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Protocol Name: Learning to Apply Mindfulness to Pain (LAMP)

Multisite RCT

Official grant title: Testing two scalable, Veteran-centric mindfulness-based interventions for chronic musculoskeletal pain: A pragmatic, multisite trial

Short title: Learning to Apply Mindfulness to Pain (LAMP)

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Principal Investigator/Study Chair: Diana J. Burgess, PhD

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Abstract

There is a pressing need to provide effective, non-pharmacological treatment to the vast number of Veterans with chronic pain. Mindfulness-Based Interventions (MBIs) are one such approach shown to be effective for treating chronic pain and comorbid conditions (e.g., PTSD, insomnia, depression, and substance abuse). However, the predominant MBI offered in the Veterans Health Administration (VHA) and other health care systems, Mindfulness-Based Stress Reduction (MBSR), has features that pose significant implementation barriers, at the patient- and organizational-levels.

The long-term goal of this two-phase project is to reduce chronic pain and co-morbid conditions among Veterans, through scalable, non-pharmacologic evidence-based strategies that are "Veteran-Centric," designed to optimize engagement, adherence and sustainability, and are deliverable to large numbers of Veterans. The current protocol describes Phase 2. We will conduct a 4-site 3-arm Pragmatic Clinical Trial (PCT) (N = up to 950) to test effectiveness of Mobile+Group and Mobile MBIs compared to usual practice. Effectiveness will be assessed by pain severity and functioning over the 12-month follow-up (Brief Pain Inventory total score). We will test the following primary hypotheses: (1) Mobile MBIs will be more effective at improving chronic pain (as measured by BPI change over the 12-month follow-up period) compared to usual practice, (2) Mobile+Group MBIs will be more effective at improving chronic pain (as measured by BPI change over the 12-month follow-up period) compared to usual practice, and (3) Mobile+Group MBIs will be more effective at improving chronic pain (as measured by BPI change over the 12-month follow-up period) compared to Mobile MBIs without the group component. We will test the following secondary hypotheses: (1) Comparison of intervention group with secondary outcomes listed below, and (2) primary and secondary hypotheses comparisons will be confirmed in gender-specific strata. The primary outcome will be measured as change in BPI total score over the 12-month follow-up period. Secondary outcomes will include measures captured in electronic health records (EHRs) (e.g., medication prescription/refills, health care visits for pain management), as well as patient-reported measures related to pain, comorbid mental health conditions and function, expected mediators of treatment effects, patient satisfaction, and adverse effects. These outcomes will be assessed at 10 weeks, 6 months and 12 months. Implementation data will be collected and described, using the guided Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

List of Abbreviations

AE	Adverse Event
ATO	Authority to Operate
BAA	Business Associate Agreement
BPI	Brief Pain Inventory
DoD	Department of Defense
CBT	Cognitive Behavioral Therapy
CCDOR	Center for Chronic Disease Outcomes Research
CDEs	Common Data Elements
CDW	Corporate Data Warehouse
CIH	Complementary and Integrative Health
COIN	Center of Innovation
COM-B	Capability, Opportunity, Motivation, and Behavior model
CONSORT	Consolidated Standards of Reporting Trials
DART	Data Access Request Tracker
DSM-V	Diagnostic and Statistical Manual version 5
DSMB	Data Safety Monitoring Board
EHR	Electronic Health Record
FFMQ	Five Facet Mindfulness Questionnaire
HCS	Healthcare System
HIPAA	Health Insurance Portability and Accountability Act
HSR&D	Health Services Research & Development
ICD 10	International Statistical Classification of Disease and Related Health Problems version 10
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IRM	Information Resource Management
LAMP	Learning to Apply Mindfulness to Pain
MBI	Mindfulness-Based Intervention
MBSR	Mindfulness-Based Stress Reduction
ME	Morphine-Equivalent
MSK	Musculoskeletal
MST	Military Sexual Trauma
MVAHCS	Minneapolis VA Healthcare System
NDS	National Data Services
NIH	National Institutes of Health
OEF	Operation Enduring Freedom - Afghanistan
OIF	Operation Iraqi Freedom
OPCC&CT	Office of Patient Centered Care & Cultural Transformation
ORD	Office of Research and Development
PCT	Pragmatic Clinical Trial
PEG	Pain intensity, Enjoyment of life, General activity scale
PHI	Protected Health Information

PIV	Personal Identity Verification
PMC3	Pain Management Collaboratory Coordinating Center
PMOP	Pain Management, Opioid Safety, Prescription Drug Monitoring Program
PRECIS	PRagmatic-Explanatory Continuum Indicator Summary
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-Traumatic Stress Disorder
PTSD PCL	PTSD checklist
RAP	Rapid Assessment Process
RCT	Randomized Controlled Trial
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance
SAE	Serious Adverse Event
SOTA	VA HSR&D State of the Art conference
SUD	Substance Use Disorder
TAU	Treatment as Usual
UC	Usual Care
UAP	Unanticipated Problem
UMN	University of Minnesota
VA	Veterans Affairs
VAHCS	VA Healthcare System
VASLC	VA Salt Lake City
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure

Contents

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2.0 Introduction

This project addresses the significant challenge of delivering non-pharmacological treatment for chronic pain to a large number of Veterans, many of whom have comorbid conditions that contribute to and are exacerbated by their chronic pain. Attainment of this goal requires scalable, non-pharmacological, "Veteran-Centric" interventions that fit Veterans' needs and preferences, are designed to optimize engagement and sustainability, and can be readily implemented in the Veterans Health Administration (VHA) and in the community to reach the large number of Veterans with chronic pain. This endeavor also requires the capacity to implement large-scale multi-site clinical trials to test the effectiveness of these interventions across settings and across important patient subgroups, such as women.

Chronic pain is a prevalent, debilitating, and costly national problem. Over 100 million adults in the US suffer from chronic pain, which is estimated to cost the nation $635 billion annually in health care and lost productivity.[1] Chronic pain affects approximately up to 50% of Veterans and 45% of service members.[2,3] Nearly half of Veterans of the recent conflicts in Afghanistan (Operation Enduring Freedom; OEF) and Iraq (Operation Iraqi Freedom; OIF) receiving VA health care have at least one pain-related diagnosis.[4] Moreover, Veterans are more likely to experience severe pain than non-Veterans.[5]

Despite its prevalence and burgeoning costs, current conventional strategies have proved inadequate, leading to troubling and maladaptive pain coping behaviors. This includes mismanagement of chronic pain with opioid analgesics, which has increased dramatically over the past decades.[6] Given limited evidence supporting efficacy of opioid therapy for chronic pain and rising rates of opioid overdose and death, this is a concerning

trend.[7-11] Among OEF/OIF Veterans with pain diagnoses, 11% receive long-term opioid therapy, with higher rates among those with comorbid PTSD and other mental health conditions.[4] Those with PTSD and comorbid substance abuse problems were five times more likely to be prescribed opioids (34%) compared to those without mental health diagnosis (7%), and those with comorbid mental health conditions also received higher-dose opioids and experienced more adverse clinical outcomes.[4] Prescription drug disorders have become a major public health crisis.[17] According to the US Centers for Disease Control, deaths from prescription opioid overdoses increased more than 400% among women and 265% among men since 1999.[12] Veterans are disproportionately affected by drug-poisoning deaths. VA patients have nearly twice the rate of accidental fatal poisoning as US adults overall and opioid analgesics are the drug class most commonly involved in these deaths.[13] Within the military, self-reported prescription pain medication misuse increased from 2% in 2002 to 11% in 2008,[14] and drug toxicity deaths more than doubled between 2006 and 2011.[15]

Musculoskeletal (MSK) pain is consistently the most common, disabling, and costly of all pain complaints in the civilian population and among Veterans.[16] Two Institute of Medicine (now the National Academy of Medicine) reports have summarized the enormous functional and economic impact of MSK pain on both the working and the retired population.[16,17] Indeed, two-thirds of pain-related outpatient visits are due to MSK pain, accounting for nearly 70 million outpatient visits in the U.S. each year.[18] Painful MSK diagnoses are increasing in prevalence among Veterans enrolled for care in the VHA, including back disorders—a particularly disabling condition that seems to be emerging at a younger age.[19] Especially concerning is that, among Veterans deployed since 2001 in Afghanistan and Iraq, 62% have painful MSK disorders.[20]

For many Veterans, their chronic pain co-exists with other mental and physical health conditions (insomnia, PTSD, substance abuse, depression) that contribute to and exacerbate their pain.[2] Of concern is that the prevalence of these comorbid mental health conditions among patients with MSK pain is increasing.[19] Within the Musculoskeletal Disorders Cohort, developed to characterize variation in pain, comorbidities, treatment, and outcomes among patients with MSK disorders within the VHA (N = 5,237,763), the percentage of Veterans with a documented mental health diagnosis increased from 13.6% in 2000 to 19.9% in 2011.[19]

Women Veterans experience elevated rates of painful MSK and mental health conditions. 57% of female Veterans receiving care in the VHA have an MSK pain diagnosis, compared to 49% of men, with MSK ranking as the top diagnosed medical condition among women Veterans.[21] An analysis of 4,128,008 Veterans with MSK diagnoses in the VHA found that women were more likely than men to report moderate to severe pain and were more likely than men to have more than one MSK diagnosis.[22] 46% of female Veteran VHA patients have a mental health/substance use disorder (SUD) diagnosis, compared to 32% of men, and among Veteran VHA patients, women were more likely to use mental health/SUD services than men (38% versus 24%).[21] Addressing the needs of women Veterans with chronic pain and mental health comorbidities is also aligned with broader efforts to advance the ability of the VHA to provide care focused on women Veterans' unique needs, and to address barriers experienced by women Veterans using the VHA.

Mindfulness-based interventions (MBIs) are evidence-based, non-pharmacological approaches that can empower Veterans to better manage their chronic MSK pain and comorbid conditions. Indeed, after reviewing the literature the workgroup from the 2016 VA Health Services Research and Development State of the Art (SOTA) conference, "Non-pharmacological Approaches to Chronic Musculoskeletal Pain Management," concluded that there is strong enough evidence for the efficacy of MBIs to warrant hybrid effectiveness/implementation trials to determine their effectiveness in real-world settings and address implementation barriers.[23] Further, the recent 2017 American College of Physicians clinical practice guidelines for low back pain have provided a strong recommendation that MBIs (and other non-pharmacologic interventions) be considered prior to pharmacologic treatments for chronic low back pain.[24]

MBIs are among the top five commonly used complementary and integrative health (CIH) practices in the U.S,[25] and there is increasing evidence of their effectiveness for chronic pain and comorbid conditions such as PTSD, insomnia, depression, and substance abuse.[26,27] Mindfulness-Based Stress Reduction (MBSR) is the most popular and formalized of the mindfulness programs, stemming from Jon Kabat-Zinn's early work that introduced systematic, secular training in mindfulness.[28] MBSR and many MBIs are offered as group format interventions focused on education, training, practice, and social support in mindfulness meditation. Described as "the awareness that arises by paying attention, on purpose, and non-judgmentally, to present moment experience,"[29] mindfulness is a skill that can be developed. Through meditation training, exercises and practice aimed at enhancing attention regulation, body awareness, emotional regulation, and shifts in self-perception,[30] pain sufferers can be become better equipped to manage pain and associated stress, which is a contributor to chronic pain.[31] By enhancing one's capacity to build and sustain awareness without judgement when confronted with pain and stressful events, automatic, maladaptive responses (e.g. hypervigilance, catastrophizing, etc.) may be decreased. According to the stress buffering model,[32] MBIs affect a broad range of mental and physical health outcomes through stress reduction and resilience pathways. Specifically, skills learned via MBIs can decrease reflexive cognitive and emotional reactivity to perceived aversive experiences, leading to more intentional, adaptive responses to pain and other stressors.[33] Thus, by providing Veterans accessible opportunities to develop their capacity and capability to better manage pain and stress, they will be better equipped to engage in healthy and adaptive pain management coping behaviors. This is the basis for the conceptual model underlying the proposed MBIs, which is depicted in Figure 1, later in this section.

Several systematic reviews have demonstrated the promise of MBIs to treat chronic pain. Although these reviews generally have shown MBIs to be effective for improving pain outcomes, depressive symptoms, and mental and physical health quality of life, they also note the methodological limitations in a number of these studies (e.g., small sample sizes, high attrition rates, and lack of high quality pre-treatment, post-treatment and follow-up measures),[34,35] underscoring the need for more methodologically rigorous studies.[34-37] [38]

More recent Randomized Controlled Trials (RCTs), however, have provided stronger evidence of the effectiveness of MBIs for treating chronic pain. Indeed, a 2016 review of Mindfulness-Based Interventions[26] concluded that, "there is now compelling evidence in several large RCTs that mindfulness interventions improve chronic pain management relative to TAU (Treatment as Usual) and initial evidence that MBIs may be superior to some active treatments (support groups, health education programs) but not to other treatments CBT (Cognitive Behavioral Therapy)." An RCT (Davis et al., 2015) of 145 adults with rheumatoid arthritis found an 8-week MBI to be more effective than arthritis education and CBT for pain in reducing pain related catastrophizing, disability, fatigue, and daily stress.[39] Another RCT of 109 patients with long-term chronic pain (La Cour et al., 2015) found that, compared to a waitlist control, those randomized to MBSR had greater improvement in the primary outcome, the SF36 vitality scale (d=.39), and on secondary variables (improvements in general anxiety and depression, mental health quality of life, feeling in control of pain, and pain acceptance), directly after the intervention. Further, improvements in vitality, coping with pain, pain acceptance and mental health quality of life were sustained at the 6-month follow up.[40] A recent pilot study has also shown that MBIs are feasible, acceptable, safe, and effective at reducing pain severity and sensitivity for chronic low back pain patients who were long-term daily opioid medication users.[41] [42] Another study found that an 8-week mindfulness-oriented recovery enhancement program reduced pain severity and interference among chronic pain opioid abusing patients post-treatment and at 3 months, relative to active support group therapy.[43]

One of the most rigorous RCTs (Cherkin et al., 2016)[44] compared 8 weeks of MBSR to CBT relative to usual care among 342 adults with chronic low back pain. Co-primary outcomes at 26 weeks were percentage of participants with clinically meaningful (≥ 30%) improvement from baseline in functional limitations and in self-reported back pain bothersomeness. The percent of participants with clinically meaningful improvement on both outcomes at 26 weeks was significantly higher for the MBSR group than for usual care (60.5% MBSR vs. 44.1% usual care for function; 43.6% MBSR vs. 26.6% usual care for pain bothersomeness). Importantly, these differences persisted at 52 weeks. Another recent and high quality RCT of 242 older adults with low-back pain, (Morone, et al., 2016) compared a modified MBSR program to an active control group matched for time, group size, attention, homework, and facilitator time.[45] Outcomes were measured at 8 weeks and again at 6 months (with monthly booster sessions offered during the period between 8 weeks and 6 months). Significant group differences in favor of MBSR were observed for the primary outcome, pain-related disability, at 8 weeks (effect size = -.23),[46] but not however at 6 months. This suggests greater attention needs to be paid to providing readily accessible support resources that participants can revisit in the long term, to enhance sustainability.

Although these studies provide support for the efficacy of MBIs, none were focused on a Veteran population with chronic pain. This is critical because Veterans—and women Veterans in particular—differ in many ways from the general population examined in chronic pain studies.[47,48] This includes a higher prevalence of chronic pain, depression, PTSD, and other co-occurring physical health conditions[47] and, among women, high levels of military sexual trauma.[49] In one study of Veterans participating in MBSR groups, nearly 75% met criteria

for PTSD, 59% had a depressive disorder, and 67% had a chronic pain condition. [47] It is also unknown how the effectiveness of MBIs may vary based on these mental health comorbidities and other key patient characteristics, such as gender, because existing trials of MBIs have not had sample sizes large enough to examine how such patient characteristics may affect outcome response.[38]

There is evidence that Veterans and active duty military personnel find complementary and integrative health (CIH) approaches, including mindfulness, appealing for pain treatment.[50-53] [54] For example, a recent qualitative study reported that many Veterans found MBSR beneficial for their pain and would recommend the program to others.[48] Many of these Veterans turn to CIH therapies because they are dissatisfied with prescription medications and conventional approaches,[50] with women Veterans being particularly receptive to CIH approaches.[53] Importantly, CIH approaches, including meditation,[55] are becoming widely endorsed by the VHA, as part of a patient-centered approach to health care and more specifically, for addressing chronic pain.[56] The importance of CIH therapies for addressing Veterans' pain has also emerged in a recent semi-structured interview study (Fletcher, 2016) examining facilitators and barriers to implementing CIH. Conducted with providers and administrators at six VAHCS's, this study found that CIH was viewed as essential for improving pain management and that there was a desire for greater availability of CIH pain therapies at their facilities.[51]

Currently there are no published RCTs examining MBIs among Veterans with chronic pain. There are, however, trials examining MBIs for other conditions, which indicate that MBIs are feasible and effective for Veterans. For example, a pilot RCT of 55 Veterans with Gulf War Illness (GWI) found MBSR combined with TAU to be more effective than TAU on reducing symptoms of GWI at 6 month follow-up, including pain and fatigue.[57] Other studies have shown MBIs to be a promising approach for improving symptoms of conditions comorbid with pain, such as PTSD,[58-60] anxiety,[61] and depression.[61] Another RCT of MBSR for Veterans with PTSD (N = 116) conducted by Co-I Dr. Polusny found a greater decrease in self-reported PTSD symptom severity and improved quality of life among those in the MBSR condition compared to those in person-centered group therapy, during treatment and at 2 month follow-up.[59]

Despite the growing evidence supporting the effectiveness of MBIs and many Veterans' and providers' desire for alternative treatment approaches, including MBIs, there are important health care system-level barriers that impede widespread use, and limiting reach and ultimate impact. In the qualitative study by Fletcher et al., (2016), providers and leaders vocalized the struggle "to meet veterans' demands for delivery of CIH," citing a lack of time, space, funding, and staff training. [51] Further, MBSR programs are typically led by instructors who complete an extensive and costly certification process (e.g. 300+hours; $17,000 - $25,000).[62] Such training ensures standardization of essential mindfulness elements (see Table 1) and enhances participant safety. However, such stringent requirements severely limit the ability of VAHCSs to offer MBIs to all Veterans who would benefit from them. These constraints also limit the widespread dissemination of MBIs in other non-Veteran populations.[63] Thus there is a need for creative formats of MBI delivery that maintain essential elements, but

also address the very real health care system level barriers in a manner that will enhance long-term sustainability.

Standard MBSR approaches also pose a number of barriers at the patient-level,[63] which can run counter to the VHA's goal of providing Veteran-centered care,[56] and impede patient engagement, adherence, and maintenance, thereby reducing treatment effects. First, the time commitment of standard MBSR (classroom attendance, including travel time, and home practice requirements of 45 minutes daily) makes these approaches inaccessible or unsustainable for many.[35] This problem is reflected in published studies by extremely low adherence and high attrition rates (up to 50% in some cases). Moreover, setting unrealistically high expectations for home meditation practice is likely counterproductive to establishing consistent, daily meditation practice, according to behavioral change theory.[64] Low participation coupled with low adherence limit the reach and effectiveness and ultimate impact for pain patients. Additionally, access barriers exist for many Veterans who are not able to easily travel to the main VHA facilities where MBIs are offered. Qualitative research on barriers to MBIs (including two studies of Veterans) provide converging evidence that time demands (classroom attendance and practice requirements) pose a major barrier. This includes affecting the likelihood of enrolling in and completing MBIs and adhering to home practice requirements.[48,65,66] Time-intensive programs, which do not provide tools for incorporating mindfulness practice into one's everyday life in the face of competing demands, may also negatively affect participants' ability to maintain the skills they learn in 8 weeks of instruction. For mindfulness practice to be a useful self-management approach and to have meaningful effects on outcomes important to patients, patients need to be able to continue their daily practice well beyond the 8-week intervention period, and to continue to use mindfulness skills in daily life, particularly when experiencing cues (such as pain and other stressors) that trigger maladaptive responses and behaviors. MBIs that include readily accessible tools and resources that encourage long term use are much needed.

The group format can also pose a barrier, especially for female Veterans. Between 15-40% of female Veterans using VA services have experienced military sexual trauma (MST)[67] (defined as "physical assault of a sexual nature, battery of a sexual nature, or sexual harassment which occurred while the veteran was serving on active duty or active duty for training"), and a recent survey found that 24% experienced sexual harassment at their VA Healthcare System (VAHCS).[68] Not surprisingly, some female MST patients report discomfort participating in Mindfulness-Based Stress Reduction (MBSR) classes with men[47,48] and may experience difficulties during certain aspects of the course (e.g., closing eyes during meditation practice), particularly in a mixed-gender setting. Several studies (two of men and women Veterans, and one of civilian women with a history of PTSD) found the group format to be an impediment to MBSR participation, citing interpersonal dynamics and discomfort with the mixed-gender class environment.[42,48,66,69] Along with lack of time and schedule conflicts, "aversion to groups" was the most-common "deal breaker" in a study of Veterans' experience with MBSR.[48] Groups were cited as a major reason preventing women Veterans from enrolling in MBIs, affecting Veterans' ability to engage in the program, and fueling drop out, with some stating that they would have preferred an all-women group.[48,70]

Taken together, these system-level and patient-level barriers have negative implications for key indicators of sustainability: reach (the percentage of the population who actually receive the intervention), treatment effectiveness, and ultimately intervention impact (the product of effectiveness and reach in a target population).[71] Without overcoming the above barriers, such interventions will fail to ultimately be successfully disseminated, implemented and used to help the many Veterans who are struggling with chronic pain.

Recent general population studies of MBIs addressing system-and patient-level barriers associated with standard MBSR have demonstrated promise for chronic pain and its associated comorbidities and symptoms.[32,38] Consistent features of these studies include MBIs that require less time than standard MBSR, and can be delivered in online formats. For example, there is evidence that abbreviated MBIs (with shorter in-class and at-home practice times) are effective at improving chronic pain and common comorbidities such as fatigue, depression and PTSD. Results of Hilton's 2016 meta-analysis concluded that the efficacy of MBIs "did not differ systematically by type of intervention…or by length and frequency of intervention." [38] Evidence suggests that long meditation times might not be necessary to effect change. For example, a trial by Henriksson et al. (2016) of chronic pain patients assessed an 8 week online MBI, consisting of 20 minutes of training per day, six days a week, compared to an active control.[72] It demonstrated an advantage for the MBI group, including increased mindfulness skills, reduced pain intensity and pain-related interference/suffering, heightened pain acceptance, lower affective distress and higher ratings of life satisfaction. For cancer survivors experiencing cancer-related fatigue, 20 minutes/day of mindfulness meditation led to significant improvement of fatigue interference and severity, and these improvements were maintained through 6 months of follow-up.[73] Similarly, another small RCT of a 4-session abbreviated MBSR program for VA primary care patients with PTSD (compared to TAU) found significant reductions in cortisol[58] and medium to large effect sizes on PTSD and depression,[74] among those who completed all 4 sessions. Taken together, these studies suggest that shorter MBIs yield important benefits. It is also possible that, by shortening home practice meditations, patients will be better able to sustain their practice over time, resulting in improved long-term pain self-management for these patients.

There is also evidence of the effectiveness of online, self-management approaches (including MBIs) for chronic pain[72,75] and comorbid mental health conditions.[76] A systematic review and meta-analysis of 15 RCTs of online MBIs assessing mental health-related outcomes concluded that MBIs have a "small but significantly beneficial effect on depression (g = .29), anxiety (g = .22), mindfulness (g = .32), well-being (g = .23), and stress (g = .51)."[76] More broadly, a systematic review and meta-analysis of MBIs and acceptance-based interventions delivered via self-help resources (including but not limited to internet-based interventions) concluded that such interventions significantly increased mindfulness/acceptance skills and decreased anxiety and depressive symptoms.[77]

Online MBIs have also demonstrated effectiveness for addressing chronic pain. Buhrman et al.'s (2013) trial of a guided internet-delivered 8-week MBI (Acceptance and Commitment

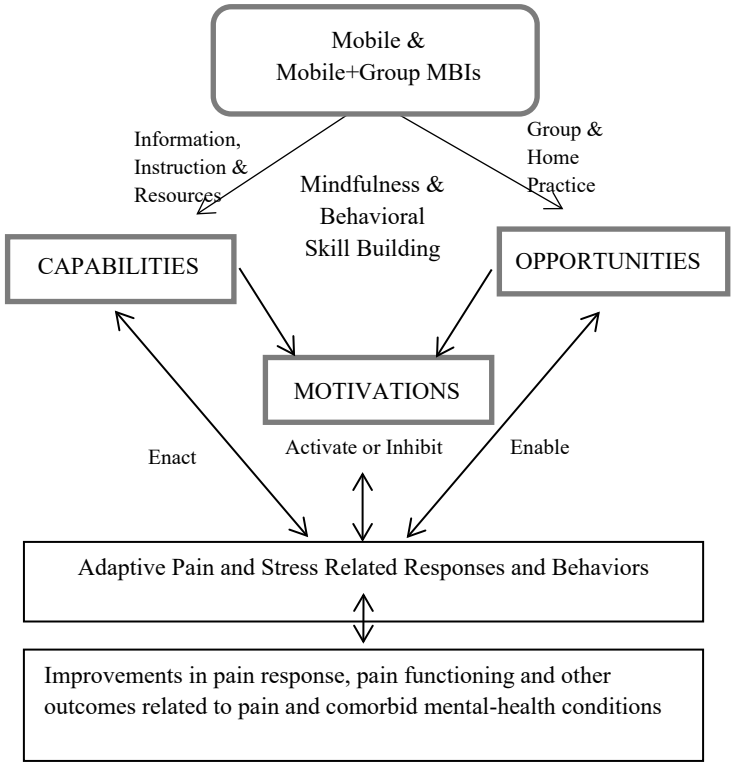
Therapy, which includes mindfulness training) for persons with chronic pain showed significant improvement on the primary measure (score on chronic pain acceptance questionnaire) and on measures of anxiety and depression that were maintained over 6 month follow-up period.[75] Davis et al.'s (2013) online MBI (which included a mindful socioemotional regulation intervention) with patients with fibromyalgia, consisting of 12 fifteen-minute modules delivered over 6 weeks, demonstrated greater improvement in social functioning, positive affect and coping efficacy for pain and stress compared to active control (but no improvement in daily pain).[78] Finally, the online MBI described above by Henriksson et al. (2016) of chronic pain patients showed improvement on a number of pain outcomes; however this study was limited by an absence of long-term follow-up measures).[72]

Mobile MBIs offer the opportunity to increase reach, thereby increasing impact. Adapting online MBIs to mobile delivery fits with the recent National Academy of Medicine recommendation to create mobile applications for chronic pain treatment to overcome barriers to access and promote reach and accessibility.[1] Recent estimates of Veterans and active military members with access to smart phones or tablets capable of running applications range from 71% to 83%, and those percentages are rapidly increasing.[79,80] Indeed, authors of a survey of active duty service members, National Guard and Reserve, and Veterans concluded that "mobile devices may offer the ideal medium for accessible and portable health education and for intervention."[80] Studies have also documented high interest among Veterans using mobile health (or mHealth) applications.[79] Mobile, self-management interventions also address system-level barriers associated with the current referral process, in which Veterans' access can be limited by failure of providers to offer CIH modalities to patients, and lack of leadership support for CIH.[51] Mobile MBIs may also be a good alternative for women Veterans who would prefer not to receive care within VA due to military sexual trauma[67] and other types of sexual harassment (including at the VA).[68,81] Mobile MBIs also could be disseminated outside of the VHA, through trusted organizations that serve Veterans and their communities.

In summary, results of emerging research leveraging technology and shorter intervention formats to address patient- and system-level barriers and facilitators to MBIs are very promising and warrant rigorous investigation in Veterans and VA settings.

Conceptual Framework. The underlying conceptual framework for our MBI interventions, depicted in Figure 1, is drawn from the COM-B (Capability, Opportunity, Motivation, and Behavior) model, stress buffering models,[32] and the literature described above. The COM-B model represents a condensed and simplified version of the Theoretical Domains Framework, which has been extensively used to address the complex nature of human related behaviors, including self-management, for a variety of health conditions, including pain.[83-85] Importantly, this model is comprehensive in nature and incorporates the necessary conditions for addressing facilitators and inhibitors related to behaviors: this includes **capabilities** (or abilities required to enact behavior); **opportunities** (factors in the environment); and **motivations** (including emotional responses, impulses, etc.). When applied to the proposed study, it provides a framework that aligns Veteran and VA system-related needs with the intervention and target outcomes. Specifically, we aim to provide **opportunities** (e.g. using online and mobile formats, supportive resources) to overcome system- and patient-level barriers that prevent Veteran participation in MBIs, and to enable Veterans to engage in adaptive responses to triggering events (e.g., pain flare ups, stress-inducing situations) when they occur. Through mindfulness skill building, coupled with evidence-based behavioral strategies (e.g. pacing, value-based goal setting, etc.), Veterans can build their capacity and **capability** in mindfulness skills. This includes attention regulation, body awareness, emotional regulation, and shifts in self-perception.[30] These important skills can help address underlying **motivations** related to pain and stress that can activate adaptive pain and stress related responses and behaviors (e.g. acceptance, unemotional problem-solving, engaging in physical and social activities, attempting non-pharmacologic pain management strategies first, etc.) and inhibit maladaptive ones (catastrophizing, fear avoidance and hyper-vigilance, physical inactivity, social isolation, overuse and abuse of medications, substances). This in turn is expected to lead to improvements in important pain and function-related outcomes.

Figure 1. Theoretical Framework



Rational for Proposed MBI Interventions. The Mobile+Group MBI consists of online training modules, delivered by a trained mindfulness instructor, which are delivered digitally, in group settings, and interspersed with group discussions. A trained facilitator (who is not required to be an expert in mindfulness) leads the group.

Due to COVID-19, VA ORD has placed an administrative hold on research activities involving non-critical, in-person contacts between study participants and VA research staff. However, VA ORD permits group meetings via platforms that are approved by the ISSO. Following these guidelines, we plan to move the Mobile+Group MBI to an online format which will be delivered weekly, per the study protocol, using University of Minnesota (UMN) Zoom, a VA and HIPAA compliant videoconferencing software. Participants will be required to log into Zoom with a unique code. We will not be video or audio recording the Zoom sessions or collecting PHI or other sensitive participant info. This Zoom technology is on the VA Technical Reference Model (TRM), a list of VA-approved technologies. The UMN Zoom platform is currently being used by Co-Investigators Evans and Haley (NIH #1R21AT009110-01A1), to deliver a Group MBI remotely, due to COVID-19.

The Mobile MBI consists of the same training modules delivered on an app (and available online), with no group interaction but with up to 3 one-on-one phone calls with a facilitator. Inclusion of this condition will allow us to rigorously test the addition of the group component of the MBI. This is important because, although the group experience is considered to be a key part of MBIs and there is some evidence that it increases engagement,[77] there is little research designed to rigorously test the added benefit of groups, relative to its costs.[48] Specifically, the Mobile MBI requires fewer VHA resources (e.g., use of trained facilitators), reduces access barriers associated with scheduling synchronous sessions and reduces barriers associated with the group format. However, the Mobile+Group MBI affords benefits related to having a facilitator and a group (e.g., accountability, support, motivation, feeling of common humanity and shared struggle),[47,77] which may increase participation, engagement and lead to improved outcomes.[77]

Both MBIs address goals of scalability (availability of qualified instructors, uneven quality of instructors, consistency) and Veteran-centeredness (reduced class time and practice demands, more effective communication regarding how MBI will address outcomes of concern to Veterans). Given studies showing briefer formats of MBSR to be efficacious,[58] [86] both MBIs will be shorter than standard MBSR. To increase treatment effectiveness, both MBIs also will include components aimed at reducing attrition and improving engagement and practice, which are not part of standard MBSR, by incorporating specific behavioral change strategies (e.g., self-monitoring, feedback on performance) through mobile tools—an innovation that also will enable us to collect real time practice data and provide feedback to participants on their engagement (e.g., course participation and practice time).[87] These “motivational affordances” in online self-management interventions have been shown to contribute to adherence.[88] Both programs will incorporate communication strategies, prior to and during the course, to ensure that Veterans understand the expected benefits of the MBI, presenting a clear rationale explaining to participants how MBI is expected to lead to desired outcomes (reduction in pain functioning, improvements in fatigue). This is important as research has shown that lack of communication, prior to and during the course of the program, about how the MBI will address outcomes of concern to Veterans, to be a barrier to enrollment and adherence.[48] We will also take advantage of the fact that the majority of individuals--80-90% in recent surveys[89,90]—have their mobile devices with them for much of the day and check them frequently. This allows for “real time engagement”[90] in which individuals can use the mobile MBI app when they

experience cues that trigger maladaptive pain- and stress-related behaviors, in order to engage in adaptive behaviors. We will build in additional design features based on Veteran and stakeholder feedback, obtained through our user-centered design process.

The proposed project will use recruitment strategies that address barriers to conducting large-scale clinical trials of nonpharmacological treatment for pain. Veterans with chronic pain will be identified by leveraging data available in the VHA electronic health record (EHR). Once identified, they will be sent Veteran-centric materials informing them of the purpose of the study. This enables the researcher to rapidly identify a large sample of potential participants, including important subgroups that can then be oversampled (e.g., women; those in the early stages of chronic pain), and avoids selection bias that occurs when providers are asked to refer patients or when patients must seek out the study. Centralized recruitment also allows for quality control so that the content and manner of recruitment are consistent.

Within clinical practice, this project will provide tools and strategies for <u>proactively</u> delivering different types of non-pharmacological chronic pain treatment to Veterans who would benefit. Current chronic pain treatment approaches require patients to request treatment or depend upon the health care provider to initiate care. This reactive approach dampens the potential reach of evidence-based non-pharmacological approaches to chronic pain, as many patients and providers are not aware of these approaches.[51] The use of the VA EHR to proactively identify and offer treatment to Veterans with chronic pain through a centralized system is a way to increase the reach of a variety of different treatment approaches (including but not limited to MBIs) for Veterans who could benefit, and would allow for targeting of specific subpopulations. This approach has been successfully used in the VHA to increase the reach of smoking cessation interventions.[91] Indeed, our mobile platform can be adapted to host a package of different non-pharmacological modalities for chronic pain (e.g., exercise, CBT for pain), which could be offered proactively to Veterans.

3.0 Objectives

The long-term goal of this two-phase project is to reduce chronic pain and co-morbid conditions among Veterans, through scalable, non-pharmacologic evidence-based strategies that are "Veteran-Centric," designed to optimize engagement, adherence and sustainability, and are deliverable to large numbers of Veterans.

This study, for which we are submitting this IRB application, comprises the multisite pragmatic clinical trial (PCT), Phase 2, which will test the effectiveness of two MBIs at improving outcomes related to pain and mental health comorbidities.

AIM 1 (EFFECTIVENESS): 4-site 3-arm PCT (N = up to 950 randomized) to test effectiveness of Mobile+Group and Mobile MBIs compared to usual practice

Primary hypotheses:

1. Mobile MBIs will be more effective at improving chronic pain (as measured by change in BPI over the 12-month follow-up period) compared to usual practice
2. Mobile+Group MBIs will be more effective at improving chronic pain (as measured by change in BPI over the 12-month follow-up period) compared to usual practice
3. Mobile+Group MBIs will be more effective at improving chronic pain, as measured by BPI change over the 12-month follow-up period, compared to Mobile MBIs without the group component.

Secondary hypotheses:

1. Comparison of intervention groups with secondary outcomes listed below.
2. Primary and secondary hypotheses comparisons will be confirmed in gender specific strata.

Endpoints: Primary outcome: Change in BPI total score over the 12-month follow-up period. Secondary outcomes will include measures captured in EHR (e.g., medication prescription/refills, health care visits for pain management), as well as patient-reported measures related to pain, comorbid mental health conditions and function, expected mediators of treatment effects, patient satisfaction, and adverse effects. These outcomes will be assessed at 10 weeks, 6 months and 12 months.

Data will be collected using online Qualtrics FedRAMP surveys, mailed paper surveys, phone surveys, mobile application, and electronic health records.

AIM 2 (PRE-IMPLEMENTATION): data will be collected & described, guided by Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

4.0 Resources and Personnel

I. Minneapolis VA Healthcare System (Mpls VAHCS) Personnel

Mpls VAHCS
Data collection and analysis will occur from MVAHCS.

Diana Burgess, PhD

a. Role: Principal Investigator
b. Will oversee all aspects of the study and be responsible for ensuring all human subject privacy and safety requirements are followed and fulfilled. She will oversee all study activities (engagement, participant recruitment, planning and conduct of the intervention, data collection, analysis and interpretation, dissemination, and project management), lead regular meetings with the entire project team and oversee meetings with subgroups that will focus on specific aspects of the project.

c. Will have access to protected health information. She will be involved in conducting interviews, recruitment and obtaining verbal informed consent. She will be involved in data analysis of coded data.

Laura Meis, PhD

a. Role: Co-Investigator
b. Dr. Meis will participate in the Engagement Subgroup and lead the Veteran Engagement Panel (VEP). She will provide expertise regarding methods and processes of stakeholder engagement, lead efforts to establish Dr. Burgess's study-specific stakeholder panels, including identifying members, training members and researchers, and facilitating the ongoing series of studios with each panel, Dr. Meis will conduct a developmental formative evaluation of the engagement plan, in order to understand, refine, and continually improve engagement activities. She also will take an active role in interpretation of quantitative and qualitative data, manuscript preparation, and other dissemination activities.
c. She will be involved in data analysis of coded data. She will have access to protected health information and have direct contact with participants only if necessary. (Dr. Meis is a clinician listed to contact if a participant is in crisis and the PI is unavailable.) Dr. Meis will not be recruiting, obtaining informed consent, or conducting surveys/interviews.

Brent Taylor, PhD, MPH

a. Role: Co-Investigator and Lead Statistician
b. Will be the senior statistician and methods expert, overseeing both the Data and Statistics Teams (responsibilities described below)**.** He will lead the Methods Subgroup, which will focus on issues related to measurement, design, and statistical analysis. He will also participate in the Operations Subgroup, which will oversee, monitor, and problem solve issues related to the delivery of the intervention centrally, and in our sites, using data monitoring tools that the CCDOR Data Team has developed. Dr. Taylor will also participate in the interpretation of quantitative and qualitative data, manuscript preparation and other dissemination activities.
c. Dr. Taylor will be involved in data analysis of coded data. He will have access to protected health information to maintain rigorous study methodology and/or for the safety of participants. He will not be recruiting, obtaining informed consent, or conducting surveys/interviews.

CCDOR Statistical team

a. Role: statisticians
b. Personnel: **Barbara Clothier, MS, MA** and **Emily Hagel-Campbell, MS**.
c. At least one member of the Masters Statistician Team will be assigned to handle the day-to-day data analyses under Dr. Brent Taylor's supervision.
d. They will be involved in performing data analysis of coded data. They will have access to protected health information. They will have no direct contact with participants (e.g., they will not be recruiting, obtaining informed consent, or conducting surveys/interviews).

CCDOR Data Management Team

a. Role: database design and development; administrative data extraction; survey design, development and support; scannable technology; design, development and implementation of custom applications and web sites
b. Personnel: **Ann Bangerter, BS, Rose Degerstrom, BA, Sean Nugent, BA, and Andrea Cutting, MA.**
c. For this project, the CCDOR Data Management Team will manage all data collected during the study. They will 1) create the secure SQL database; 2) extract patient data from CDW for identified facilities; 3) extract primary care provider data from the Primary Care Management Module for identified patients; 4) train the Project Coordinator and Research Assistants to design the app using MEI Research, Ltd. Software, and supervise the data quality assurance process, and ensure secure data transmission between MEI Research servers and VA VINCI servers; 5) train the Project Coordinator and Research Assistants to design the surveys (Qualtrics FedRAMP data collection system, mailed paper, and phone versions), 6) request special permission from National Data Systems to access patient name and address information in order to create a patient mailing list for project staff; 7) extract and clean administrative data, clean paper survey data, and create data files for analysis; and 8) assist with preparation of reports and dissemination of results.
d. They will have access to protected health information but will not have direct contact with participants (e.g., they will not be recruiting or obtaining informed consent). They will be creating coded data files for analysis.

Lee Cross, MPH

a. Role: Study Coordinator, Back-up Intervention Facilitator
b. She has been an integral part of the developmental, planning, and fielding stage of several multi-site projects. She will work closely with Dr. Burgess throughout this project as part of the Core Leadership group. Ms. Cross will plan and organize meetings, including the initial kick-off meeting and Subgroup meetings, and document decisions and action items. Ms. Cross will lead the efforts to ensure all logistical and human subjects protection matters are taken care of for a successful demonstration project. This will include planning travel, IRB approvals, informed consent, incentive payment, audio recording, transcription, and budgeting. She will take the lead in documenting all study procedures (e.g., mailing protocols, recruitment staff training, recruitment instructions, email and telephone support line procedures, communication with participants, mental health crisis management). She will provide training and guidance to staff in these procedures as well as in conduct of human subjects research, good clinical research practices, and data privacy and security. Ms. Cross will serve as the coordinator between all four sites and will be in regular contact with the MBI facilitators and research assistants at each site. She will be an active member of the Qualitative Subgroup and participate in manuscript preparation, and other dissemination activities.
c. Ms. Cross will have access to protected health information. She will be involved in recruiting subjects, obtaining informed consent, administering survey/interview procedures, and will be involved in data analysis of coded data.

Mariah Branson, BA

a. Role: Primary Research Assistant, Back-up Intervention Facilitator
b. Will assist the Project Coordinator during the development phase (Years 1-2) with meeting planning and coordination. Will assist with the Mobile+Group MBI sessions.
c. Will have access to protected health information. Will be involved in recruiting subjects, obtaining informed consent, administering survey/interview procedures, and will be involved in data analysis of coded data.

Mallory Mahaffey, MPH, MA

a. Role: Lead Intervention facilitator
b. Ms. Mahaffey will perform medical chart reviews and determine continued eligibility of participants who complete the baseline survey and will conduct the UMN Zoom group meetings with the participants randomized to the Mobile+Group MBI intervention arm. She will coordinate and communicate with the Study Coordinator, and provide regular progress reports, which will include required human subjects' research documentation and ensuring all human subjects' ethics regulations are followed.
c. Ms. Mahaffey will have access to protected health information. She will be involved in recruiting subjects. She may be involved in data analysis but only of coded data.

Kimberly Behrens, MA

a. Role: Associate Intervention Facilitator
b. Ms. Behrens will conduct UMN Zoom group meetings with the participants randomized to the Mobile+Group MBI intervention arm. They will coordinate and communicate with the Study Coordinator and Lead Intervention Facilitator and provide regular progress reports, which will include required human subjects' research documentation and ensuring all human subjects' ethics regulations are followed.
c. They will have access to protected health information. They will be involved in recruiting subjects. They may be involved in data analysis but only of coded data.

TBD

a. Role: Interns; hourly employees, as needed
b. Will assist with mailing, randomization phone calls, and participant engagement.
c. Will have access to protected health information. Will be involved in recruiting and randomizing subjects, obtaining consent, and administering survey/interview procedures

II. University of Minnesota Personnel

University of Minnesota - Center for Spirituality and Healing

A payment and work agreement between the University of Minnesota Center for Spirituality and Healing, and the Minneapolis VA Medical Center will be established.

Roni Evans, PhD, MS, DC

a. Role: Co-Investigator

b. Dr. Evans will lead the MBI subgroup and will be integrally involved in developing the facilitator training manual and training and supervising the facilitators.
c. Dr. Evans will not have access to identifiable data. She will be involved in performing data analysis of coded data. She will not have access to protected health information or have direct contact with participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys/interviews).

Gert Bronfort, PhD, MS, DC

a. Role: Co-Investigator
b. Dr. Bronfort will participate in the Methods Subgroup.
c. He will be involved in performing data analysis of coded data. He will not have access to protected health information or have direct contact with participants (e.g., he will not be recruiting, obtaining informed consent, or conducting surveys/interviews).

Alex Haley, JD, MBA

a. Role: Co-Investigator
b. Mr. Haley will significantly contribute to the MBI and Operations subgroups. He will be integrally involved in training and supervising the facilitators.
c. Mr. Haley will not have access to identifiable data. He will be involved in performing data analysis of coded data. He will not have access to protected health information or have direct contact with participants (e.g., he will not be recruiting, obtaining informed consent, or conducting surveys/interviews).

University of Minnesota - Department of Psychiatry
Melissa Polusny, PhD

a. Role: Co-Investigator
b. Her primary role in the current project will on the MBI (Mindfulness-Based Intervention) subgroup, which will train facilitators, monitor the fidelity of intervention delivery, and provide guidance on participant safety issues.
c. She will be involved in data analysis of coded data. She will have access to protected health information and have direct contact with participants only if necessary. (Dr. Polusny is a clinician listed to contact if a participant is in crisis.) Dr. Polusny will not be recruiting, obtaining informed consent, or conducting surveys/interviews.
d. Dr. Polusny is affiliated at both the Mpls VAHCS and UMN. A payment and work agreement will be established between the University of Minnesota and the Minneapolis VAHCS.

III. Indiana University & Indianapolis Richard L. Roudebush VA Medical Center Personnel

Roudebush VA Healthcare System

Marianne Matthias, PhD

a. Role: Co-Investigator.

b. Dr. Matthias will not have access to identifiable data. She will be involved in performing data analysis of coded data. She will not have access to protected health information or have direct contact with participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys/interviews).
c. Dr. Matthias is affiliated with the Indianapolis Roudebush VA and the Indiana University. A payment and work agreement will be established between the Indiana University and the Minneapolis VAHCS.

IV. VA Greater Los Angeles Healthcare System (VAGLAHCS) & University of California Los Angeles (UCLA) Personnel

VAGLAHCS

Stephanie Taylor, PhD, MPH

a. Role: Co-Investigator.
b. She will participate in the Operations and Engagement subgroups.
c. Dr. Taylor will not have access to identifiable data. She will be involved in performing data analysis of coded data. She will not have access to protected health information or have direct contact with participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys/interviews).
d. Dr. Taylor is affiliated with the VAGLAHCS and UCLA. A payment and work agreement will be established between the Minneapolis VAHCS and the VAGLAHCS.

John Gregory (Greg) Serpa, PhD

a. Role: Consultant
b. He will provide guidance on adapting the MBIs to fit the needs of Veterans with chronic pain and mental health comorbidities.
c. Dr. Serpa will not have access to identifiable data. He will be involved in performing data analysis of coded data. He will not have access to protected health information or have direct contact with participants (e.g., he will not be recruiting, obtaining informed consent, or conducting surveys/interviews).
d. Dr. Serpa is affiliated with UCLA and the VAGLAHCS. A payment and work agreement between Minneapolis VAHCS and UCLA and/or VAGLAHCS (as appropriate) will be established.

V. University of North Carolina (UNC) – Chapel Hill & Durham VA Healthcare System Personnel

Durham VA Healthcare System

Kelli Allen, PhD

I. Role: Co-Investigator.
II. She will participate in the Operations Subgroup.
III. Dr. Allen will not have access to identifiable data. She will be involved in performing data analysis of coded data. She will not have access to protected health information or have direct contact with participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys/interviews).
IV. Dr. Kelli is affiliated with UNC Chapel Hill and the Durham VAHCS. A payment and work agreement will be established between Minneapolis VAHCS and the UNC Chapel Hill.

VI. Contract with MEI Research, Ltd. and Jon Moon, PhD, FTOS, President of MEI Research, Ltd.

The purpose of contracting with MEI Research, Ltd. is for the mobile application development and licensing fees. MEI will provide MVAHCS a license to their PiLR Health software platform in all study years.

Years 3 through 6: Annual license to mobile and data system comprising: PiLR Health platform, PiLR EMA, raining and technical support as needed. The license period can be extended as needed.

Further software development, special testing, data analysis, extraordinary contract negotiations, and assistance with matters such as IRB and IT documentation or intellectual property will be available at the standard hourly rate.

VII. Contract with Carahsoft Technology Corp

The purpose of contracting with Carahsoft Technology Corp is to use the Qualtrics FedRAMP capabilities for online data collection. Qualtrics FedRAMP is authorized by an ATO to collect data from Veterans and store data on VA cloud servers.

5.0 Study Procedures

5.1 Study Design

All study steps (i.e., Aim 1: recruitment, enrollment, intervention, and follow-up; and Aim 2: pre-implementation surveys) will be initiated and completed by staff at the Minneapolis VA Healthcare System. Potentially eligible individuals for Aims 1 and 2a will be identified and recruited using information provided in the National Data Services (NDS), which authorizes limited access to VA data via the Data Access Request Tracker (DART). The DART request is initiated from Minneapolis staff and all extracts of the Corporate Data Warehouse (CDW) that contains national data will be stored on secure VHA servers, behind the VA firewall (local Minneapolis servers and National VA VINCI servers). Potentially eligible individuals will include

patients at the Minneapolis, Durham, Indianapolis, and Los Angeles VAs. Eligible participants for Aim 2b will be VA employees in the positions listed below.

Aim 1

AIM 1 (EFFECTIVENESS): 4-site 3-arm Pragmatic Clinical Trial (PCT) (N = up to 950) to test effectiveness of Mobile+Group and Mobile MBIs compared to usual practice

Primary hypotheses:

1. Mobile MBIs will be more effective at improving chronic pain, as measured by change in the Brief Pain Inventory (BPI) over the 12-month follow-up period, compared to usual practice.
2. Mobile+Group MBIs will be more effective at improving chronic pain, as measured by BPI change over the 12-month follow-up period, compared to usual practice.
3. Mobile+Group MBIs will be more effective at improving chronic pain, as measured by BPI change over the 12-month follow-up period, compared to Mobile MBIs without the group component.

Secondary hypotheses:

1. Comparison of intervention groups with secondary outcomes listed below.
2. Primary and secondary hypotheses comparisons will be confirmed in gender specific strata.

Endpoints: Primary outcome: Change in BPI total score over the 12-month follow-up period. Secondary outcomes will include measures captured in EHR (e.g., medication prescription/refills, health care visits for pain management), as well as patient-reported measures related to pain, comorbid mental health conditions and function, expected mediators of treatment effects, patient satisfaction, and adverse effects. These outcomes will be assessed at 10 weeks, 6 months and 12 months.

Randomization. Participants will be randomized to Mobile+Group MBI, Mobile MBI or Usual Care (UC; 1:1:1) after all eligibility components are completed. (See 5.4 for eligibility component details.) During the phone call the participant will be randomized and will be told whether they have been selected to be in UC or one of the two intervention groups. The randomization list will be concealed from the research team within the tracking application, so team members will not know the next study assignment. Permuted blocks will be used to aid in the concealment of treatment assignment while ensuring balance in treatment arms across time.

Usual Care Control Condition. Participants assigned to the Usual Care (UC) condition will be told their group assignment during the randomization phone call described in the Randomization paragraph above. They will also be mailed a letter confirming their assignment.

Intervention Conditions. Participants assigned to the Mobile MBI or Mobile+Group MBI intervention groups will be told their group assignment during the randomization phone call

described in the Randomization paragraph above. Both groups will be given their login ID and will be walked through the procedure for downloading the mobile app that contains the intervention. Both groups will be given logistical information about their interventions and will be given opportunities to ask questions. Both groups will then be sent a welcome packet that will include tailored informational materials, including a letter, a study workbook, directions and a login ID for using the intervention on the mobile application (the video content of which will be the same in both intervention groups), and directions to use the video conferencing platform if they're in the Mobile+Group MBI. Materials will include targeted messages to enhance persuasive appeal among men and women Veterans with chronic pain. Study staff will be available via email and phone to provide support for them to access the app, answer any questions, and, in the Mobile+Group condition, answer any questions related to the group sessions. After welcome packets have been mailed, study staff will contact participants in both MBI conditions to confirm that they understand when the first session is and provide the opportunity to ask questions about the app, video conferencing, or any other aspect of the study. In keeping with our pragmatic approach, patients will not be asked to limit any other treatment.

Experimental Interventions. Both the Mobile and Mobile+Group MBIs are based on the MBSR framework successfully used in pain and Veteran populations.[44,59] Table 1 below depicts elements that are common to, and differ, among MBSR, Mobile MBI, and Mobile+Group MBI. The experimental interventions will take place over about a 9-week period and cover the same components and mindfulness skill building addressed in standard MBSR programs. The program differs in mainly the dose and format of delivery, requiring less time and smaller doses of "practice" to enhance engagement and fit the needs of Veterans, and the addition of behavioral change strategies aimed at increasing treatment effectiveness. Additionally, the online and mobile format (used slightly differently between the Mobile and Mobile+Group) enhances accessibility and potential long-term sustainability by standardizing MBI instruction in a cost-efficient manner. Protocols have been informed by the RE-AIM and PRECIS frameworks and discussions with administrators from participating health systems. Previous and ongoing studies by the investigators, including qualitative work of chronic pain patients' perspectives,[114,115] have also contributed to intervention design.

Mobile MBI. The Mobile MBI is an asynchronous intervention that is not delivered in real time. The training schedule for participants includes 8 weekly lessons of approximately 30-60 minutes (which can be spread out, to accommodate participants' schedules), up to 20 minutes of mindfulness practice daily, and 3 scheduled calls with study staff (at the beginning, middle, and end of the program to check in and help guide participants). Weekly lessons will be available on the app and online in a modular format, and aimed at cultivating mindfulness by addressing intention, attention, and attitude which are considered core components of MBSR training. Mindfulness skill building will involve instruction, practices, and exercises incorporating some of the same features and focus of MBSR, adapted to cultivate mindfulness-oriented pain management. Key topics will include working with perceptions, stressors, presence, embodiment, habits, stress reactivity, maladaptive coping, cognitive reappraisal, community building, applicability to everyday life, and establishing accountability and resources. The

platform of delivery will be on an app, using narrated videos, readings, guided meditations and mindfulness exercises, presented by a trained mindfulness instructor. Each lesson will cover an introduction and exploration of key mindfulness related topics, guided meditations via narrated video and audio formats, readings, and written reflective exercises. The online mobile application will incorporate resources and strategies to increase adherence and practice (e.g., self-monitoring via daily diary, ability to engage in real-time mindfulness strategies, and guided meditations of varying lengths that can be performed during daily activities). It will also allow participants to work through the materials at their own pace and revisit topics as needed. Study staff will schedule 3 calls with participants (at the beginning, middle, and end of the 8 weeks) as check-ins designed to increase engagement. Participants will have access to email and telephone support lines, staffed by a trained team member, who will provide technical assistance and be able to answer basic questions related to mindfulness practices. We will continually update our protocol and training manual to reflect commonly asked questions.

Mobile+Group MBI. The Mobile+Group MBI offers the same weekly lessons as described for the Mobile MBI and also includes a group component delivered via UMN Zoom, a VA and HIPAA compliant videoconferencing software (see description on p. 18). Participants in the Mobile+Group MBI will be enrolled in a group with other Veteran study participants with chronic pain, who will gather about weekly (8 sessions, each approximately 1.5 hours long) to view online narrated videos, guided meditations and mindfulness exercises, presented by a trained mindfulness instructor. These online components will be interspersed with group discussions led by a facilitator. These facilitators will not be certified in MBSR but will have sufficient familiarity and understanding of mindfulness and MBIs to provide participant support (see Facilitator Training below). This has several advantages. First, it will facilitate consistency and fidelity across study cohorts. Second, by not needing extensive training and certification of facilitators (which is what is required for MBSR instructor certification), there is a greater likelihood that the intervention can be adopted and sustained in VA settings. From a future implementation perspective, it will allow us to use existing VA staff as facilitators. We have already identified staff members who are interested in facilitating through a preliminary study at the Minneapolis VAHCS. Participants will also have access to the email and telephone support lines that those in the Mobile MBI condition will have access to (described in the section above).

Table 1: Components of Mobile+Group MBI and Mobile MBI, compared to Standard MBSR

Feature	Standard MBSR Course	Mobile+Group MBI	Mobile MBI	Purpose of modification
Key Components	Intention, attention and attitude	Same as MBSR	Same as MBSR	N/A

Table 1: Components of Mobile+Group MBI and Mobile MBI, compared to Standard MBSR				
Feature	**Standard MBSR Course**	**Mobile+Group MBI**	**Mobile MBI**	**Purpose of modification**
Mindfulness Skill Building	Instruction, exercises in perceptions, stressors, presence, embodiment, habits, stress reactivity, maladaptive coping, and cognitive reappraisal, community building, applicability to everyday life, and establishing accountability and resources; meditation practice	Same as MBSR	Same as MBSR	N/A
Total hours	29-33 hours	12+ hours	9+ hours	
Class schedule	Introductory session: 2.5 hrs; 8 weekly sessions lasting 2.5 hours each; 6 ½-8-hour retreat	8 weekly sessions, 1.5 hours each (45 min. recorded session, 45 min. group with option to review again, at own pace at home) & 1 technical session	8 weekly sessions, 30-60 minutes each (with option to review again at own pace) & 3 scheduled check-ins	Reduced class schedule to improve adherence/ sustainability
Delivery method/ Instructors	In person, group sessions, delivered by certified MBSR instructors	Group settings, using pre-recorded online lessons presented by a trained mindfulness instructor interspersed with group discussions led by a trained facilitator (not required to be an expert in MBSR)	Online, individual based, using pre-recorded online lessons presented by a trained mindfulness instructor; written reflective exercises (done on own) replace group discussion	MBSR- or mindfulness-trained instructor not required; increases reach; Asynchronous (Mobile MBI)

Table 1: Components of Mobile+Group MBI and Mobile MBI, compared to Standard MBSR				
Feature	**Standard MBSR Course**	**Mobile+Group MBI**	**Mobile MBI**	**Purpose of modification**
Out-of-class mindfulness practice	≥45 minutes daily	Up to 20 minutes daily guided meditation on the app (with opportunity for additional practice, including very brief guided meditation of 1-5 minutes); guided meditations to do during daily activities (e.g., walking, eating) and in response to pain and co-occurring states that can trigger maladaptive coping responses (e.g., stress, anxiety, anger).		Shorter practice sessions to improve adherence and sustainability; opportunity to use mindfulness to inhibit maladaptive and activate adaptive pain responses
Resources provided	Audio CDs for practice (Guided Mindfulness Meditation, Series 1 and 2) and Course Workbook	Mobile application including video, audio, available online and offline, guided/unguided of varying lengths. Course workbook available in hard and electronic copy.		Mobile+Group MBI participants have opportunity to make up or review missed sessions via the app
Behavioral change strategies		Use of mobile tools to facilitate behavioral change strategies such as self-monitoring, feedback on performance; activation of adaptive pain and stress-related response strategies in "real time".		Increase adherence to class sessions and practice; inhibit maladaptive and activate adaptive pain responses
Additional framing specific to Veterans and chronic pain		Communication strategy throughout course aimed at reinforcing understanding and purpose of course activities and how they are expected to improve chronic pain and comorbid outcomes.		Consistent and motivational communication to increase retention, adherence and practice

Facilitator Training. The investigators have previous experience successfully designing and delivering similar interventions. Training will occur prior to the start of recruitment and annually thereafter. Training will be provided by Co-I Haley (certified mindfulness instructor and trained

facilitator/coach); Co-I Evans (who has substantial experience training facilitators to deliver self-care interventions for pain conditions); PI Burgess (who has experience training counselors to deliver a self-management intervention for Veterans with chronic pain), and Mallory Mahaffey, who was the primary facilitator for the pilot study. The goals of the proposed facilitator training are to empower individuals within the VA system to be able to support MBIs in a sustainable fashion, and to ensure consistency and reliability in MBI delivery (treatment fidelity). We will provide standardized training to ensure facilitators have the necessary skills and comfort levels to deliver the intervention. Given that the facilitators will play a supportive role to the standardized mindfulness based online video recordings, focus will be placed on developing skills that encourage reflection and discussion about patients' experiences with mindfulness (similar to what would occur in an MBSR program). Basic skill building will focus on establishing rapport; remaining on schedule and adapting as necessary; applying principles of the program to patients' situations; encouraging patient involvement; pacing sessions effectively; using effective interpersonal skills; and exercising professionalism and judgement. More advanced skills also will be addressed including effective communication such as using open-ended questions; providing affirming responses; reflecting; providing summaries; and dealing with resistance.[116] [117] Initial training will include interactive workshops presented via videoconference (total of about 8 hours) scheduled at times convenient for facilitators. These will be supplemented by webinars and online training (total of about 8 hours). Videoconferences (about monthly for 1 hour) will be held and led by Mr. Haley, Dr. Evans, and Dr. Burgess, to build a community of practice to problem-solve, facilitate consistency, and ensure adherence to study protocols, between facilitators and across sites. Annual refresher training will include workshops (total of about 4 hours) with webinars and online training modules (total of about 2 hours). Fidelity to group sessions will be assessed through structured fidelity checklists (adapted from those used previously)[132] [133] applied to random observation of intervention sessions (10%).

Risk vs. Potential Benefit. The proposed research poses "minimal risk" to subjects. There are no experimental procedures involved in this study. The potential risks to study participants include loss of privacy and confidentiality. There are no economic and minimal social risks of participating in the study. The surveys will not ask very sensitive questions and subjects can refuse to answer any question(s). The potential risks associated with the individual interviews include psychosocial stress (any research project with direct contact with human subjects contains some risk of deleterious effects due to psychosocial stress). This is true for both usual care as well as intervention groups.

Mindfulness-based interventions are regarded as relatively safe interventions. A 2018 systematic review examining the safety of randomized controlled trials of mindfulness-based interventions found very few adverse events, with no significant differences in reported adverse events between intervention and control groups.[138] Nonetheless, we have developed a crisis management protocol to address issues involving participant safety and systematically collect safety information, including severe adverse events (SAEs), unanticipated problems (UAPs), and adverse events (AEs). In the follow up questionnaires, participants will be asked to report side effects/adverse events related to the interventions by choosing from a list generated from the literature and the investigators' experience (see below).

Since you started your participation in the study have you experienced any of the following. Check all that apply.

1. Increase in disturbing memories
2. Feeling more upset than usual when something reminded you of the past
3. Increased feelings of sadness
4. Increased feelings of anxiousness
5. Seizures
6. Feeling more tired or fatigued than usual
7. Feeling more isolated or lonely
8. Other physical or mental symptoms; please specify: _____

If yes, please explain further:

Specifying conditions that would trigger an immediate suspension of the research is not applicable to this minimal risk study. If information does arise that necessitates communication, the study team will contact participants by phone and providers via encrypted email.

Dr. Burgess will be responsible for overseeing and ensuring an IRB-compliant process for reporting Adverse Events (AEs), including Serious Adverse Events (SAEs), and Unanticipated Problems (UAPs), should any occur. If/when Dr. Burgess is unavailable (e.g., away from her post), Drs. Polusny and Meis will serve as backup persons responsible in Dr. Burgess's stead.

Behavioral health contact information will be included in printed study materials and on the mobile application. Contact information will include the national Veterans Crisis Line (1-800-273-8255 [TALK] and press 1) and local VA Health Care System contacts. If the participant endorses self-harm ideation or is in emotional distress when in group or on the phone with a member of the study staff, staff will follow a mental health protection for human subjects protocol, on which all study staff will be trained.

Our hypothesis is that participants in the Mobile and Mobile+Group MBIs will experience relief from chronic pain in terms of intensity and interference. It is possible participants in the UC group may also experience a decrease in pain intensity and interference. Still, it is possible that participants will experience no direct benefit from taking part in this research study. However, the information participants provide from this study might help us treat future chronic pain patients. This research will help guide the development of strategies to improve health care within the VA, particularly for veterans with chronic pain.

Aim 2

Data will be collected and described, guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

AIM 2a (PRE-IMPLEMENTATION): We will use surveys with closed- and open-ended questions, aimed at understanding participants' experiences (e.g., barriers and facilitators) with different intervention components. A final question will ask, "Our team would like to share Veterans' experiences participating in the LAMP study. Would you be willing to be contacted by

our research team in the future for this?". Participants who say yes to this maybe be re-contacted in the future regarding additional study opportunities, either with LAMP or with other research studies. A letter letting participants know about the re-contact possibility will be mailed ahead of any re-contact attempts and will include the option of opting out of re-contact attempts.

AIM 2b (PRE-IMPLEMENTATION): The purpose of this study is to identify barriers and facilitators to the successful, long-term implementation of the LAMP program in the VHA, to inform future implementation efforts. Participants will be VA employees who could provide input to guide the future implementation of LAMP (such as providers involved in treating pain). We will identify these participants with input from our facility, VISN, and national partners, including our operational partners from the Office of Patient Centered Care & Cultural Transformation (OPCC&CT) and the Pain Management, Opioid Safety, Prescription Drug Monitoring Program (PMOP). Recruitment, interviews, and data analysis will be conducted by study staff, including the Principal Investigator Dr. Burgess.

Risk vs. Potential Benefit. The proposed research poses "minimal risk" to subjects. There are no experimental procedures involved in the study. The potential risks to study participants include loss of privacy and confidentiality, and minimal economic and social risks. All efforts will be made to de-identify transcripts, keep data confidential and results anonymous.

Participants will be assigned their position title or other general label instead of actual names in the field notes, interview transcripts, and interview file names. Other individuals referred to by participants will be assigned their position title or other general label instead of names. When disseminating results, whether oral or written, the research team will collapse information across stakeholders to ensure that no sensitive or identifiable information is included.

We anticipate few direct benefits to participants in our pre-implementation study. However, the information participants provide from this study might help us treat future Veterans with chronic pain. This research will help guide the development of strategies to improve health care within the VA, particularly for Veterans with chronic pain and underserved subgroups of Veterans (e.g., women, rural, and racial/ethnic minorities).

Vulnerable populations. Stakeholders involved in our study may be considered vulnerable, either because they are from underserved populations, minority populations, are women, and/or are employees of the VA. All study subjects are expected to be 18 years of age or older (no children will be included). We will follow all required protocols when working with VA employees as study participants, including communication with employee unions.

5.2 Recruitment Methods and Participant Enrollment

Aim 1

We anticipate recruiting up to 950 participants from our 4 sites, using our proactive recruitment protocol (see below). The subject population for our study will be chronic pain patients from the Minneapolis, Durham, Indianapolis, and Los Angeles VA medical centers They will be 18 years or older. Using this protocol, we plan to recruit up to 950 participants with about 40% being female. Participants will be randomized to one of the 3 study arms and asked to participate in the subsequent intervention. Thus 250 participants will be in each arm (Mobile+Group, Mobile, and UC). All participants will be asked to complete the screener, and then complete the baseline and 10-week, 6-month, and 12-month follow-up surveys. Participants will be given $25 for each survey they complete (possible total of $100). Completion of the eligibility components will result in randomization to one of the three study arms, (Mobile+Group MBI, Mobile MBI, or UC (1:1:1)).

Proactive recruitment protocol.

For the PCT, these patient study IDs will be imported into Qualtrics FedRAMP. Participants will be recruited using two different approaches. All participants will receive pre-notification of the study by postal mail. In Approach #1 ("postal mail-only"), introductory letters will be mailed that include instructions for accessing the study website via a secure URL, an opt-out option, and information about the monetary incentive that study participants will receive. Participants will also be sent an information sheet, informational newsletter, and general introductory brochure. In Approach #2 ("postal mail + email), participants will be notified about the study by postcard, which will: 1) inform them that they will be receiving an email inviting them to be in a research study for Veterans and 2) provide instructions for opting out via email or phone. This postal mailing will be followed by an email, using the email in the VA EHR, which will contain the same information (in email form) provided to those in paper form in Approach #1. This "email recruitment packet" will contain instructions for accessing the study website via a secure URL (which has been approved by the ISSO in a prior amendment) and direct links to the information sheet, informational newsletter, and general introductory brochure, which reside on the website. The email will also contain an opt-out option, information about the monetary incentive that study participants will receive, and information contained in the paper brochure. Emails will be sent using Qualtrics FedRAMP. Qualtrics FedRAMP is authorized by an ATO to collect data from Veterans and store data on VA cloud servers.

In Approach #1, participants who do not respond will be sent a reminder postcard to encourage a response of some sort. In Approach #2, participants who do not respond will be sent reminder postcards and/or emails to encourage a response of some sort. Participants who log into the study website will then be directed to the study screener. Study staff will potentially follow-up with participants who start the screener and/or baseline but do not finish, as well as participants who do not respond in any way. Communications will include answering participant questions, encouraging people to do the screener and baseline online, reviewing what is coming next in the study (medical chart review, baseline survey, follow-up call for randomization, etc.), and

asking questions about how to improve the recruitment process. Trained study staff will respond to participants who reach out via email or phone with questions.

Refer to the 5.4 Inclusion/Exclusion section below for eligibility criteria.

Aim 2a: Pre-implementation data will be collected from Veteran participants via survey.

Pre-implementation data will be collected from Veteran participants as an "extra" survey intervention participants can opt into at the end of their 10-week follow-up survey. The pre-implementation survey will be administered using Qualtrics FedRAMP, as are the other surveys in this study. Participants will be paid an additional $25 for completing the pre-implementation survey. We will send them minimal text and email reminders if they indicate they would like to complete the extra survey but don't do so within a few days.

Aim 2b: Pre-implementation data will be collected from VA employee stakeholders using rapid qualitative analysis methods

Recruitment protocol. We will recruit a total of n=30 employee stakeholders by email. The email will come from the Principal Investigator (Dr. Burgess) and will invite the participant to completed a semi-structured interview (lasting 30-45 minutes), conducted over video, aimed at helping the research team identify barriers and facilitators to implementing a new mindfulness program for Veterans with chronic pain, within the VHA. Participants will also be asked to complete a short demographic questionnaire only using VA-approved Qualtrics FedRAMP. Limited reminder emails will be sent to non-responders.

Study Procedures and Materials. All qualitative interviews will be video and/or audio recorded using VA-approved technology (e.g., Microsoft Teams). Meeting times will be agreed upon ahead of time between facilitators and stakeholders. All reasonable efforts will be made to work with each stakeholders' schedule and preference for meeting.

5.3 Informed Consent Procedures

5.3a. Informed Consent Procedures for Veterans (Aims 1 and 2a)

We will seek waivers of both informed consent and HIPAA authorization for the initial search of EHRs for potential participants. The research meets all of the criteria for requesting a waiver of the informed consent process, including involving no more than minimal tangible or intangible risk to the participants, the waiver will not adversely affect the rights and welfare of the participants, the research could not practicably be carried out without the waiver, and when possible, participants will be provided with additional pertinent information after participation.

The information requested in the waivers is needed on all identified subjects so that we are able to conduct analyses to assess and correct for non-response bias. Specifically, we plan to conduct analyses to determine whether the participants who responded to our request for

participation differ from those who did not respond, on a number of characteristics that are available through the administrative data set (e.g., age, healthcare comorbidity). If we do find that non-response bias exists, we would then be able to statistically adjust for this bias using the data on non-respondents available from the administrative dataset. Requiring HIPAA authorization for the VA administrative data requested in this waiver from subjects would not allow us to conduct these analyses. In addition to the initial search of EHRs, we are seeking a waiver of HIPAA authorization for the entire study.

We are seeking a waiver of documentation of informed consent for the PCT portion of the study, the "pre-implementation" follow-up surveys with a portion of intervention participants, and re-contacting a portion of the pre-implementation follow-up survey completers. We are not asking sensitive questions in this survey. Asking subjects to return signed consent and authorization documents for this minimal risk study would dramatically reduce response rates and introduce bias. Additionally, the signed consent form would potentially increase risk for loss of privacy as all identifying information will be destroyed as soon as feasibly possible. Participants will receive mailed, pre-notification (postcard or letter, depending upon the recruitment approach; see Section 5.2) that contains an opt-out option for those who do not want to be contacted any further. Participants in recruitment approach #1 (postal mail only) will receive, with their pre-notification letter, an information sheet containing: 1) information explaining the risks and benefits of study participation, 2) their rights as study participants and their privacy rights and 3) required elements of informed consent. Participants in recruitment approach #2 (postal mail + email) will be given a link to an electronic copy of the information sheet, as part of their email recruitment packet. Randomized participants in recruitment approach #2 will be sent a paper copy of the information sheet in their randomization packet.

Prior to randomization, participants will be contacted via a phone call in which all participation components will again be reviewed. This will include requiring participants to provide an emergency contact person and explaining that study staff will do the following if they are concerned about a participant's or others' safety. Study staff will explain: If we are concerned for your immediate safety, we may try calling, and/or emailing you, contacting your emergency contact person, and will then escalate further (for example, asking the Veteran Crisis Line staff to contact you, asking the Suicide Prevention team at your VA site to contact you, or asking your local police to do a wellness check) as it seems necessary to protect you or others. Only if participants agree to continue, they will be randomized a study group.

5.3b. Informed Consent Procedures for VA employee stakeholders (Aim 2b)

We are requesting a waiver of documentation of informed consent for this portion of the study as it does not exceed minimal risk. Participants will be provided with an Information Sheet describing the same aspects of the study as an informed consent form would do. It will be explained that the recordings will only be heard/viewed by authorized members of the research team and will be de-identified. Participants can stop the interview at any time. A copy of the VA CIRB information sheet will be provided to each stakeholder ahead of data collection. Stakeholders will have multiple opportunities to ask questions prior to data collection.

5.4 Inclusion/Exclusion Criteria

5.4a. Inclusion/Exclusion Criteria for Veterans (Aims 1 and 2a)

Several evaluation components will be used to assess eligibility. In keeping with the pragmatic nature of our design, we will have minimal exclusion criteria.

Participants eligible to receive an introductory letter will be those have received a qualifying pain diagnoses on at least 2 occasions, at least 90 days part, within the same pain category, during the previous 2 years. The pain categories were initially defined by Goulet et al using International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnostic codes (ICD-9-CM/ICD-10-CM) and updated based on our team's participation in the PMC3 Phenotypes and Outcomes Working Group. Participants must have received care at one of the study sites.

Screener questions will be asked (online via Qualtrics FedRAMP or over the phone) to assess whether the following are true:

- Eligible participants must have pain duration of ≥ 6 months, and moderate to severe pain intensity (defined as a numeric rating score of ≥ 4 on a 0 to 10 scale).
- Participants must have access to a smart phone that meets the requirements of the mobile app software (this is pragmatic as access to such devices would be required for participation in a non-research context).
- Participants must have access to a device (e.g., smart phone, iPad, desktop computer) that enables them to participate in online UMN Zoom meetings).
- Participants must be willing and able to download the mobile app onto their phone and agree to the app-required permission settings.
- Participants must have adequate wireless or cellular internet access on a daily basis in a private space (e.g., at home).
- Participants must be willing to meet via Zoom at the specific date and time that Mobile+Group sessions are held.
- Participants must be willing to attend all sessions of the arm to which they are randomized.

As part of the screener, participants will be asked whether they prefer to receive communication by phone, email, and/or text message. They will have the opportunity to provide their phone number to allow phone calls, email if they would like us to contact them by email using Qualtrics FedRAMP or the LAMP study email address (vhaminlamp@va.gov), and they can choose to provide their mobile phone number if they would like us to contact them via text message.

Study staff will conduct a medical chart review in the electronic medical record of all participants who meet the screening criteria, in order to exclude any patients with active psychotic symptoms, suicidality, severe depression, and/or active manic episode or poorly controlled bipolar disorder. Some experts consider these disorders as contraindications for MBIs.

We will not exclude Veterans who are prescribed medication or receiving other treatments for chronic pain. However, we will collect information about medication and other treatment use and take this into account in our analyses.

Besides meeting all eligibility criteria, PCT participants must also complete the baseline survey before randomization will occur.

5.4b. Inclusion/Exclusion Criteria for VA Employee Stakeholders (Aim 2b)

Participants will be VA employees who could provide input to guide the future implementation of LAMP (such as providers involved in treating pain). We will identify these participants with input from our facility, VISN, and national partners.

5.5 Study Evaluations

5.5a. Study Evaluations for Veterans (Aims 1 and 2a)

Data Collection. Data will be collected using Qualtrics FedRAMP surveys, paper surveys, telephone surveys, the mobile application, and EHRs. These measures are described below and in Table 2.

Qualtrics FedRAMP electronic survey software accessed via the VA cloud will be used. Qualtrics FedRAMP has been approved for use from the VA OIT Security standpoint (Authority to Operate or ATO). The ATO status is currently approved for 1 year and a full 3-year ATO is in the works. (See ORD IT Service Catalog 190530 memo for more details.) Qualtrics FedRAMP surveys will contain a study ID number, time of data entry and limited individually identifiable information. Within the VA firewall, the study team at the VA will create a custom-built tracking app that will track each participant's enrollment and study status. Data will be routinely extracted from Qualtrics FedRAMP in the VA cloud and stored on secure CCDOR servers, using SQL database connections. All data will be stored and utilized within secure CCDOR servers that are part of the Minneapolis VAMC network and which operate behind the VA firewall. All data is tracked using a SQL database, with a GUI-front end system that restricts access to only those with approval to study data.

Qualtrics FedRAMP surveys will contain minimal individually identifying information. The only identifying information will be information that is self-reported by the participants (e.g. name, phone, email, which is best method of contact). No sensitive data will be stored outside of the VA protected environment. Once data are transferred for data analysis, data will be maintained on password-protected VA computers in the VA environment and on secure VA servers.

Study staff will monitor the functioning of the Qualtrics FedRAMP application. Only staff affiliated with this research protocol will have access to Qualtrics FedRAMP data collected for this study. The PI or her designee will be responsible for monitoring data storage location and transfer of data between the VA cloud and VA server.

We will have dedicated research personnel at the central Minneapolis site to coordinate study data acquisition based on regularly updated reports. We will use several strategies to follow-up with participants who have not completed their assessments. To help decrease the number of participants who don't complete their assessments, we will mail a newsletter between each survey and a reminder postcard shortly before each survey is emailed. After sending assessments, we will contact non-responders via their specified preferred method and using additional contact information they provided. We will encourage online completion but mail paper copies or complete surveys by phone as preferred. We will email, mail, call, and text participants with reminders to complete the surveys. The emails will be sent using the LAMP study email address or via Qualtrics FedRAMP. Text messages will be sent via Qualtrics FedRAMP. Participants will be contacted to follow-up on any missing data that doesn't seem deliberate (e.g., if a couple of survey pages are completely blank but the rest of the survey is answered, it is likely the couple pages got stuck together rather than deliberately skipped). Participant flow data using the Consolidated Standards of Reporting Trials (CONSORT) framework[118] will be collected, including recruitment, enrollment, intervention adherence, intervention fidelity, and data collection rates.

For intervention participants, all mobile app data collected will occur via a secure cloud-based application designed by MEI Research Ltd to support data capture for research studies and will be accessed as part of the mobile application. Because we are collecting mobile app data, we will be temporarily storing IP addresses, URLs, device identifiers, serial numbers, since this type of mobile app data may need to be collected as participants use their smartphones to interact online with the study application. The secure cloud-based application designed by MEI Research Ltd. to support data capture for this research study must be accessed as part of the study intervention. As the participant's smart phone engages online with the study application some information (IP addresses, URLs, device identifiers, serial numbers) may be captured by the cloud-based application in order appropriately deliver the correct content to the participant's device. However, we will not use this information in our research or transfer it to the VA. Co-I Dr. Ferguson has successfully conducted VA-funded studies using this data collection approach.

Data coordination and management. Data collection and management will be overseen at the Minneapolis VA HSR&D Center of Innovation (COIN) by Dr. Brent Taylor. Regular meetings of investigators and study staff within and between sites will take place to routinely review data collection and management issues. To prevent improper use of any data collected for research projects conducted at the Minneapolis COIN we will use a combination of local Minneapolis VA secure servers as well as the national secure VA Informatics and Computing Infrastructure (VINCI) and the secure Qualtrics FedRAMP system in the VA cloud. The local VA secure servers facilitate data collection and provide a platform for the customized research tracking application, while the VINCI platform provides a robust environment for pooling the primary research collected data with direct connections to daily or weekly updated mirrors of nearly the entire VHA EHR. VINCI also provides access to extensive storage area networks, drives, file shares, databases, SharePoint for collaboration and correspondence sites, SAS/Grid, and servers containing virtual machines with an extensive collection of software called the VINCI Workspace. We will request access to the Joint Legacy Viewer (JLV) in order to capture the

highest follow-up response rate that is feasible. It is very important that we reach the participants in a timely manner; being able to access current address and phone numbers will help in tracking hard to reach participants. A secure link between local VA secure servers, the data collected on the MEI designed mobile applications, and Qualtrics FedRAMP will be created. Limited study specific data will be collected on the mobile applications and Qualtrics FedRAMP and will contain a study specific participant ID code. Only after the data are securely transferred to the local VA server environment will the mobile study data be linked to participant VHA data using the study ID. VINCI allows individual researchers and their staff the means to securely conduct their research projects within a secure and well controlled technical environment. All of these VA systems undergo backups of the servers nightly and servers are updated when new security patches become available. All individuals with administrative privileges to the VHA servers have been screened and have been assigned security clearance putting them in trusted positions to work with patient-level data.

Measures

Table 2: Study Measures

Legend: EHR: Electronic Health Record; S: Survey; M: Mobile app; F: Facilitator Records	BL	10 wk	6 mo	12 mo
Flow data (recruitment, enrollment, intervention adherence and fidelity, data collection rates)	x	x	x	x
Demographic and health-related characteristics				
Demographics, physical & mental health characteristics, military sexual trauma screen, medication use, prior treatment for pain, pain over past 6 months (S, EHR)	x			
EFFECTIVENESS MEASURES				
Primary Outcome				
Pain Intensity and Interference (Brief Pain Inventory Total Score; BPI) (S)	x	x	x	x
Secondary Outcomes				
Physical function, anxiety, depression, fatigue, sleep disturbance, participation in social roles and activities, patient-ratings of improvement, PTSD (S)	x	x	x	x
Process Measures				
Medication, health care utilization related to pain treatment (S, EHR)	x	x	x	x
Satisfaction (S)		x		
Adverse events (S; Veteran report; events reported to C-IRB)		x	x	x
Pain management self-efficacy Pain Self-Efficacy Questionnaire' PSEQ) (S)	x	x	x	x
Pain catastrophizing, Pain Catastrophizing Scale (PCS) (S)	x	x	x	x
Applied Mindfulness Process Scale (AMPS) (S)	x	x	x	x
Perceived stress (NIH Toolbox Perceived Stress Fixed Form) (S)	x	x	x	x

Amount of meditation practice, app use, and class attendance (M, F, S)		x	x	x
Use of non-pharmacological pain management strategies (S) COVID-19 questions	x x	x	x	x

Baseline Measures will include demographic data (assessed by self-report and the EHR) and clinical data (assessed by the EHR) to capture common mental health comorbidities (e.g., depressive disorder, PTSD, anxiety, sleep-related disorders, and substance use disorders), medication use, and prior treatment for pain**.** These will be assessed by the baseline survey. We will also include the Pain Management Collaboratory Coronavirus Pandemic (COVID-19) Measures, comprised of seven items assessing the potential impacts of the coronavirus pandemic.

Our Primary Outcome will be pain severity and functioning, defined as a change in the Brief Pain Inventory (BPI) total score (assessed by survey). The Brief Pain Inventory (BPI) assesses two key domains—intensity and interference—recommended for pain studies[99] and has been validated in primary care.[119] The BPI is the average of pain intensity and pain interference scores. The pain intensity score is an average of 4 ratings of 0 (no pain) to 10 (pain as bad as you can imagine) for current, least, worst, and average pain in the past week. The pain interference score averages seven ratings, 0 (does not interfere) to 10 (interferes completely), of interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The BPI has been shown to be highly responsive to change in clinical trials[112] and to have strong internal consistency (Cronbach's $\alpha = 0.77$).[119]

Secondary Outcomes. To facilitate data sharing and comparison between studies we have incorporated Common Data Elements (CDEs), for use in our patient surveys. Specifically, we will use measures from the PROMIS-29 Profile v2.0 Instrument (www.nihpromis.org) as recommended by the NIH Research Task Force.[123] This includes quality of life, emotional functioning and mental health-related outcomes (anxiety, depression), and outcomes related to fatigue and sleep. Self-reported data will also be collected on PTSD symptoms using the PTSD checklist (PCL), version C, DSM-V update,[124] and patient satisfaction (using a short measure used by investigators Bronfort and Evans).[125] These outcomes will be assessed via survey.

Adverse events will be monitored throughout the study period, using a process similar to other MBIs with Veterans. Specifically, Veterans will be given contact information encouraged to report exacerbation of symptoms or adverse effects to the class facilitators or study coordinator.[126]

We will use electronic medical data from VA health care records to assess other measures of chronic pain burden including change in analgesic use (including opioids), and frequency and health care utilization (e.g. MRIs, injections, hospitalizations, surgery). Among those prescribed opioids, we will assess change in opioid use from baseline using VA pharmacy dispensing data. Opioid daily dose at any given time will be calculated as the mean dose over the prior 90 days. Established conversion tables will be used to calculate morphine-equivalent (ME) mg. Receipt

of pain-related services outside of intervention visits will be estimated by capturing pain-related specialty visits and pain-related mental health visits. Complementary therapies are not all well captured in VA databases, but therapies with specific codes (e.g., acupuncture) will be assessed. Other complementary services may be variably recorded under general codes; for example, yoga could be coded as a recreational therapy visit.

Process Measures/Mediators will include items to assess Capabilities, Opportunities, Motivations, and Adaptive Pain-Related Behaviors that the intervention is designed to address (delineated in our Theoretical Framework, see Figure 1). Mindfulness skills will be assessed through the Applied Mindfulness Process Scale (AMPS), a 15-item validated scale will be used to assess the extent to which participants used mindfulness practice in their daily life (e.g., to "calm my emotions when I was upset," "stop reacting to my negative impulses," "relax my body when I was tense," and "stop my unhelpful reactions to situations").[85] Opportunities will be assessed by the amount of training and practice participants engage in, captured by the mobile application and self-report. Motivations will be assessed by increases in pain acceptance and pain management self-efficacy and decreases in pain-related fear avoidance. Pain catastrophizing will be assessed with the Pain Catastrophizing Scale (PCS). Pain management self-efficacy will be assessed with the 8-item Pain Self-Efficacy Questionnaire (PSEQ),[131] which has been used in numerous studies with chronic pain patients. Adaptive pain-related behaviors include reduction in opioid analgesics (assessed by EHR data) and increase in use of non-pharmacologic pain management strategies (assessed by EHR data and self-report). We also will assess perceived stress, with the NIH Toolbox Perceived Stress Fixed Form Age 18+ v2.0.

5.5b. Study Evaluations for VA Employee Stakeholders (Aim 2b)

Note: These questions may be tailored to different subgroups.

1. Who are the decision-makers we would need to get buy-in from at your facility or VISN, in order to implement this program? (Probe for roles; who are they, may include interviewee…)
2. What would these decision-makers need to persuade them that this program is worth implementing, even on a trial basis?
3. Who else is critical to implementing this program and making is successful?
4. What are the obstacles we would need to address in order to implement this program and make it a success?
5. What are some things that would help us successfully implement this program?

Demographic questions (asked via Qualtrics FedRAMP online survey):

1) What is your age?
2) How would you describe your gender? (Select one.)
   a. Man (1)
   b. Woman (2)
   c. Another gender category, please specify:_____(3)___
   d. Decline to answer (4)
3) What is your ethnicity? (Choose the one with which you MOST CLOSELY identify.)
   a. Hispanic or Latino (1)

b. Not Hispanic or Latino (2)

4) What is your race? (Choose all those with which you identify.)
   a. Black or African American (1)
   b. American Indian/Alaska Native (2)
   c. Asian (3)
   d. Native Hawaiian/Pacific Islander (4)
   e. White (5)

5) What is your occupational role?_____

5.6 Analysis Plan

AIM 1: EFFECTIVENESS

Primary effectiveness will be assessed by **pain severity and functioning** over the 12-month follow-up (Brief Pain Inventory total score). Secondary analyses will examine the effectiveness of the intervention separately by gender.

Secondary outcomes will include measures captured in health care records (e.g., medication prescription/refills, health care visits for pain management) as well as patient-reported measures related to pain, comorbid mental health conditions and function, expected mediators of treatment effects, patient satisfaction, and adverse events. We will also explore patient characteristics that may predict treatment response. These outcomes will be assessed at baseline, 10 weeks, 6 months, and 12 months. Aim 2.1 methods involving recruitment, study design, intervention, data collection, and outcomes are described in the prior section. Methods related to expected participation, data analysis, and data coordination and management are described in the following section.

Expected participation in Phase 2 trial

We base proposed estimates on our experience conducting previous successful trials with Veterans with chronic pain (ACTION, SPACE, EPOCH, ECLIPSE). Study participants will be recruited from the Minneapolis, Indianapolis, Greater Los Angeles and Durham VA Health Care Systems, using a process successfully used in prior studies by members of our research team, and piloted during Phase 1 of this project. The four facilities have about 80,000 patients who meet our initial eligibility criteria. We estimate from our Phase 1 pilot a randomization rate of 2.5% but an increased randomization rate when using approach #2, email recruitment. Therefore, we will need to screen approximately 100,000 patients in order to reach our recruitment goal of up to 950 randomized. We want an approximately balanced sample of men and women. We estimate women will respond at up to 3 times the rate of men (approximately 4.5% for women and almost 2% for men). If we screen a large portion of the sample of eligible women (about 20,000) and about 1/3 of the eligible men (about 80,000), then we should reach our recruitment goal of up to 950 randomized, with nearly balanced men and women. Among those randomized, we are conservatively planning that up to 20% might be missing complete follow-up data but based on past work we believe the actual level of missing data will be closer

to 10-15%. Ultimately, this would yield a randomized N= up to 950 and with retention of 600 or greater participants at 6 and 12 months.

Power and Sample Size Estimate

Our power calculation uses the total BPI score as the primary outcome measure. For our primary analysis we estimate there will be 200 participants in each of the three treatment arms with complete data for a total of 600 people with complete data from a total of up to 950 randomized. Two hundred participants in each arm would yield 80% power to reject the null hypothesis of equal means if any of the three arms differed from each other by an effect size of 0.33 or greater. This is based on an alpha level of 0.0167 (Bonferroni correction of 0.05/3 = 0.0167) for each of the three comparisons (Mobile+Group vs Usual Care, Mobile vs Usual Care, and Mobile+Group vs Mobile). Using the same assumptions, there would be 90% power to detect differences of 0.38 or greater. The BPI has been found to have a minimally clinically important difference of approximately 1 point and the standard deviation from prior studies is around 2 points, which is consistent with a minimally important clinical difference in effect size of around 0.5.

As a secondary analysis we will look at a categorical responder analysis, in which we define clinically significant changes as a 30% reduction in BPI score from baseline. This is an accepted threshold for clinically significant improvement in clinical trials and recommended by the IMMPACT guidelines.

Previous studies demonstrate that a 30% reduction on the BPI is a clinically important difference. Prior studies have shown that 15-20% of UC patients demonstrate a 30% reduction in pain function score from baseline to follow-up. With 200 people in each arm there would be 80% power to detect absolute differences of greater than 13.3%, 14.3%, and 16%, respectively, based on assumptions of 15%, 20% or 35% in the comparison arms (accounting Bonferroni corrections for comparisons of Mobile+Group vs Usual Care, Mobile vs Usual Care, and Mobile+Group vs Mobile).

Based on the conservative estimate of 20% attrition, we propose randomizing at least 250 per arm to ensure that we maintain a minimum effective size of 200 per group (250 people per group*.80=200). If we instead achieve the anticipated attrition rate of only 10% then our sample will be approximately 225 per arm.

General Analytic Approach.

We will use an intention-to-treat approach. Preliminary descriptive analyses will summarize the distributions of the baseline measures across treatment arms overall and by gender and will similarly assess the outcome distributions across assessment time points. We will summarize the completeness of the self-reported outcome assessments and examine associations between completeness and baseline measures as well as the association with secondary outcome assessments that are collected from the electronic medical record (e.g. medications, health care utilization related to pain treatment). In previous studies, we have observed outcome completion rates in excess of 90% at each assessment time-point. Initial analyses will use all

available follow-up data and subsequent sensitivity analyses will examine the potential effect of response bias.

For analyses of the primary outcome, all repeated measurements of the BPI score will be fitted in a mixed model for repeated measures as a function of the group assignment, while controlling for time points and baseline values of the outcome as fixed effects, with participants as random effects. Between-group differences over the entire follow-up period will be tested as the primary test of treatment group differences (this will be done for all three comparisons of the Mobile, Mobile+Group, and Usual Care arms). Between-group differences will be estimated for each of the time points (e.g. 10 weeks, 6 months and 12 months). The secondary outcomes physical function, anxiety, depression, fatigue, sleep disturbance, participation in social roles and activities, patient-ratings of improvement, and PTSD) will be similarly analyzed using the same linear mixed effect models for normal continuous measures and appropriate generalized linear mixed effect models for non-normal measures. For example, the BPI responder analyses will use generalized linear mixed effect models with binomial distributions and either log or logit links, which ever best fit the data, for the repeated dichotomous outcomes of a 30% reduction from baseline in BPI scores over the 12-month study period.

Additional exploratory analyses involve the assessment of the extent to which amount of mindfulness practice, pain acceptance, pain-related fear avoidance, pain management self-efficacy, mindfulness skills, and perceived stress mediate the effects of the intervention. The indirect effects of these potential mediators will be tested using the bootstrap approach to obtaining confidence intervals to avoid the often-violated assumption underlying Sobel's (1982) method that the sampling distribution of the indirect effect will be normal. Similar to the methods described above for the primary analyses, weighted selection model analyses will examine sensitivity of results to response biases.

To assess the sensitivity of these initial analyses to response bias, we will fit a series of weighted selection model analyses. Each analysis will use an EM algorithm to estimate weights to assign to potential values of the missing outcomes for use in the regression model. Models will be varied to use different combinations of the following variables—intervention, observation and value of the outcome at various assessments, and baseline covariates together with pain measurements and services utilization over the follow-up period—as predictors to consider different potential missing at random and missing not at random mechanisms generating the missing data.

It has been hypothesized that men and women may respond differently to the interventions and this might be particularly true for the group-based portions of the intervention. An interaction between treatment and gender will be assessed, however tests for interaction tend to be underpowered and this is an important area of concern, so gender stratified results will be presented in secondary analyses even if statistical evidence of interaction is not found.

PMC COVID-19 Questionnaire Pooled Analysis Plan

We will analyze the clinical and demographic variables that are associated with a high impact from the 2019 Coronavirus pandemic. We will create a dataset (all 18 HIPAA identifiers will be removed) with clinical variables (pain scores, depression scores, suicidal ideation present), demographic variables (age, military branch, race, ethnicity, sex), and COVID-19 questionnaire variables.

A purpose of the Pain Management Collaboratory (PMC) is to support analyses of data pooled from different studies. We will contribute deidentified demographic and clinical data from the LAMP project in the PMC for analyses such as the COVID-19 analysis described above. Study participants will only be identified by a unique identifier that we will securely maintain and the other PMC research projects involved will not have access to. We will combine data from the other studies with ours to create a combined dataset for analysis. Data will be transferred from our group electronically using email and PKI encryption. Data will be stored, managed, and analyzed in the VA environment (research investigator folder and VINCI environment) by project staff on this study. We will enter into a data sharing agreement with groups sharing data that specifies (1) the information will only be used for research purposes and not to identify any individual participant; (2) the information will be secured using appropriate computer technology and (3) the data will be destroyed or returned after analyses are completed. This same request has previously been CIRB-approved for the Pain Management Collaboratory project with PIs Drs. Rosen and Martino.

AIM 2 (PRE-IMPLEMENTATION): data will be collected & described, guided by Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Aim 2a: Pre-implementation data will be collected from Veteran participants via survey
We plan to collect “pre-implementation” data from a subset of intervention participants. We will conduct descriptive analyses of quantitative data separately by intervention condition (Mobile, Mobile + Group); and explore differences that may emerge by gender. Independent t-tests (for means) and z-tests (for proportions) will be used to assess group differences when appropriate. We will use Rapid Assessment Process (RAP) analyses to analyze open-ended responses

Aim 2b: Pre-implementation data will be collected from VA employee stakeholders using rapid qualitative analysis methods.
Our qualitative data analysis strategy was developed specifically for rapid health services research.[139] Prior to conducting any interviews, we will use our interview guide to develop an analytic matrix template, organized by topical area. Interviews will be transcribed. Guided by the transcript, we will complete a matrix for each individual interview. Matrix completion will involve summarizing the unique, substantive participant observations made during the interview for each topical area and transcribing time-stamped participant quotations illustrating each summary. After an initial matrix is completed for each interview, a combined master matrix will be created. All identified observations and illustrative quotations will be compiled into this master matrix.

5.7 Withdrawal of Subjects

Participants can withdraw or be terminated from the study at any point. They can withdraw from the study at any time they feel uncomfortable or choose to do so. We anticipate terminating participation if:

1. The participant displays abusive behavior toward other participants and/or the study staff.
2. Study staff believe the participant cannot meaningfully participate in the study.
3. Study staff believe it is not in the participant's best interest to stay in the study.
4. The participant becomes ineligible to participate.
5. The participant does not follow instructions from the researchers.
6. The study is suspended or canceled.
7. Any other condition that renders patients unable to benefit from treatment.
8. The participant chooses to withdraw consent.

6.0 Reporting

We will follow the VA Central IRB reporting requirements for all issues that must be reported (i.e. unanticipated serious adverse events (U-SAEs), unanticipated problems (UAPs), protocol deviations/violations/noncompliance, and any changes with respect to the protocol). The study staff will remain in regular contact (by phone, email, and face-to-face) to discuss study processes, progress, and any issues encountered. Any issues will be reported directly to the PI. Data will be reviewed regularly to ensure accuracy and data privacy. In the case of problems, the project coordinator will immediately discuss with the study PI. The PI in turn will report any problems to the Central IRB accordingly (e.g., completing forms 119 or 129) within 5 business days of learning of the problem(s). If there are modifications or amendments to the study the study PI will also complete the appropriate Central IRB form (i.e., 116) and wait for approval prior to implementation. Additionally, all unanticipated deaths that are related to a research study overseen by the VA Central IRB must immediately be reported orally to the VA Central IRB via the toll-free number (877) 354-3130.

The current application is for a low-risk clinical trial. The Study Coordinator and participants are not blinded to the study condition group assignment. Therefore, we believe, Dr. Burgess, as the PI, can be responsible for carrying out the Data Safety Monitoring Plan (DSMP) throughout the entire study period. Dr. Burgess will thus be responsible for overseeing and ensuring an IRB-compliant process for reporting Adverse Events (AEs), including Serious Adverse Events (SAEs), and Unanticipated Problems (UPs), should any occur.

7.0 Privacy and Confidentiality

- This study will utilize a combination of primary data collection via an MEI Research, Ltd. created app linked to secure cloud-based servers, a study participant tracking application housed on secure VA CCDOR servers, Qualtrics FedRAMP, links to existing VHA administrative data using VINCI (*a Health Services Research & Development (HSR&D) Resource Center*), and audio/video/transcribed recorded qualitative interviews.
- For each research project, National Data Services (NDS) authorizes limited access to VA data via the Data Access Request Tracker (DART). After obtaining CIRB approval, we will request as needed access to extracts of the Corporate Data Warehouse (CDW) that contains national data from several clinical and administrative systems in a common relational database.
- Secure workspace will be allocated to the project for data extraction, processing, analyses and storage on a cluster of secure VINCI servers located at the Austin Information Technology Center (AITC). All access, processing, and analyses of VA EHR study data will be done within VINCI by the CCDOR Statistical & Data Group (CCDOR/SDG). Patient and provider identifiers will be used within VINCI when necessary to link records obtained from different files.
- With the exception of the initial app data, the entire study database (information retrieved from EHR data, recruitment outcomes) will be fully contained on secure VHA servers, behind the VA firewall (local CCDOR servers and National VA VINCI servers).
- Initial screening and survey data will be securely stored on Qualtrics FedRAMP VA cloud servers that are approved and fully compliant to house VA research data. Study participants have a study ID number will be used as the unique identifier for the Qualtrics FedRAMP system. Participant self-reported data that are collected via the app will only be identifiable using this study ID. The participant's preferred method of communication will be collected along with their email and phone number, if they choose to provide it. All crosswalk files that link the study ID to other participant identifiable data will be kept securely within the VA firewall. Data will be securely transmitted from the secure Qualtrics FedRAMP VA cloud servers to the local VA platform.
- Initial app data will be securely stored on MEI Research cloud-based servers that will be approved and fully compliant to house VA research data. When study participants are enrolled into the study they will be given a unique study ID number. This study ID number will be used as the unique identifier for the app. Participant self-reported data and app usage data that are collected via the app will only be identifiable using this study ID. All crosswalk files that link the study ID to other participant identifiable data will be kept securely within the VA firewall. App data will be securely transmitted from the secure MEI Research cloud servers to the VINCI platform.
- All typed field notes, electronic recordings, interview transcripts, and analytic notes will be stored on VA servers. During the data gathering process in the field, all entries will be made onto VA-sanctioned devices.

- VHA CCDOR servers will be used for running the customized tracking application software that contains participant contact information. EHR data will be extracted from within the VHA's secure VINCI platform. Only once the app data are within the VA firewall will the app data be linked to the participant EHR data. Therefore, participant identifiable data will be robustly protected throughout the project lifecycle within the VA firewall.
- Reminders to complete surveys will be sent to the participant's preferred method of contact, phone, email, mail, or text. Continued non-response will activate reminders sent via other methods, including phone, email, mail, and text message. Email will be sent using the LAMP study email or via Qualtrics FedRAMP. Text messages will be sent via Qualtrics FedRAMP.
- ORD Guidelines regarding using email and text messaging for communicating with VA research participants, as drafted in the following document, will be followed: https://www.research.va.gov/resources/policies/guidance/draft-electronic-mailtext.pdf. This includes:
    - No PHI or PII will be transmitted by study personnel through unencrypted email or text message.
    - The following text will be included in all emails and text messages so as to try and prevent participants from including PHI or PII in their responses: "Email and texting is not secure. Please do not reply back to this message with any personal information or personal health information. Please call 877-467-5079."
    - Specific PHI or PII will not be shared in emails from VA staff, but if there is a concern for the participant's immediate safety, and all other forms of communication (phone, emergency contact person's phone) are not successful, emails with general statements like the following will be sent: "My role as your facilitator is to create a safe space to share and also to make sure you are safe. I have tried reaching you by phone during and after group tonight. To make sure you are safe and doing ok, please reach out to me. My VA cell is 612-446-8937. You can also contact the Veteran Crisis line directly by calling 1-800-273-8255 and Press 1."
    - If a participant sends PII or PHI as part of a response using the individual's personal email or text messaging, study staff will either respond by telephone to the individual or respond using email or text messaging with redaction of any PII or PHI conveyed by the participant.
    - Email addresses of participants will be kept secure and not shared with other participants.
    - Emails and text messages sent and received for the LAMP study will be saved and maintained in accordance with the VHA Record Control Schedule.
- CCDOR maintains strong protections for coded analysis datasets that will be stored on local VA server space. CCDOR provides protections for research data at least equal to that provided by the Minneapolis VA Health Care System for patients' private health information (PHI). Access to data is on a "need to know" basis. For example, data analysts will not have access to project data unless they can demonstrate that they are somehow needed for a particular analysis.
- Access to project data is obtained through Windows authentication (i.e., PIV card and password to the network). It is virtually impossible for any person without a login name, PIV

card and password to the Minneapolis VA hospital's domain network to access data on the Center's servers. Thus, all data housed on the CCDOR Server is extremely secure. Access by unauthorized persons is highly unlikely.

- CCDOR maintains several secure servers that are located in the Minneapolis VA OIT server room. Physical access to the server room is limited to VA Office of Information and Technology staff. All individuals with administrative access privileges to the Center's servers, including VA OIT personnel and CCDOR programmers, have been screened and assigned a security clearance putting them in trusted positions of the hospital with authorization to work with patient-level data. VA OIT's access to the data is strictly limited to backing up server data, which prevents catastrophic loss of data. Backups are written to tapes that are stored in a secure location accessible only to OIT personnel.
- VA regulations require that all investigators and individuals who work on the study undergo comprehensive training annually in research integrity and protection of human subjects. The CCDOR data group will ensure that all project staff have proper access to the VA network (i.e., will assist local OIT for project staff not in Minneapolis), so those who require access to study data will have permissions to the data they need.
- Securing Other Physical Confidential Research Data: Primary data (e.g. interview transcripts and survey responses) are identified only by participant number. The original data sources (e.g. encrypted digital recordings and paper notes) will either be kept in locked cabinets within a locked room or stored in a secure folder stored on the CCDOR server.
- Only individuals with a need to access the data, as vetted by the project's Principal Investigator are granted access. Even then, only the absolute minimum number of data elements is released. This protects the integrity of the data as well as its confidentiality.
- Study data will be destroyed in accordance with VA policy. Data will be handled in accordance with all VA and VHA privacy, confidentiality, and information security policies and procedures.
- The current team and other VA investigators have used these procedures in previous studies, and they have proved both feasible to execute and acceptable to multiple Institutional Review Boards (IRBs).

8.0 Communication Plan

PI Dr. Diana Burgess will meet regularly with Lee Cross,the project coordinator. At these meetings, Dr. Burgess will check in with Ms. Cross to ensure that the following key communications occur:

1. Ensure that required local site approvals are obtained
2. Notify the Director of any facility where the research in being conducted, but the facility is not engaged.
3. Keep engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization
4. Inform local sites of any SAEs, UAPs, or interim results that may impact conduct of the study.

5. Notify all local facility directors and LSIs when the study reaches the point that it no longer requires engagement of the local facility

The study team will also review relevant sections of the protocol periodically, so that we can make sure that the different phases of the study are conducted according to the IRB-approved protocol.

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