Human Subjects Protocol

VA Puget Sound IRB

An Evaluation of MBSR and CBT for Veterans with Chronic Pain

Lay Title: **I**nvestigating **M**ethods of **P**ain **R**ecovery with **O**utpatient **V**eteran **E**ducation ("IMPROVE")

Funding Agency: VA Office of Rehabilitation Research and Development

Principal Investigator: Tracy Simpson, PhD

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Abstract

Pain is one of the most common reasons Veterans seek health care. Mental health conditions (including PTSD, anxiety, and depression) are estimated to co-occur for 30-50% of Veterans with chronic pain. Mindfulness-Based Stress Reduction (MBSR) and Cognitive Behavioral Therapy for chronic pain (CBT-CP) teach skills intended to enhance functionality and quality of life in the face of chronic pain. The study will recruit and randomize up to 222 Veterans with chronic musculoskeletal pain. One third of these (n=74) will be randomly assigned to the Mindfulness-Based Stress Reduction (MBSR) group, one third of these (n=74) will be randomly assigned to the Cognitive Behavioral Therapy for Chronic Pain (CBT-CP) group, and one third of these will be assigned to Treatment as Usual (TAU). The MBSR and CBT-CP sessions meet by video once a week for 8-weeks, MBSR sessions are 2 hours long per session, and CBT-CP sessions are 1.5 hours long. The **Primary Aim** is to assess if MBSR and CBT-CP each result in greater reductions in the pain interference subscale of the Brief Pain Inventory (BPI) as compared to usual care, from baseline to 6 months post-treatment. The **Secondary Aim** is to evaluate if MBSR and CBT-CP are each superior to usual care in producing improvements in pain severity, treatment satisfaction, and depression.

Measures pertaining to the primary outcome of pain interference will be collected at baseline, at the post-MBSR/CBT-CP time point, and at 6-month post treatment follow-up. In addition, measures of pain intensity, depression, and treatment satisfaction will be applied to more fully characterize the impact of MBSR relative to CBT-CP and usual care. Exploratory analyses will assess if outcomes differ for MBSR and CBT-CP, the impact of the interventions on opioid use and indicators of suicidality, and whether Veteran characteristics assessed at baseline function as treatment moderators. Mixed models will assess whether MBSR, CBT-CP each produce greater reductions in outcome variables from baseline to follow-up compared to usual care. If MBSR and CBT-CP are each shown to be superior to usual care for treatment of chronic pain among Veterans, it would support providing MBSR and CBT-CP for this population.

List of Abbreviations

MBSR – Mindfulness-Based Stress Reduction

CBT-CP – Cognitive Behavioral Therapy for Chronic Pain

CPRS – Computerized Patient Record System (electronic medical record)

PROMIS – Patient-reported Outcome Measures Information System

TAU- Treatment as Usual

VVC- VA Video Connect technology (telehealth video portal)

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Protocol Title: A Randomized Clinical Trial of Group Interventions Compared to Usual Care for Veterans with Chronic Musculoskeletal Pain

1.0 Study Personnel

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2.0 Introduction

Pain is one of the most common reasons for seeking health care among both Veterans[1, 2] and the US population at large.[3] When pain persists for at least 3 months after the initial injury or disease process may have resolved, it is referred to as chronic pain. In the US population, it is estimated that chronic pain affects approximately 100 million American adults – more than the total affected by heart disease, cancer, and diabetes combined.[3] Musculoskeletal pain is the most costly, debilitating, and prevalent pain condition.[2, 4, 5] Chronic pain accounts for nearly 70 million outpatient visits per year in the United States[6] and is associated with lost productivity, medical treatment, and disability payments that result in an estimated $600 billion per year in costs.[7] At least one-third of Veterans report chronic musculoskeletal pain, and rates may be even higher among female Veterans.[2, 5, 8, 9] Chronic musculoskeletal pain is not limited to older Veterans – an analysis of >700,000 OEF/OIF/OND Veterans, found that musculoskeletal disorders affected

56% of the sample[1] and another analysis confirmed that almost 60% have musculoskeletal conditions, such as back pain.[9]

Management of chronic pain is often compounded by other life problems, including medical, psychological, and social difficulties (including disability, substance use, and poverty).[10, 11] Mental health diagnoses (including PTSD, anxiety, and depression) occur in 30-50% of people with chronic pain, and PTSD contributes significantly to the level of distress experienced by Veterans with chronic pain.[12] For Veterans with polytrauma, the overlap of clinical syndromes appears particularly common. One study reported a prevalence of chronic pain of >80% for polytrauma patients, with pain rarely occurring in the absence of PTSD or post-concussive symptoms.[11] As a result, Veterans with chronic pain often experience impairment of occupational, social, and recreational activities, as well as negative mood and increased isolation. When VHA clinicians and decision makers seek guidance from the literature regarding how to treat chronic pain, recognition of the added complexity of pain presentations among Veterans also raises questions about whether clinical trials performed outside the VA can be generalized to care-seeking Veterans.[9]

The recommended VHA strategy for management of chronic pain involves a stepped approach.[13] In the stepped care model, most Veterans are managed in primary care, where pharmacological and non-pharmacological treatments are provided as indicated. Although opioids are sometimes prescribed for chronic pain, a recent RCT compared opioids to non-steroidal anti-inflammatory drugs among Veterans with chronic pain and found that outcomes for those treated with opioids were not superior to those treated with nonopioid medications.[14] Prescribing opioids entails risks, including addiction, overdose, fractures, cardiovascular events, bowel obstruction, and cognitive impairment.[10, 15, 16] Because of these risks, VA Clinical Practice Guidelines recommend against the initiation of opioids for chronic pain and instead recommend the use of self-management strategies and other non-pharmacological treatments, such as Cognitive Behavioral Therapy (CBT).[10] Institute of Medicine guidelines also recommend use of non-pharmacological approaches as standard of care for chronic pain before prescribing opioids.[17] Similarly, the American College of Physicians guidelines for treatment of chronic low back pain recommend non-pharmacological therapies as initial treatment, and list CBT and Mindfulness-Based Stress Reduction (MBSR) as options that should be offered as standard care.[18]

Psychological interventions have been advocated as non-pharmacological therapies for chronic pain based on evidence that psychological processes play key roles in pain outcomes. Depression, pain catastrophizing, and

anxiety are positively correlated with pain severity and pain disability in cross-sectional studies, and longitudinal studies indicate that reductions in these factors are associated with improved pain severity and disability.[12] For example, a clinical trial involving 250 Veterans with chronic pain treated with a stepped care strategy demonstrated that the strongest predictor of improvement in pain severity, interference, and disability was the change in depression score.[19] Two categories of psychological interventions for chronic pain are Mindfulness-Based Interventions (such as MBSR) and CBT. Although both MBIs[20] and CBT[21, 22] are increasingly available for chronic pain, there have been few adequately designed studies of MBIs for chronic pain, and although the broader research base on CBT for chronic pain indicates benefit, [21] there is limited research on clinical outcomes using the format of CBT for chronic pain (termed CBT-CP) disseminated by VA.[23] Formal collection of additional data by VHA in the context of a clinical trial comparing outcomes of CBT and MBSR to usual care, and performing exploratory analyses comparing outcomes for each active intervention, would help to guide clinical care for Veterans with chronic pain in the future.

Mindfulness-Based Interventions (MBIs) such as Mindfulness-Based Stress Reduction (MBSR) emphasize patient education and self-management, and foster the ability to attend to thoughts, emotions, and bodily sensations with an attitude of curiosity, openness, acceptance, and love.[8] Such an attitudinal shift has been theorized to promote cognitive and behavioral changes, and to foster more adaptive responses to stress and pain.[9] There is evidence that MBIs also influence the key components of the biopsychosocial model: biological (e.g. the stress response), psychological (e.g. anxiety about symptoms, interpretations of symptoms), and social (e.g. engagement in health care/self-care activities and social support).[8,10,11] MBIs can be considered an integrative approach, because of their potential to foster improvement across multiple domains of health,[11-14] and thus may be particularly well suited to the health concerns of GW Veterans. Participation in an MBI can be framed as teaching a person a life skill, the benefits of which can grow over time.[12] MBSR teaches self-care practices (mindfulness meditation) that participants are encouraged to utilize on a regular basis after finishing the course (and uptake of these practices has been shown to occur at a high rate; at least 75% report using mindfulness techniques in daily life at follow-up ranging from 6-48 months).[9,15]

MBIs have been applied to the hallmark of symptoms of chronic musculoskeletal pain; a brief summary of the effect of MBIs on these cardinal symptoms of chronic musculoskeletal pain is provided below.

A meta-analysis of acceptance-based approaches for chronic pain found medium effects for pain intensity (d=0.48).[14] Another review of 16 trials of MBIs showed reductions in pain intensity in 6 of 8 randomized controlled trials (RCTs), with medium effect sizes.[12] Furthermore, when analyses were limited to samples involving clinical pain, 9 of 11 studies showed reductions in pain intensity.[12] There have been few comparisons of MBSR to an active control. One non-randomized pilot study (n=50) compared MBSR to CBT and found a larger effect size in favor of MBSR (d=0.87).[16] Another non-randomized study (n=58) compared MBSR to a social support group and found medium effects in favor of MBSR for sensory/affective pain, and large effects (d=1.10) using a pain visual analogue scale.[17] The findings of prior pilots – subject to the limitations of small sample sizes – are generally consistent with the data from our small pilot study among GW Veterans (n=55), which showed greater reductions in pain severity after MBSR as compared to usual care (d=0.66).

One mechanism hypothesized to account for reduced pain is that enhanced mindfulness leads to 'uncoupling' of the cognitive and emotional elements from the sensory experience of chronic pain, which results in decreased distress and suffering[18]; it has been proposed that the affective component of pain can be distinguished from pain intensity, and that the affective component can be differentially targeted[19]. Data from both correlational and experimental studies performed in chronic pain populations suggest that enhanced mindfulness is associated with reduced pain intensity ratings.[12,20,21] Studies of healthy volunteers also support reduced pain intensity associated with MBIs. One study found that three days of mindfulness meditation training led to reduced pain intensity ratings following electrical stimuli[22] and another study showed that three days of mindfulness training was superior to guided imagery in increasing pain tolerance to the cold pressor test.[22] Other research has found that anxiety decreases pain threshold and lowers pain tolerance.[23] Thus, interventions that reduce anxiety would be expected to lead to reductions in pain severity.

Cognitive Behavioral Therapy (CBT) is the most widely used non-pharmacologic intervention for chronic pain[21] and a version of CBT specifically addressing chronic pain (CBT-CP) has been developed for use in VA with Veterans.[23] Fundamentally, CBT is an approach that seeks to

ameliorate dysfunctional relationships between an individual's thoughts, feelings, and behaviors to improve functioning and quality of life. Evidence supports use of CBT as an intervention for chronic pain. A Cochrane review of psychological therapies for chronic pain found that there were positive effects on pain-related disability and catastrophizing compared with active controls,[21] and another recent systematic review and meta-analysis of CBT for low back pain involving 23 studies found that CBT was superior to guideline-based active treatment in improving pain and disability at both short and long-term follow-up.[24]

We will not be including any vulnerable populations in our research, except for pregnant women. There is no scientifically supported or theoretical reason to believe that participation in the MBSR or CBT-CP group, or other study procedures, would pose special risk to a pregnant woman or her fetus. Given the reasons that are supported for believing participation in either of these groups could provide benefit to a pregnant woman, we will not exclude this population (although we are not targeting them specifically with any recruitment materials).

3.0 Objectives

The Primary Aim of this study is to determine whether MBSR and CBT-CP each result in greater reductions in the pain interference subscale of the Brief Pain Inventory (BPI) as compared to usual care, from baseline to 6 months post-treatment for Veterans with Chronic Musculoskeletal Pain.

Hypothesis: Veterans with chronic pain randomized to each active intervention (MBSR or CBT-CP) will report changes in BPI pain interference that are each superior to usual care, from baseline to 6-month follow-up.

Secondary Aim: Evaluate if MBSR and CBT-CP are each superior to usual care in producing improvements in pain severity, treatment satisfaction, and depression. **Exploratory Aim 1:** Evaluate whether outcomes for patients randomized to MBSR and CBT-CP differ for changes in pain interference, pain severity, depression, and treatment satisfaction. **Exploratory Aim 2:** Evaluate the impact of MBSR and CBT-CP on utilization of opioid analgesics and markers of suicidality. **Exploratory Aim 3:** Evaluate moderators of response to MBSR and CBT-CP to lay the groundwork for identifying Veterans more likely to succeed in one or the other treatment. Potential moderators assessed will include: age,

gender, baseline depressive symptoms, anxiety sensitivity, and pain catastrophizing

4.0 Resources and Personnel

The study procedures will take place at VA Puget Sound, Seattle Division, executed by the IMPROVE study team:

Tracy Simpson, PhD (Principal Investigator): Dr. Simpson will have overall responsibility for the conduct and performance of the study. She will take the lead on recruitment, as well as the organization, quality control and oversight of the MBSR courses. She will have primary responsibility for supervision of the project manager and research coordinator and will also be responsible for human subjects regulatory requirements. She will oversee all aspects of data collection, data quality control, and she will take the lead on manuscript preparation. Dr. Simpson will have access to PHI, and she can obtain informed consent if the Project Manager and Research Coordinator are not available to do so.

Lisa Glynn, PhD (Co-Investigator): Dr. Glynn will be actively involved in all phases of the project, including planning, recruitment, and implementation. She will have primary responsibility for troubleshooting any issues with the CBT-CP classes or group leaders. Dr. Glynn will participate in all manuscript preparation. Dr. Glynn will have access to PHI.

Anna Korpak, PhD (Co-investigator): Dr. Korpak will be responsible for statistical analyses. She will supervise the work of the analyst and will work with the investigative team to design data collection and extraction procedure for administrative data and oversee quantitative assessments of implementation. Dr. Korpak will participate in all manuscript preparation. Dr. Korpak will have access to PHI.

Meghan Storms, MSW, LICSW (Project Manager): Ms. Storms will be the Project Manager and will work closely with the principal investigators to provide day to day oversight of the study activities as well as supervision of the research assistant. She will monitor the day-to-day activities of the project, including tracking the progress of approvals needed during the planning phase and overseeing recruitment and randomization. She will directly interface with the MBSR and CBT-CP clinical programs to troubleshoot any issues that arise. Ms. Storms will participate in collection of study measures and assist in performing fidelity coding. She has significant experience in recruitment and assessment, using methodology

similar to that described in the current project, under the supervision of Dr. Simpson . She will help manage IRB materials, and will work to help gain the necessary approvals necessary to implement the project. She will be involved in the creation and management of the necessary databases for the study, under the supervision of Drs. Simpson and Korpak and the data analyst. Ms. Storms may assist in manuscript preparation. The Project Manager will have access to PHI and obtain informed consent.

Rhonda Williams, PhD (Data Safety Monitor): The PI and study team will submit periodic reports to the Data Safety Monitor. The Data Safety Monitor will review the reasons for study termination for any participant who discontinues the study before completion, and any adverse events that take place.

Kimberly Moore (Research Coordinator): The Research Coordinator will work closely with the investigators and administer the study assessments, under supervision of the Project Manager and PI. The study coordinator will also perform initial telephone screens and assist in recruitment and scheduling. She will organize study materials and files, carry out data management and cleaning in consultation with Dr. Simpson and the co-investigators. The Research Coordinator will have access to PHI and obtain informed consent.

Consultant

Daniel Cherkin, PhD is an Emeritus Scientific Investigator at Kaiser Permanente Washington Health Research Institute. He is a national expert on non-pharmacologic approaches to managing chronic pain. He has previously conducted more than 10 clinical trials involving pain management, including a large trial that compared MBSR to CBT. He will provide advice and input as needed during all phases of the study, including implementation, data collection and analysis phases.

5.0 Study Procedures

5.1 Study Design

The proposed study is a three-arm comparative effectiveness trial that will randomly assign Veterans with chronic musculoskeletal pain to MBSR, CBT for chronic pain (CBT-CP) or usual care to assess the effectiveness of MBSR or CBT-CP for Veterans with chronic musculoskeletal pain. Veterans with chronic

musculoskeletal pain (N =222) will be randomized to either 8 weeks of MBSR (n =74), 8 weeks of CBT-CP (n =74) or usual care (n=74), and will complete assessments at baseline, immediately post-treatment and at 6-month post-treatment. Randomization will be performed through REDCap, and stratified by sex assigned at birth and pain severity score. Sessions will be audio recorded using both Philips DPM 8000 recorders and OBS Studio software. Fidelity coding from audio recordings will evaluate protocol adherence for both MBSR and CBT-CP.

A comprehensive outline of the various data collection tools/measured to be administered at each of the three assessments is provided in **Section 5.5 Study Evaluations**.

Risk and Benefit: The risks for this study involve the potential for psychological distress associated with collection of self-report data, and the possibility that undergoing either the MBSR class or CBT-CP could be stressful and worsen symptoms. There is also a risk of confidentiality due to the group nature of MBSR and of CBT-CP, and the delivery of these groups by the VVC internet based platform; those who are unwilling to be in an MBSR class or CBT-CP group that is being audiotaped will need to seek other services. Further, there is a risk that MBSR and CBT-CP will not be efficacious for some individuals. We plan to educate patients about the possible risks and benefits prior to study enrollment by providing a thorough orientation to the research and an overview of each intervention prior to giving informed consent. Potential benefits for those randomized to either condition may take the form of reduced chronic musculoskeletal pain symptoms, and increased health-related quality of life. Veterans' families may also benefit as a result of the shift in emotional state. However, a participant may not benefit directly from participation in the study. Information gained in the study may be of benefit in the future to persons with chronic musculoskeletal pain. Specific measures for minimizing risk are outlined below.

Procedures to Minimize Risk to Subjects and Protect Confidentiality:

1) Group sessions will include reminders to patients that they can choose what they will and will not do, and that it can be flexible in meeting an individual's needs (e.g. in MBSR a patient may meditate with eyes open, choose not to lie down, shorten the meditation time, choose not to practice some of the yoga postures, etc., while in CBT-CP a patient may choose to share more or less of their personal material with the group, etc.)

2) If a research subject experiences distress or worsening of his/her condition, we will consult the individual's primary provider for assistance. If the condition involves a psychiatric emergency, we will utilize the psychiatric emergency services available in order to help stabilize the Veteran's condition. If needed, the Veteran can be admitted to a psychiatric inpatient unit for further care. The Veteran will not bear any additional costs for care.
3) Any decision to withdraw from the protocol due to suicidality, depression, anxiety or increased PTSD symptoms will be made on a case by case basis, with input from the Veteran and his/her mental health provider. If there is clear evidence of decompensation or functional regression that is considered likely to lead to unsafe behavior, the Veteran will be advised that another course of treatment could be better for them, and the study staff will assist them in making that change.
4) *Confidentiality:* We plan to maintain the confidentiality of patient records as described below in section 7.0. If at any point in the recruitment process or during the course of the study, a participate appears to be at risk to themselves or others we will initiate a series of harm-prevention steps according to our protocol for severe distress, If necessary, a referral will be made to the appropriate agency. Any serious adverse events will be immediately reported to the IRB and the Data Safety Monitor.
5) If some participants experience unexpected levels of distress following participation in the research, we will take the following steps to minimize this possibility: We will state clearly in the consent forms that participation in the research study may involve discussing details about traumatic events and about symptoms. In addition, at the beginning and end of each of the assessment sessions, we will provide participants with time to ask questions. We will inform participants, both prior to the initial screening questions on the phone and prior to beginning treatment, that some individuals do experience increases in symptoms after discussing aspects of the traumatic experience and that if these symptoms do not return to their prior levels within a few days, participants are encouraged to call the Investigative Team. We will provide all participants with a study phone number they can use to alert us if they are experiencing distress. The phones will be checked daily for messages and distressed participants will be called the same day (for calls made during business hours or the next business day for after hour calls).
6) If any point in the study during the assessments or treatment sessions a participant endorses suicidality or homicidality, the group instructor(s) will notify the PI (Dr. Simpson), or Dr. Glynn, who will contact the patient. Drs. Simpson and Glynn are licensed Clinical Psychologists with extensive experience in assessment and treatment of Veterans. Should there be concern

about risk of harm, a clinical interview will be conducted to assess level of risk and need for intervention. Participants who indicate acute suicidality or homicidality including a plan will be immediately referred for VA mental health services. It is important to note that in more than 7 years of conducting clinical research, we have never had a participant unwilling to accept referral for suicidality and have never had to make an involuntary admission or report.

7) All data and other information in this study will be maintained using procedures that preserve confidentiality, but will not be anonymous due to the longitudinal nature of participation. Detailed contact information as well as responses to study questionnaires will be collected at all assessments. Due to the sensitive nature of the study, e.g., the assessment of PTSD, depression, alcohol, and substance use, several steps will be in place for data collection and storage to protect participant confidentiality. First, a unique ID code (PIN) is given to each participant, serving to link their information together in the on-line database. No names or identifying information will ever be stored in the on-line database or data files that will later be used for statistical analyses. All information will be secured in a restricted VA network folder.

8) Participants' names, addresses, and phone numbers will be accessible to project staff in order to engage in telephone contacts and to schedule study visits with participants. However, these data will be kept separate from actual study data and from study ID codes. These data will not be shared with individuals who are not directly involved in the study. All participant data will be coded in a way that does not contain any participant identifiers. The data safety and monitoring plan is described below.

9) As per VA regulations, each participant will have their participation in the study documented in the Computerized Patient Record System (CPRS; i.e., enrollment as well as completion or early termination). No assessment information will be included. Access to VA medical records is strictly controlled and only VA affiliated individuals who have undergone extensive background checks and have either clinical privileges or clinical research access may enter the system

5.2 Recruitment Methods

The recruitment goal is 222 total.

Similar to a previous trial that compared pain management strategies among Veterans, we will include Veterans with musculoskeletal pain involving the spine, hips and extremities.[25] Prior studies indicate that among

people with musculoskeletal pain, the lower back, legs, hips and knees are the most common sites.[25]

Recruitment will occur via the following mechanisms: a). IRB- approved Informational flyers distributed at both campuses on VA Puget Sound research kiosks, hospital health fairs, hallway information tables and bulletin boards; at presentations by investigators; and via emails to clinicians and staff; b) Provider referral from VA outpatient clinics as a result of informational inservices and email announcements for VA providers, which will include Primary Care, Specialty Care (e.g., Rheumatology), Rehabilitation Medicine and the Pain Service clinics, Mental Health, and others. Providers will be given detailed information about study inclusion/exclusion criteria, recruitment process, and treatment goals. If needed to increase recruitment, study staff may also attend team meetings in relevant clinics to increase awareness of the study. Providers can refer Veterans by either alerting study staff in CPRS, via an encrypted VA email or TEAMS, via phone call, or in-person. We will ask providers to include both the contact information of the potential participant as well as confirmation that the Veteran verbally agreed to be contacted by the research study; c) Sending informational letters to patients referred to MBSR or the Pain Service for clinical care, which ask if they are interested in participating in the study; d) Sending letters to Veterans who have received care at VA Puget Sound who have had a clinical encounter with a musculoskeletal disorder ICD10 code identified via a VINCI data pull: M05-M19,M21-M25,M30-M36, M40-M43, M45-M49, M50-M54, M60-M63, M65-M67,M70-M79, L40.5. We will also use VINCI to eliminate from this list Veterans with diagnoses that would make them ineligible- Dementia, Schizophrenia, Borderline Personality Disorder or Anti-Social Personality Disorder. If the Veteran does not respond to the letter, he/she may receive up to 3 phone calls about the study to assess level of interest. (We have two recruitment letters for this study- one prompting the Veterans to call us if interested, and one stating that the Veteran may receive up to 3 calls. We have found in the past that study interest wanes over time, so we have given ourselves the flexibility to use an opt-out method with calling if necessary for later study Cohorts.) The strategy of sending letters to patients with pain codes has been highly effective in a prior trial conducted by our team; this has met with IRB approval. Veterans who are referred to the trial or respond to the letter or phone call indicating interest will undergo telephone assessment of inclusion/exclusion criteria. If eligible by telephone screening, consent forms will be mailed to the Veteran, and a phone appointment will be scheduled to consent the Veteran by phone. The

Veteran will return these signed consents in a prepaid envelope. Once they are received by study staff, a phone baseline visit will be scheduled to fully assess eligibility and obtain informed consent. Using this method, in our trial of MBSR for Gulf War Illness (see preliminary studies) approximately 4% of Veterans with chronic pain diagnoses who received a letter followed by a telephone call were successfully randomized. We plan to duplicate this method of recruitment for the proposed trial. Extrapolating to this proposal, we estimate that sending out 5,550 letters and making 5,550 telephone calls over 27 months of recruitment will result in successful recruitment of at least 222 Veterans with chronic musculoskeletal pain. Our experience has shown us that this number of phone calls takes approximately 2 hours of staff time per day. Thus, the recruitment goals are very feasible using these methods. As shown below in Table 1, chronic pain is very common; we expect that the large number of Veterans at our site potentially eligible for enrollment will lead to an adequate number of Veteran enrollees.

Conditions Included	No. of Patients With 1+ Outpatient Visits and 1+ Pain Musculoskeletal Condition
Musculoskeletal conditions included: ICD10 codes: M05-M19,M21-M25,M30-M36, M40-M43, M45-M49, M50-M54, M60-M63, M65-M67,M70-M79, L40.5 (arthropathies, osteoarthritis, other joint disorders, connective tissue disorders, dorsopathies, spondylopathies, myopathies, disorders of synovium and tendons, shoulder lesions, bursopathies, soft tissue disorders, arthropathic psoriasis)	41,033

Participants will paid $45 for baseline, $60 for the post-assessment, and $75 for the 6-month after intervention follow-ups. The maximum remuneration is $180 if randomized. Subject payments will be processed within a week of the assessment to which they apply.

5.3 Informed Consent Procedures

We request a waiver of informed consent for recruitment/screening purposes only. This will allow us to create recruitment mailing lists that can target the most-likely-to-be-eligible populations, and not waste resources

and other patients' time advertising the study to patients who won't be eligible to participate.

We will obtain informed consent prior to beginning any data collection study procedures that will be maintained for analysis. Informed consent will take place prior to the appointment that includes the subject's final eligibility screening and (if still eligible) baseline assessments. The study coordinator, project manager, or other approved researcher will mail or send by docusign interested Veterans consent forms, and obtain informed consent over the phone. We will not enroll anyone with impaired decision-making ability who requires the use of a legally authorized representative.

All study personnel will be trained in human subjects protections requirements as required by R&D (e.g. Privacy Policy & HIPAA training), and the PI or Project Manager will train any other study team members how to appropriately obtain informed consent as needed.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria: All participants must meet criteria for chronic musculoskeletal pain, defined as: 1) musculoskeletal pain of low back, cervical spine, or extremities (hip, knee, or shoulder) 2) pain for at least 3 months; and 3) Pain severity (worst or average pain score ≥ 4)(i.e., score of 4 or greater on BPI items 3 or 5) and average pain interference (BPI items 9A-9G) rated ≥ 3 of 10 over prior week, as measured using the Brief Pain Inventory (BPI).19, 37, 70

Exclusion criteria: At phone screen, researchers will check medical records for a diagnosis of schizophrenia, dementia, antisocial personality disorder, or borderline personality disorder. Researchers will also exclude anyone with a flag in their medical record that indicates they are at high risk of suicide or homicide. Veterans will also be excluded if there is mention of psychotic symptoms in any recent treatment notes, or if there is an inpatient admission for psychiatric reasons in the past month. Veterans will be excluded if they endorse attempts to harm themselves or someone else in the past 30 days. Veterans will be excluded if they endorse severe medical conditions that would limit participation (e.g., Class III or IV heart failure) or pending back surgery that would occur during study participation. Additional exclusion criteria include prior formal participation in MBSR or CBT-CP, and

lack of access to internet and the technology needed to participate in a telehealth group.

At baseline, the MINI psychiatric interview[26] will determine psychiatric exclusion criteria: 1) uncontrolled psychotic disorder; 2) current bipolar affective disorder with mania; 3) moderate or higher suicide risk 4) use of drugs (besides marijuana or alcohol) more than once in the past 3 months. We will include subjects with Alcohol Use Disorder (AUD; defined by the MINI) but exclude those for whom alcohol use poses a safety threat (defined as current drinking and a past-year history of alcohol-related seizures or delirium tremens). We will also include those with Opioid Use Disorder (OUD) and other Substance Use Disorder (SUD; each defined by the MINI). Medication, supportive individual or group counseling, case management, and self-help programs will be allowed and assessed as potential covariates.

5.5 Study Evaluations

Study Construct/Variables	Study Phase	Measurement Scale	Domain/Purpose
Inclusion/Exclusion Criteria (eligibility Evaluation)			
MINI International Neuropsychiatric Interview V-5 (DSM-V version) (covers suicidality, mania, alcohol and drug abuse, and psychosis)	B	dichotomous	Sample description, exclusion, SUD classification (possible moderator)
Brief Pain Inventory (BPI) questions 3, 5, and 7a-7g, modified to past week	Phone screen		exclusion
Medical history interview (seizures, DT's)	Phone screen	dichotomous	exclusion
Sample Description Data (to describe subject population)			
Demographic information	B	dichotomous	Sample description, blocking (sex assigned at birth); moderators
Life Events Checklist (LEC)	B	dichotomous	Sample description; Trauma history
Rome IV – IBS	B, 6	Dichotomous	Sample description (indicates current symptoms of IBS)
Anxiety Sensitivity Index	B	Continuous	Sample description,

			moderator
Tracking			
Contact form	B, P, 6		retention
Primary Outcomes			
Pain interference subscale of the Brief Pain Inventory (BPI)	B, P, 6	continuous	Pain interference / physical functioning
Secondary Outcomes			
Pain severity subscale of the Brief Pain Inventory (BPI)	B, P, 6	continuous	Pain intensity
Analgesic use and Underlying pain	B, P, 6	Continuous	Underlying pain intensity
PHQ-9 (depression)	B, P, 6	continuous	Depressive symptoms
PTSD Checklist (Civilian version) (PCL-5)	B, P, 6	continuous	PTSD symptoms
SF-12 (Mental and Physical Component Summary Scores)	B, P, 6	continuous	Sample description; Health-related quality of life (HRQOL)
Five-Facet Mindfulness Questionnaire (FFMQ-15) SF	B, P, 6	continuous	Dispositional mindfulness, and mindfulness subscales: Observing, Describing, Acting with Awareness, Nonjudging and Nonreactivity to inner experiences; potential mediator
Coping Strategies Questionnaire	B, P, 6		Mediator of pain catastrophizing
NIH Patient Reported Outcome Measures Information System (PROMIS) for Alcohol Use and Negative Consequences, short form	B, P, 6	continuous	Substance Use Disorder (SUD) symptom severity for alcohol

NIH Patient Reported Outcome Measures Information System (PROMIS) for Gastrointestinal Distress: Belly Pain, Diarrhea, Constipation, Gas & Bloating	B, P, 6		Gastrointestinal Symptoms, including IBS
Drug Abuse Screening Test (DAST) for drug use other than alcohol or tobacco	B, P, 6	categorical & continuous	Cannabis Use
Client Satisfaction Questionnaire (CSQ-8)	P, 6	continuous	Satisfaction
OME Opioid Use Tracking	B, P, 6		Opioid Use
VA mental health care			
VINCI data pull			Opioid use, prescription sleep medication use, other care (visits for pain, pain-related procedures), markers of suicidality (high-risk suicide flag, psychiatric admissions, deaths due to suicide)
CPRS review for engagement in other treatments	8-months post-baseline	dichotomous	Other care received during study

Full text of measures in appendix.

5.6 Data Analysis

Sample size calculations were determined using Stata statistical software.[27] The study is powered for the overall omnibus F test used in the Fisher protected least significant difference test. The study is also powered for the ability to detect at least a moderate effect size between each pairwise sub-test (MBSR/usual care, CBT-CP/usual care, and as an exploratory aim MBSR/CBT-CP), which will be performed if the omnibus test is significant. The study is powered to detect a difference of Cohen's d ≥ 0.50 between treatment arms (which represents a change of 1.05 points on the BPI pain interference subscale, based on data from Veterans with chronic pain).[28] Sample size calculations for the omnibus ANOVA

assume a 1:1:1 treatment allocation, desired power of 80%, 2-tailed α = 0.05, and estimate that BPI pain interference scores will be 1.05 points lower in both the MBSR and CBT-CP arms compared to usual care (using a SD=2.1 for BPI scores).[28] Using these parameters, 59 patients per arm of the study are needed (N=177). The sample size was inflated to 222 to account for possible attrition. Sample size estimates for comparisons between subtests (e.g., MBSR/usual care, CBT-CP/usual care) were also calculated using t-tests. For a desired power of 80% and a 2-tailed α = 0.05, 64 patients for each of the three arms of the study are required (N = 192). Further inflation of this sample size by 15% to account for attrition or the effects of clustering resulted in a total of 222 patients. Detecting an effect size of Cohen's d ≥ 0.50 has been advocated as a reasonable threshold of clinical significance when assessing patient reported outcomes, including pain and physical and emotional functioning.[29] In our pilot study of MBSR for Veterans with Gulf War illness (preliminary studies) the intraclass correlation for measures of pain was ρ= 0.00 at follow-up, indicating that we likely do not need to account for clustering in our sample size estimates. To provide 80% power if ICC = 0.02 is found, inflation of the sample size by 6% would be required; the inflation of the sample size by 15% was performed as a conservative measure to account for possible clustering or attrition. The sample size required per arm of the study for treatment comparison (at 80% and 90% power) is presented across a range of effect sizes in Table 2.

Table 2. Effect size (d)	two-tailed α = 0.05, β = 0.20	two-tailed α = 0.05, β = 0.10
0.40	100	133
0.50	64	86
0.60	45	60
0.70	34	44

Data will be analyzed following the completion of the final assessments of the last subject cohort, which is projected to take place in the last six months of Year Three of the study. The dataset will be analyzed by Dr. Korpak.

5.7 Withdrawal of Subjects

If the study subject becomes a threat to the safety of others in his or her treatment group, or to the research team, that subject's participation in the study will be termintated, and they will be withdrawn from the research without their consent.

If a study subject demonstrates behavior that repeatedly violates the community guidelines of their treatment group, so much so that they actively prevent the group from being able to achieve the day's curriculum or they create a hostile environment for other group members or research staff, that subject's participation in the groups will be terminated, and the PIs will determine if they can continue to participate in the study and complete the research assessments with study staff.

If a subject wishes to withdraw from the study before all procedures are complete, he or she simply needs to notify the study's project manager, study coordinator, or other study team member by phone or in person that he or she no longer wishes to participate, and the subject with be withdrawn from the study and no longer contacted regarding study procedures. A primary study contact number will be provided to each participant, so they know how to reach the study team to request early withdrawal (or for any other questions).

6.0 Reporting

Safety Monitor: Rhonda Williams, PhD, a clinical psychologist based at the Seattle division of VA Puget Sound, will serve as the unbiased safety monitor for the study. Dr. Williams has extensive experience in clinical psychology. She is outside of the key study investigators and she will review any adverse or unanticipated events and provide an unbiased written report to the PI's within 10 calendar days. She will assess whether there is a relationship between the adverse or unanticipated event and the study procedures, and will indicate whether they concur with the details of the report provided by the PI's. Any events deemed by the safety monitor team or the PI's to be possibly related to the study procedures will be promptly forwarded to the VA Puget Sound IRB Office of Risk Management.

When an unexpected serious adverse event occurs, we will log it in an "Adverse Events & Problems" log, to be used for providing reports to the Data Safety Monitor, in addition to submitting a report to the IRB within 5 days as required. All other adverse events, problems, and protocol deviations will be logged and reported to the Data Safety Monitor and the IRB with annual reviews.

At the midpoint of the study, the data monitor would then analyze whether significantly greater adverse events occur in one arm of the study, which might warrant stopping the study.

7.0 Privacy and Confidentiality

The study will obtain Protected Health Information by collecting data (e.g. medications and other treatment relevant to the symptoms evaluated for the study) from the subjects' CPRS records, as well as contact information (PII) for following up with subjects regarding ongoing study procedures. Health information will also be collected through the questionnaires and interviews. This health information will be maintained as de-identified study data and will not be disclosed to unauthorized entities. We will be obtaining a Certificate of Confidentiality for this study, as we ask about substance use.

Because we are using VVC for group delivery, and internet based platform, we will warn participants of potential risks to confidentiality of this delivery method, do visual confirmations of group participants, and lock group rooms to prevent intrusions.

A password-protected crosswalk will be maintained to link identifying information (full names and last 4 SSN) to study subjects' unique study IDs (e.g. 695-001, 695-002, 695-003….695-308). All files containing study data, hard copy or electronic, will include only the subject's study ID so that no data can be linked directly to an individual. All study team members, as VA employees (WOC or otherwise) are required to undergo Privacy & HIPAA training as well as VA Privacy and Information Security Awareness and Rules of Behavior. Any non-VA-affiliated study team members will be required to undergo equivalent training. Only study team members will have access to the electronic study folder, located on the R: drive on the VA server. Hard copy data and consent forms will be stored in locked filing cabinets in the offices of the PI and/or the Project Manager.

8.0 Communication Plan

N/A, this is not a multi-site research project.

9.0 Information Security and Data Storage/Movement

Consent forms and other hard copy documents with identifying information (e.g. emergency contact page) will be filed in separate hanging folders from

any documents with study IDs and study data on them, so that the identifying information cannot be linked to the corresponding data.

Data from self-report measures will be collected through REDCap. The administering researcher will open the REDCap database from the study folder on a VA computer, and then ask the participants the questionnaires over the phone and record their answers directly into REDCap. Each set of questionnaires will be linked to subjects through their study IDs or other unique identifiers (no PII recorded in REDCap), and these identifiers will be recorded and tracked by the study team. When needed, a report or query of these outcome/response data from these questionnaires will be generated from REDCap and saved to the study folder.

Data pertaining to medication usage and other treatment received during the subject's study enrollment period will be gathered from VINCI and saved to the study folder. This data will be linked to participants by Study ID only.

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