Human Subjects Protocol

VA Puget Sound IRB

[MIRB 00873] A Randomized Clinical Trial of Group Interventions for Veterans with Chronic Multi-Symptom Illness

Funding Agency: VA HSR&D

Principal Investigator: Tracy Simpson, PhD

Version 10; 7/7/2021

Abstract

The study will recruit and randomize up to 308 participants. Half (n=154) of these will be Gulf War Veterans who meet criteria for Chronic Multi-Symptom Illness (CMI), and the other half (n=154) will be Veterans from other periods of service who also meet criteria for CMI. Half of the Gulf War Veterans (n=77) and half of the non-Gulf War Veterans (n=77) will be randomly assigned to the Mindfulness-Based Stress Reduction (MBSR) group, and the other 154 participants (77 Gulf War Veterans, 77 non-Gulf War Veterans) will be randomly assigned to the augmented Chronic Disease Self-Management Program (aCDSMP) group. As of July 2020, these groups will be conducted remotely using the VA's Video Connect software, due to the restrictions resulting from the COVID-19 virus. Each of the group sessions are 2.5 hours long, and they meet once a week for 8-weeks, as well as once on a Saturday for 4 hours (between Week 6 and 7). As of July 2020, we will no longer be including Saturday sessions, given the difficulties of doing so in a remote learning format. Each cohort will randomize 30 subjects or until one intervention reaches 18 randomized participants, whichever occurs first. As of July 2020, groups are capped at 10 participants each, or 19 subjects randomized per cohort; this cap reflects ideal group sizes for the remote learning format.

Data will be collected from subjects during five assessments while they are enrolled in the study: 1) at Baseline, which will take place within 6 weeks prior to beginning MBSR or aCDSMP; 2) at "Midpoint," between Week 4 and Week 5; 3) at "Post," within a month following the completion of the group series; 4) at 3-months after the group ended; and 5) at 6-months after the group ended.

At each of these assessments except the Midpoint, researchers will provide and administer self-report measures to the participants using a VA computer to assess changes in the following symptoms and attitudes over time and between the two study arms: pain, fatigue, cognitive failures, depression, PTSD, health- and mental-health-related quality of life, drug use, alcohol use and negative consequences, gastrointestinal distress, mindfulness, self-compassion, and decentering. These assessments can be completed both in person or by phone, as of March of 2020 all assessments will be completed by phone because of COVID-19 restructions. At the Midpoint, participants complete a pen-and-paper set of questionnaires assessing potential mediations (e.g. mindfulness and self-efficacy) and primary endpoints, which will allow mediation analyses to be performed in the future.

At the Post Assessment, a qualitative interview will be conducted with Gulf War veterans to explore impressions of, and satisfaction with, the two different treatments (MBSR and aCDSMP). List of Abbreviations

CMI – Chronic Multi-Symptom Illness

GW – Gulf War

GWS – Gulf War Syndrome

MBSR – Mindfulness-based Stress Reduction

aCDSMP – adapted Chronic Disease Self-Management Program

CPRS – Computerized Patient Record System (electronic medical record)

PROMIS – Patient-reported Outcome Measures Information System

VVC- VA Video Connect

Contents

Protocol Title: A randomized clinical trial of group interventions for Veterans with Chronic Multi-Symptom Illness

1.0 Study Personnel

- Provide name, contact information, and affiliations/employee status for the following:

Principal Investigator:

Tracy Simpson, 206-277-3337, Tracy.Simpson@va.gov, VA employee 8/8ths

Co-Investigators:

Tiffanie Fennell, 206-277-4434, Tiffanie.Fennell@va.gov, VA employee 8/8ths

George Sayre, 206-277-4187, George.sayre@va.gov, VA employee 8/8ths

Collaborators (at other institutions, not covered under the VA IRB approval): N/A

2.0 Introduction

There have been numerous attempts to determine the cause of CMI among Gulf War (GW) Veterans[1,2], but studies of treatment approaches to CMI remain limited, and thousands of Veterans continue to suffer.[3] Treatment models developed for CMI recommend interventions that are integrative and include educational and self-management components.[4,5] To date, there has been one published clinical trial for GW Veterans with CMI that evaluated an integrative approach and it suggested a modest benefit of cognitive behavioral therapy (CBT) and/or exercise on symptoms of CMI, which declined over follow-up.[6] In addition, there was no significant effect of CBT on fatigue relative to usual care, limited effects on pain, and adherence to the treatment regimen was poor – only 38% of the CBT plus exercise group, 36% of the CBT group, and 47% of the exercise group attended two-thirds or more of the treatment sessions. The relative paucity of integrative treatment trials is noted in a recent Institute of

Medicine (IOM) report,[7] which emphasizes the need for additional rigorous studies of integrative approaches, including Complementary and Alternative Medicine (CAM) interventions.

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

MBIs have been applied to the hallmark of symptoms of CMI, including musculoskeletal pain, fatigue, and concentration/memory or mood disturbances. A brief summary of the effect of MBIs on these cardinal symptoms of CMI is provided below.

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

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

For fatigue, a meta-analysis of MBIs found that participation in an MBI led to improvement in symptoms for somatoform disorders (a categorization similar to CMI), including both fatigue and pain.[13] For chronic fatigue syndrome, there is initial evidence that MBIs result in clinical improvement.[21] In three small exploratory studies of an MBI for chronic fatigue syndrome, large effect sizes were reported in a small RCT in comparison to a waitlist (d=0.93) as well as in pre-post designs (d=0.84, d=1.6),[21] which are consistent with our pilot work. Reappraisal of thoughts and feelings that contribute to fatigue, as taught in MBIs, is theorized to lead to cognitive and behavioral changes that lessen fatigue. [21]

CMI can also include decrements in concentration, memory, and mood. There is evidence of a negative correlation between measures of mindfulness and cognitive failures[24-26] which is consistent with our pilot work. Lapses in attention and memory are associated with cognitive failures in daily life, and enhanced mindfulness, which involves consciously paying more thorough attention to what is at hand, may lead to a reduction in these common errors and mishaps.[26] Additionally, mood disturbances often occur in CMI,[27] and multiple prior studies of MBIs[28] indicate improvement in depressive symptoms.

(A more thorough review of the evidence supporting this research is provided in the study grant, which is included in the application packet.)

We will not be including any vulnerable populations in our research, except for pregnant women. There is no scientifically supported or theoretical reason to believe that participation in the MBSR or CDSMP group, or other study procedures, would pose special risk to a pregnant woman or her fetus. Given the reasons that are supported for believing participation in either of these groups

could provide benefit to a pregnant woman, we will not exclude this population (although we are not targeting them specifically with any recruitment materials).

3.0 Objectives

The purpose of this study is to determine whether there is clinical evidence to support the use of Mindfulness-Based Stress Reduction as a treatment for Veterans with Chronic Multi-Symptom Illness: pain, fatigue, and cognitive or mood disturbances.

Hypothesis One (re: outcomes): Participants randomized to CDSMP will derive benefit for the primary outcomes, but with smaller effects than the participants randomized to MBSR. We hypothesize that Veterans randomized to MBSR will report significantly greater reduction in each of the three primary outcome measures (pain, fatigue and cognitive failures) at 6-month follow-up as compared to aCDSMP.

Hypothesis Two (re: acceptability): MBSR will be an acceptable and satisfactory program for Veterans with CMI, as indicated by attendance rates, a self-report measure of satisfaction, and qualitative interviews. We hypothesize that Veterans with CMI randomized to MBSR will report greater satisfaction with care than their peers randomized to CDSMP.

4.0 Resources and Personnel

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

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

Tiffanie Fennell, PhD (Co-investigator): Dr. Fennell will be responsible for troubleshooting any issues with the CDSMP classes or group leaders. She will also train the CDSMP group leaders to administer the three additional sessions

(designed to make CDSMP the same duration as MBSR). Dr. Fennell will participate in all manuscript preparation. Dr. Fennell will have access to PHI.

George Sayre, PsyD: Dr. Sayre will provide expertise on qualitative methods, developing the interview protocol, conducting qualitative survey questions, and analysis of qualitative data. He has successfully provided qualitative research expertise for multiple VA funded qualitative research projects including MBSR. Dr. Sayre will oversee the qualitative methodology in the study procedures. Dr. Sayre will have access to the qualitative data.

Carol Malte, MSW: Ms. Malte will assist the study coordinator in organizing and managing the study dataset, and will serve as the Senior Biostatistician for this project, providing consultation and advice to the primary investigators.

Meghan Storms, MSW (Project Manager): Ms. Storms will be the Project Manager, and will work closely with the principal investigator (Dr. Simpson) to provide day to day oversight of the study activities as well as supervision of the research assistant. The project manager will help to create the study management database as well as the randomization protocol. She will monitor the day to day activities of the clinical trial, including tracking the progress at all sites and troubleshooting any issues that arise. The project manager will conduct randomization. The project manager will also conduct the semi-structured qualitative interviews, as well as have shared responsibility for performing activities at the Seattle VA related to the activities of a research coordinator (e.g. recruitment of potential participants; conducting initial phone screens and major assessments; assisting with monitoring compliance and follow-up on missed appointments. The Project Manager will perform basic statistical analyses as the study proceeds to assist the principal investigators and the statisticians, and may assist in manuscript preparation. The Project Manager will have access to PHI and obtain informed consent.

A Data Safety Monitoring Board has been appointed by VA HSR&D. The PI and study team will submit period reports to the centralized Data Safety Monitoring Board. The Data Safety Monitoring Board will review the reasons for study termination for any participant who discontinues the study before completion, and any adverse events that take place.

Ashley Morris (2017-2019), Kimberly Moore (2019-current) (Research Coordinator): The Research Coordinator will work closely with the investigators and administer the study assessments, under supervision of the Project Manager and PI. The study coordinator will also perform initial telephone screens and assist in recruitment and scheduling. She will organize study materials and files, carry out data management and cleaning in consultation with Dr. Simpson and

the co-investigators. The Research Coordinator will have access to PHI and obtain informed consent.

Contracted Services & Team Members

The following individuals may be contracted to serve as MBSR Teachers for participants randomly assigned to MBSR; only two are needed for each MBSR group cohort:

- Carolyn McManus, PT, MA, MS
- Jonas Batt, MA, LMHC
- Kurt Hoelting, M.Div
- Lisa Hardmeyer Gray
- Diane Hetrick, PT

The following individuals have committed to lead CDSMP groups for this project.

- Melissa Packard
- Pamela K. Johnson, RNa

5.0 Study Procedures

5.1 Study Design

This study is a randomized controlled trial comparing Mindfulness-Based Stress Reduction (MBSR) with an active control, augmented Chronic Disease Self-Management Program (aCDSMP), to assess the efficacy of MBSR for Gulf War Veterans with Chronic Multi-symptom Illness (CMI). GW Veterans (n=154) with CMI will be randomized to either 8 weeks of MBSR (n=77) or aCDSMP (n=77). All participants will complete assessments at baseline, immediately post-treatment, as well as at 3-months and 6-months post-treatment. They will also complete a short Midpoint assessment halfway through the class series.

Brief semi-structured interviews will also be included in the MBSR/CDSMP assessments of the Gulf War veterans at the post-test time to collect data for qualitative analysis. The qualitative analysis will be conducted to develop a more complete understanding of the acceptability and satisfaction with MBSR and aCDSMP by GW Veterans. These interviews will be conducted on a subset of GW Veterans who either complete or fail to complete (attend fewer than 4 class sessions) for both MBSR and CDSMP. For Veterans who discontinue treatment, interviews will be conducted within

two weeks of discontinuation. Interviewers will be provided interview training specific to this study methods by Dr. Sayre. Data will be catalogued using Atlas.ti software system where upon the data cleaning and quality assurance process will be conducted to assure creditability and trustworthiness. Dr. Sayre will conduct a comparison of the notes, taped interviews and transcripts to assess the following: interview protocol adherence, creditability of memos and notes, and detection of leading questions and produce a quality assurance report that will be presented to the research team members.

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

The active control, aCDSMP, will account for the non-specific elements of MBSR (e.g. group support, positive expectancy). The standard CDSMP program is a group-based 6 session, 2.5 hour per session program. For this study, we added three sessions after the completion of standard CDSMP so that each intervention will be of identical duration and structure. Fidelity coding from audiotapes will evaluate protocol adherence for both MBSR and CDSMP. Similar to MBSR, CDSMP is taught by trained, experienced facilitators who believe in the benefit of the program; allegiance of researchers or therapists has been shown to be a predictor of treatment outcomes.

Risk and Benefit: The risks for this study involve the potential for psychological distress associated with collection of self-report data and the qualitative interview, and the possibility that undergoing either the MBSR class or CDSMP could be stressful and worsen symptoms. Further, there is a risk that MBSR and CDSMP will not be efficacious for some individuals. We plan to educate patients about the possible risks and benefits prior to study enrollment by providing a thorough orientation to the research and an overview of each intervention prior to giving informed consent. Potential benefits for those randomized to either condition may take the form of reduced CMI symptoms, and increased health-related quality of life. Veterans' families may also benefit as a result of the shift in emotional state. However, a participant may not benefit directly from participation in the study. Information gained in the study may be of benefit in the future to persons with CMI. Specific measures for minimizing risk are outlined below.

Procedures to Minimize Risk to Subjects and Protect Confidentiality:

1) Group sessions will include reminders to patients that they can choose what they will and will not do, and that it can be flexible in meeting an individual's needs (e.g. in MBSR a patient may meditate with eyes open, choose not to lie down, shorten the meditation time, choose not to practice some of the yoga postures, etc., while in aCDSMP a patient may choose to share more or less of their personal material with the group, etc.)
2) If a research subject experiences distress or worsening of his/her condition, we will consult the individual's primary provider for assistance. If the condition involves a psychiatric emergency, we will utilize the psychiatric emergency services available in order to help stabilize the Veteran's condition. If needed, the Veteran can be admitted to a psychiatric inpatient unit for further care. The Veteran will not bear any additional costs for care.
3) Any decision to withdraw from the protocol due to suicidality, depression, anxiety or increased PTSD symptoms will be made on a case by case basis, with input from the Veteran and his/her mental health provider. If there is clear evidence of decompensation or functional regression that is considered likely to lead to unsafe behavior, the Veteran will be advised that another course of treatment could be better for them, and the study staff will assist them in making that change.
4) *Confidentiality:* We plan to maintain the confidentiality of patient records as described above in the Source of Materials section. If at any point in the recruitment process or during the course of the study, a participate appears to be at risk to themselves or others we will initiate a series of harm-prevention steps, which will include a licensed psychologist in the State of Washington assessing the patient, short term contracts with the participant, calling the Mental Health Professional (Crisis Line) to discuss the situation, as well as informing our Human Subjects committee administrator. If necessary, a referral will be made to the appropriate agency. Any serious adverse events will be immediately reported to the IRB and the Data Safety Monitor.
5) Since studies with trauma exposed populations have found that some participants experience unexpected levels of distress following participation in the research, we will take the following steps to minimize this possibility: We will state clearly in the consent forms that participation in the research study may involve discussing details about traumatic events and about symptoms. In addition, at the beginning and end of each of the assessment sessions, we will provide participants with time to ask questions. We will inform participants, both prior to the initial screening questions on the phone and prior to beginning treatment, that some individuals do experience increases in symptoms after discussing aspects of the traumatic experience and that if these symptoms do not return to their prior levels within a few days, participants are encouraged to call the Primary Investigators. We will provide all participants with a study phone

number they can use to alert us if they are experiencing distress. The phones will be checked daily for messages and distressed participants will be called the same day (for calls made during business hours or the next business day for after hour calls). Lastly, all participants will be provided with the county crisis clinic phone numbers and the VA suicide hotline so that they can reach someone immediately should they feel they need immediate assistance.

6) If any point in the study during the assessments or treatment sessions a participant endorses suicidality or homicidality, the group instructor(s) will notify the PI (Dr. Simpson), or Dr. Fennell, who will contact the patient. Drs. Simpson and Fennell are licensed Clinical Psychologists with extensive experience in assessment and treatment of Veterans. Should there be concern about risk of harm, a clinical interview will be conducted to assess level of risk and need for intervention. Participants who indicate acute suicidality or homicidality including a plan will be immediately referred for VA mental health services. It is important to note that in more than 7 years of conducting clinical research, we have never had a participant unwilling to accept referral for suicidality, and have never had to make an involuntary admission or report.
7) All data and other information in this study will be maintained confidentiality, but will not be anonymous due to the longitudinal nature of participation. Detailed contact information as well as responses to study questionnaires will be collected at all assessments. Due to the sensitive nature of the study, i.e., the assessment of PTSD, depression, alcohol, and substance use, several steps will be in place for data collection and storage to protect participant confidentiality. First, a unique ID code (PIN) is given to each participant, serving to link their information together in the on-line database. No names or identifying information will ever be stored in the on-line database or data files that will later be used for statistical analyses. All information transferred between client and server machines will be secured in a restricted VA network folder. We have previously used these procedures to conduct web-based assessment of sensitive and illegal behaviors.
8) Participants' names, addresses, and phone numbers will be accessible to project staff in order to engage in telephone contacts and to schedule study visits with participants. However, these data will be kept separate from actual study data and from study ID codes. These data will not be shared with individuals who are not directly involved in the study. All participant data will be coded in a way that does not contain any participant identifiers. The data safety and monitoring plan is described below.
9) Participants may refuse to be recorded for the assessments without jeopardizing their participation in the study. However, due to the group nature of MBSR and of aCDSMP, those who are unwilling to be in an MBSR class or CDSMP group that is being audiotaped will need to seek other services.

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

5.2 Recruitment Methods

The recruitment goal is 308 total, at least half (n=154) of whom will be Gulf War Veterans with CMI. The remaining subjects will be non-GW Veterans with CMI.

In order to provide groups that are the same size as typically offered for both MBSR and CDSMP, we plan to form MBSR/aCDSMP groups of up to 18 participants per MBSR or aCDSMP group until 30 Veterans per cohort have been recruited (i.e., 30 Veterans will be recruited per research cohort, and we will randomize participants until 30 total Veterans per cohort are enrolled or one intervention reaches 18 participants, whichever occurs first; these 30 Veterans will be randomized in equal proportion to MBSR or aCDSMP). (As of July 2020 groups will be capped at 10 per group, in order to meet the recommended class size for remote instruction.) However, in order to allow us to answer additional scientific questions about CMI outcomes among non-GW Veterans, and because we think it could be challenging to form cohorts comprised entirely of GW Veterans (which would require recruitment of 30 GW Veterans per cohort), we designed the study so that only approximately half of each cohort (15 Veterans) will be GW Veterans. (10 GW Veterans post July 2020) The remaining 15 Veterans in each cohort will be Veterans who meet all other inclusion / exclusion criteria (including presence of CMI) but who were not deployed during the GW. The non-GW Veterans will complete the same study measures at the same points as described for GW Veterans throughout this application, but non-GW Veterans are not considered in the power calculations for the primary study hypotheses. We think that this approach provides the ability to answer additional questions (described below) while simultaneously enhancing the feasibility of the study.

The recruitment strategy described above affords several practical and theoretical advantages, including: 1) it will allow groups of sufficient size (30 Veterans per cohort) to be formed more easily, which will assure that there will be enough participants in each study cohort to allow the groups to proceed; 2) as part of an

exploratory aim, it will allow assessment of outcomes for Veterans with CMI who are not GW Veterans, which will provide the opportunity to compare outcomes for GW vs. non-GW Veterans; 3) if outcomes for non-GW Veterans are shown to be similar to GW Veterans, it would support a role for MBSR for Veterans with CMI more generally, and 4) as part of ancillary analyses, it will provide enhanced statistical power to detect small changes in CMI outcomes for the entire population recruited (both GW and non-GW Veterans).

The primary mechanism of recruitment of GW Veterans will be letters and a pamphlet sent to Veterans with an indicator in the hospital database that their period of service was the Persian GW, and who were at least 18 years old in August 1990. We also will access the Gulf War Registry to recruit Veterans known to be deployed during the Gulf War. The letter will inform veterans that they may receive up to 3 calls from study staff members inviting them to participate in the study. If they do not wish to receive study contact, they may contact the study coordinator and they will not receive any further study contact. The list of potentially eligible Persian GW Veterans will be generated using a VistA/fileman query or a VINCI query; this meets the approval of our local IRB. If they respond to the letter, they will be screened by telephone for inclusion criteria, which will be confirmed at an in-person baseline visit. Using this method, in our pilot trial of MBSR for GW Illness (see preliminary studies) *we successfully recruited 6-8 GW Veterans per month – a rate higher than the proposed trial*. Over a 1.5 year time period we recruited and randomized 55 GW Veterans with CMI; we developed the methodology to send letters *midway* through this pilot project; upon initiation of this method of recruitment, it markedly increased our enrollment rates. Currently, we are applying the same recruitment methodology to a CSR&D trial for Veterans with PTSD, which has resulted in recruitment of approximately 2-5 Veterans per week (we have about a 4% response rate for letters, and half of those (2% of letters sent) pass a phone screen for eligibility). Extrapolating to this proposal, we would need to send out 7,700 letters to recruit 154 GW Veterans. We performed a data pull as preparation for this proposal, and found that there are 30,452 unique Veterans with a period of service of 'Persian GW' who received care at VAPSHCS in FY14 and were at least 18 years old at the time of GW I (August, 1990). Thus, the recruitment goals are feasible.

We will apply a similar strategy to recruit non-GW Veterans with CMI. Non-GW subjects will be recruited by sending letters to Veterans with an indicator in VistA that they have a diagnosis related to 1) a chronic pain condition or 2) a diagnosis related to chronic fatigue. In a data pull performed as preparation for this proposal, there were 29,160 unique Veterans who received care at VAPSHCS in FY14 with a diagnosis related to pain who could be contacted as potential non-GW Veteran participants. CMI is very common in primary care; we expect that this strategy will easily lead to an

adequate number of non-GW Veterans enrollees. Non-GW participants must meet the same criteria for CMI as GW Veterans.

Participants will paid $40 for baseline, $20 for the midpoint, $40 for the post-assessment, $45 for 3-month, and $55 for the 6-month follow-ups. In addition, Gulf War subjects who complete the qualitative interview at the post-assessment time point will be paid $30. The maximum remuneration is $230 if randomized to MBSR or aCDSMP. Subject payment checks will be processed within a week of the assessment to which they apply.

5.3 Informed Consent Procedures

We are requesting a waiver of informed consent for recruitment/screening purposes only. This will allow us to create recruitment mailing lists that can target the most-likely-to-be-eligible populations, and not waste resources and other patients' time advertising the study to patients who won't be eligible to participate.

We will obtain informed consent prior to beginning any data collection study procedures that will be maintained for analysis. Informed consent will take place at the beginning of the appointment that includes the subject's in-person screening and (if still eligible) baseline assessments. The study coordinator, project manager, or other approved researcher administering the screening and baseline measures will obtain informed consent at this time. We will not be enrolling anyone with impaired decision making ability who requires the use of a legally authorized representative.

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

5.4 Inclusion/Exclusion Criteria

Inclusion criteria: *All* participants (*both GW and non-GW Veterans)* must meet criteria for CMI, defined as self-report of at least two of the following 1) fatigue that limits usual activity; 2) musculoskeletal pain involving two or more regions of the body; 3) cognitive symptoms (memory, concentration, or mood disturbances).[13] GW Veterans must have been deployed to the GW theater of operations between 8/1990 – 8/1991,

have symptoms of CMI that began after 8/1990, lasted at least 6 months, and are present at the time of the interview.

Exclusion criteria: At baseline, the MINI psychiatric interview[75] will determine psychiatric exclusion criteria: 1) current psychotic disorder; 2) current bipolar affective disorder with mania; 3) current suicidal or homicidal ideation. Additional exclusion criteria include a chart diagnosis of borderline or antisocial personality disorder or prior *formal* participation in MBSR or CDSMP. We will include subjects with the entire range of alcohol SUD (defined by the MINI), but exclude those for whom alcohol use poses a safety threat (defined as current drinking and a past-year history of alcohol-related seizures or delirium tremens). We will also exclude current DSM-V substance use disorder other than cannabis or nicotine, as well as inpatient psychiatric admission within the past month. Medication, supportive individual or group counseling, case management, and self-help programs will be allowed and assessed as potential covariates. As of July 2020, participants must have the required technology in order to participate in VVC intervention groups.

5.5 Study Evaluations

(B=baseline; M=midway through treatment; P=post-treatment; 3=3-months post-treatment; 6=6-months post-treatment)

Measure/Data Collection Tool	**Assessment**	**Purpose/Variable that the tool measures**
Study Sample Description Data (describes subject population and generalizability of results)		
Demographic Information	B	Sample description, blocking (gender), moderators
Life Events Checklist (LEC)	B	Sample description; trauma history
Deployment Risk and Resilience Inventory (DRRI)	B	Wartime exposures
Rome III – IBS	B	Sample description, to indicate prevalence of Irritable Bowel Syndrome in sample
Eligibility Evaluation (inclusion/exclusion criteria)		
Chronic Multi-Symptom Illness (CMI) Questionnaire	B	Sample description, eligibility evaluation
MINI International Neuropsychiatric Interview V-5 (DSM-V)	B	Sample description, eligibility evaluation, SUD classification (possible moderator)

Medical history interview (seizures, delirium tremens)	B	Sample description; eligibility evaluation
Tracking		
Contact form	B, P, 3, 6	Updating subject contact information; retention
Primary Outcomes		
Short Form McGill Pain Questionnaire (SF-MPQ-2) total score	B, M, P, 3, 6	Pain
General Fatigue subscale of the Multidimensional Fatigue Inventory (MFI)	B, M, P, 3, 6	General fatigue symptoms
Cognitive Failures Questionnaire (CFQ)	B, M, P, 3, 6	Concentration and memory disturbances
Client Satisfaction Questionnaire (CSQ-8)	P, 6	Satisfaction with the group (MBSR or aCDSMP)
Qualitative Interviews	P	Data merging and mixed methods techniques, used to analyze patient impressions of, and levels of satisfaction with, MBSR and aCDSMP
Secondary Outcomes		
Patient Health Questionnaire (PHQ-9)	B, P, 3, 6	Depressive symptoms
PTSD Checklist – Civilian Version (PCL-C)	B, P, 3, 6	Post-traumatic Stress Disorder symptoms
SF-12 (Mental and Physical Component Summary Scores)	B, P, 3, 6	Health-related quality of life
Drug Abuse Screening Test (DAST) for drug use other than alcohol or tobacco	B, P, 3, 6	Drug use: frequency and severity
NIH Patient Reported Outcome Measures Information System (PROMIS) for Alcohol Use and Negative Consequences, short form	B, P, 3, 6	Substance Use Disorder (SUD) symptom severity for alcohol
NIH Patient Reported Outcome Measures Information System (PROMIS) for Gastrointestinal	B, P, 3, 6	Gastrointestinal Symptoms, including IBS

Distress		
Potential Mediators		
Pain Self-Efficacy Questionnaire (PSEQ)	B, M, P, 3, 6	
Coping Strategies Questionnaire (CSQ)	B, M, P, 3, 6	
Five-Facet Mindfulness Questionnaire (FFMQ-15)	B, M, P, 3, 6	Dispositional mindfulness, and mindfulness subscales: Observing, Describing, Acting with Awareness, Nonjudging and Nonreactivity to inner experiences
Self-Compassion Scale (short form)	B, M, P, 3, 6	Self-compassion
Experiences questionnaire	B, M, P, 3, 6	Decentering
Potential Moderator (in addition to demographic info)		
Credibility/Expectancy Questionnaire	M	Participants' belief in treatment rationale/Treatment credibility and positive expectancy
VA Health Care		
CPRS review for engagement in other treatments since baseline	6	Other care received during study as possible moderator

5.6 Data Analysis

We powered the study to detect a between group effect size Cohen's d ≥ 0.50 for each of the primary outcome measures. An effect size d = 0.5 represents a medium effect, and a change smaller than d=0.50 has been advocated as a reasonable threshold of clinical significance when assessing patient reported outcomes, including pain and physical and emotional functioning.[8] The literature (see section on MBIs for CMI), and our pilot data (preliminary studies section) suggest medium to large effect sizes for CMI, supporting the feasibility of detecting this level of difference. Although effect sizes derived from small samples are inherently unreliable,[7] we included effect sizes from our pilot work as part of a broader review of the literature on outcomes of CMI symptoms after MBIs. As described above, the ability to detect a medium effect

size is supported by evidence of only modest effects in the proposed comparison condition. Overall, we think that powering the study to detect a difference of d=0.50 or greater between arms is conservative and clinically relevant.

Assuming a between group effect size of at least d=.50, equal allocation to either intervention, a two-sided $\alpha = 0.05$, and $\beta = 0.20$, at least 64 GW Veterans are required in each randomization arm.[97] To protect against the effects of attrition, we added 20% to this final sample size for a recruitment goal of 154 GW Veterans with CMI. This attrition estimate is conservative; it is slightly greater than in on our pilot RCTs comparing MBSR to TAU.[3] The sample size required *per arm* of the study (at 80% and 90% power) is presented across a range of effect sizes (Table 3).[97]

Intraclass correlation (ICC): our pilot study of MBSR for GW Veterans (preliminary studies) showed an ICC for primary outcomes of $\rho = 0.00$ at follow-up. Because our data do not indicate significant ICCs for any of the primary outcome measures, the proposed analyses do not incorporate ICC results and are not powered to account for them.

Qualitative data will be coded (a sort of pre-analysis) continuously as participants complete their qualitative interviews; when saturation is reached, and no new codes are being generated, the research team will stop conducting the interviews and begin to analyze the qualitative data more extensively. The Project Manager and Dr. George Sayre will be primarily involved in the qualitative data analysis.

Quantitative data will be analyzed following the completion of the final assessments of the last subject cohort, which is projected to take place in the last six months of Year Four of the study. The dataset will be analyzed by Carol Malte, in consultation with Dr. Zhou.

5.7 Withdrawal of Subjects

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

If a subject wishes to withdraw from the study before all procedures are complete, he or she simply needs to notify the study's project manager, study coordinator, or other study team member by phone or in person that he or she no longer wishes to participate, and the subject with be withdrawn fro the study and no longer contacted regarding study procedures. A primary study contact number will be provided

to each participant so they know how to reach the study team to request early withdrawal (or for any other questions).

6.0 Reporting

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

Adverse Events related to worsening depression symptoms will be actively monitored by tracking PHQ-9 scores. We will define as an AE an increase in PHQ-9 depression score by 2 or more severity categories. For example, if a patient experiences an increase in depression from moderate to severe, this would be an increase in two categories of severity. The PHQ-9 categorizes depression as none, mild, moderate, moderately severe, and severe according to the total score; this has been previously validated. At the midpoint of the study, the data monitor would then analyze whether significantly greater adverse events occur in one arm of the study, which might warrant stopping the study.

7.0 Privacy and Confidentiality

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

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

folder, located on the R: drive on the VA server. Hard copy data and consent forms will be stored in locked filing cabinets in the offices of the PI and/or the Project Manager.

8.0 Communication Plan

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

9.0 Information Security and Privacy

Data pertaining to medication usage and other treatment received during the subject's study enrollment period will be gathered from accessing CPRS and recording the information on a hard copy paper, linked to the participant by Study ID only, which will be filed in a locked researcher file cabinet (in the office of the Project Manager or the PI). Consent forms and other hard copy documents with identifying information (e.g. emergency contact page) will be filed in separate hanging folders from any documents with study IDs and study data on them, so that the identifying information cannot be linked to the corresponding data.

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

Audio files from the qualitative interviews will be available to certified medical transcriptionists through secure VA folders; all transcriptionists are VA employees. Additionally, the interviewer does not use the name of the subject during the interviews to help maintain confidentiality.

Participants in VVC interventions will be notified about the limits to confidentiality inherent in an internet delivered group format at the time of their consenting.

10.0 References

1. Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War. Washington, DC: National Academies press, 2006.

2. IOM (Institute of medicine). Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War. Washington, DC: The National Academies Press, 2010.

3. Li B, Mahan CM, Kang HK, et al. Longitudinal health study of US 1991 Gulf War veterans: changes in health status at 10-year follow-up. American Journal of Epidemiology 2011: kwr154.

4. Hunt SC, Richardson RD, Engel CC. Clinical management of Gulf War veterans with medically unexplained physically symptoms. Military Medicine 2002; 167:414-420.

5. Engel CC, Roy M, Kayanan D, et al. Multisciplinary treatment of persistent symptoms after Gulf War service. Military Medicine 1998; 163:202-208.

6. Donta ST, Clauw DJ, Engel CC, Jr, et al. Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses: A Randomized Controlled Trial. JAMA 2003;289:1396-1404.

7. Institute of Medicine. Gulf War and Health, Volume 9. Treatment for Chronic Multisymptom Illness. Washington, DC, 2013.

8. Siegel DJ. The Mindful Brain: Reflection and attunement in the cultivation of well-being. New York, NY: W.W. Norton & Company, Inc., 2007.

9. Baer RA. Mindfulness training as a clinical intervention: A conceptual and empirical review. Clinical Psychology: Science and Practice 2003; 10:125-143.

10. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. The journal of alternative and complementary medicine 2009; 15:593-600.

11. Grossman P, Niemann L, Schmidt S, et al. Mindfulness-based stress reduction and health benefits—A meta-analysis. Journal of Psychosomatic Research 2004; 57:35-43.

12. Reiner K, Tibi L, Lipsitz JD. Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. Pain Medicine 2013; 14:230-242.

13. Lakhan SE, Schoefield KL. Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. PloS one 2013; 8e71834.

14. Veehof MM, Oskam M-J, Schreurs KM, et al. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. Pain 2011; 152:533-542.

15. Kabat-Zinn J, Lipworth L, Burney R, et al. Four-year follow-up of a meditation-based program for the self-regulation of chronic pain: Treatment outcomes and compliance. The Clinical Journal of Pain 1987; 2:159-173.

16. Smith BW, Shelley BM, Dalen J, et al. A pilot study comparing the effects of mindfulness-based and cognitive-behavioral stress reduction. The Journal of Alternative and Complementary Medicine 2008; 14:251-258.

17. Grossman P, Tiefanthaler-Gilmer U, Raysz A, et al. Mindfulness training as an intervention for fibromyalgia: Evidence of postintervention and 3-year follow-up benefits in well-being. Psychotherapy and Psychosomatics 2007; 76:226-233.

18. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. General Hospital psychiatry 1982; 4:33-47.

19. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

20. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological al symptoms and well-being in a mindfulness based stress reduction program. Journal of Behavioral Medicine 2008; 31:23-33.

21. Surawy C, Roberts J, Silver A. The effect of mindfulness training on mood and measures of fatigue, activity, and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: A series of exploratory studies. Behavioural and Cognitive Psychotherapy 2005; 33:103-109.

22. Zeidan F, Gordon NS, Merchant J, et al. The effects of brief mindfulness meditation training on experimentally induced pain. Journal of Pain 2010; 11:199-209.

23. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: Research findings and theoretical considerations. Psychosom Med 2002; 64:773-86.

24. Lau MA, Bishop SR, Segal ZV, et al. The Toronto mindfulness scale: Development and validation. Journal of Clinical Psychology 2006; 62:1445-1467.

25. Cheyne JA, Carriere JS, Smilek D. Absent-mindedness: Lapses of conscious awareness and everyday cognitive failures. Consciousness and cognition 2006; 15:578-592.

26. Herndon F. Testing mindfulness with perceptual and cognitive factors: External vs. internal encoding, and the cognitive failures questionnaire. Personality and Individual Diffrences 2008; 44:32-41.

27. The Iowa Persian Gulf Study Group. Self-reported Illness and Health Status Among Gulf War Veterans: A population-based study. JAMA 1997;277:238-245.

28. Hoffman SG, Sawyer AT, Witt AA, et al. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. Journal of Consulting and Clinical Psychology 2010; 78:169-183.