is gaining recognition as a significant population health problem in its own right, as it has been linked to numerous diseases that create a high societal burden, such as cancer, cardiovascular and autoimmune diseases.[112] While this study will focus on chronic pain, it is also likely that any discoveries related to the tested interventions will be relevant in the management of other chronic diseases. Additionally, understanding how non-pharmacological interventions can be adopted and how they affect confidence in controlling symptoms may be an important approach towards reducing reliance on opioids, sedatives and other medications and reducing the significant risks and societal costs associated with these pharmacological interventions.

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K. Appendix 1: Evaluation Timeline, Main Study

Assessment	Screening	Enrollment: Day 0*	Pre-Treatment (Weeks 1-2)*	Treatment Session #1 (Week 3)	Treatment Session #2 (Week 4)	2-Week Assessment (Weeks 4-5)	Treatment Session #3 (Week 5)	Treatment Session #4 (Week 6)	4-Week Assessment (Weeks 6-7)	Treatment Session #5 (Week 7)	Treatment Session #6 (Week 8)	6-Week Assessment (Weeks 8-9)	Treatment Session #7 (Week 9)	Treatment Session #8 (Week 10)	Post-Treatment (Weeks 11-12)	3 Month Assessment (Weeks 22-23)	6 Month Assessment (Weeks 34-35)
Inclusion/Exclusion Criteria	X																
Informed Consent Form		X															
Cognitive Assessment		X															
Hypnotic and Relaxation Exercise		X															
Baseline Data and Demographic Form		X															
Pain Intensity (Primary Outcome)			X			X			X			X			X	X	X
Secondary Outcomes (e.g. Depression, Anxiety)			X			X			X			X			X	X	X
EEG Data (Mediators: Biological)			X												X		
Mediators: Psychological (e.g. Pain Acceptance, Catastrophizing)			X			X			X			X			X	X	X
Pain Intensity, Comfort Levels				X	X		X	X		X	X		X	X			
Treatment Homework Completion				X	X		X	X		X	X		X	X			
Participant Engagement				X	X		X	X		X	X		X	X			
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X		

* Onset of both enrollment and pre-treatment relative to the onset of treatment may vary given the timing of group sessions