Clinical Intervention Study Protocol

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SMART Stepped Care Management for Low Back Pain in Military Health System

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Tool Revision History:

Version Number: 1.0

Version Date: May 18, 2018

Summary of Revisions Made: Original Version

Version Number 1.1

Version Date: December 18, 2018

Summary of Revision Made:

i) Appendix V added. Appendix V contains the document outlining responses to NCCIH OCRA and PMC Collaboratory Study Design Work Group comments and responses

Version Number 2.0

Version Date: February 20, 2019

Summary of Revisions Made:

i) Grant number changed from UG3 to UH3

ii) List of participating sites was updated to include site PIs and Research Coordinators at each Military Treatment Facility at which the study will be conducted.

iii) Added "chronic" to description of the LBP patient population in Objective section of the PRECIS and elsewhere in the Study Rationale and Safety Assessment Sections of the Protocol.

iv) Corrected timeframes for assessments listed in sections 5.1 and 9.6 for consistency with the schedule of events which clarifies that follow-up assessments occur 8 and 18 weeks after enrollment.

v) Section 4.1, eligibility criterion #5 clarified to reflect ability to attend 16 weeks of treatment without a planned absence of 2 weeks or more.

vi) Sections 4.3, 9.2.2 - additional details of randomization procedures in RedCap are provided.

vii) Section 5.2 – clarified that intervention dose will be based on the number of sessions attended.

viii) Section 6.2.1.1, word "soldier" replaced with "participant" because active duty status is not required for participation.

ix) Section 6.2.1.1 – typo corrected. Statement now reads "*Individuals will be provided two copies*..."

x) Section 6.2.2.3, additional details for Phase I and Phase II randomization procedures are provided. Stratification variables at each randomization are clarified.

xi) Section 6.2.3, clarified the blinding status of study statisticians

xii) Section 7.2 – procedures for collecting AEs and SAEs were clarified.

xiii) Section 7.4 - clarified reporting procedures for AEs and SAEs.

xiv) Section 7.6 – clarifications of the DSMB procedures. Specified the specialty areas for DSMB members, persons who will attend closed meeting and the establishment of a charter document at the first DSMB meeting.

xv) Section 9.2.1 – specified procedures for sensitivity analysis should missing data prove to be missing not at random

xvi) Sections 9.3 and 9.6 – clarification was added to state that intention-to-treat will guide analyses throughout the study.

xvii) Section 9.6 – added clarification to data analysis for Aim II that Phase I treatment will be included as a covariate.

xviii) Section 10.3.3 – added monthly reports of quality metrics to be generated by the Quality Control Committee for review by research team and site research staff.

xix) Section 12 – added description of Project Steering Committee including membership, roles and responsibilities.

Version Number 2.1

Version Date: March 22, 2019

Summary of Revision Made:

i) Study Team Roster – updated contact information for COL Deydre Teyhen

ii) Clarification made in PRECIS on stratification variables to be used in Phase I and Phase II randomizations.

iii) Sections 4.3 and 9.2.2 – clarified that an independent statistician will develop random allocation tables for Phases I and II.

iv) Section 6.1 – Schedule of Events: added the Start Back Screening Tool to the Baseline Evaluation

v) Section 6.1 – Modified the time windows for completion of follow-up assessments

vi) Section 6.2.3 – added the following statement: "An unblinded study statistician will prepare aspects of the Data Safety Monitoring Reports that provide unblinded information for closed session consideration until such time that the study database is closed and locked."

vii) Section 6.2.4 – updated the time windows for completion of follow-up assessments and clarified the mode for conducting each follow-up assessment as in-person or remotely via RedCap link.

Version Number 2.2

Version Date: May 21, 2019

Summary of Revisions Made:

i) Study Aim V modified to remove PTSD and post-concussive symptoms as sub-grouping variables. Baseline opioid use added to Specific Aim V as sub-grouping variable. Change made to PRECIS and sections 1.1 and 9.6.

ii) Section 9.6 – clarified the operational definitions for sub-grouping variables

iii) Section 5.4 – clarified the definitions of adherence by treatment group that may be used for a "per-protocol" analysis.

iv) Section 5.5 – this section was added to describe opportunities for future implementation of study findings as appropriate based on the results.

Version Number 2.3

Version Date: October 1, 2019

Summary of Revisions Made:

i) Section 4.2 – exclusion criteria: clarified that exclusion criterion 5 excludes individuals with any spinal surgery, not exclusively lumbar spine surgery, in the past year.

ii) Section 4.2 – exclusion criteria: clarified exclusion criterion 6 by removing "retiring from active duty". Exclusion criterion 6 now reads "Pending a medical evaluation board, discharge from the military for medical reasons, or pending or undergoing any litigation for an injury.

iii) Section 6.1 we will also collect limited duty days as an exploratory outcome for the subset of participants who are active duty. This data will be administratively collected at the conclusion of the participant's study participation from the Military Operational Data System (MODS). This additional also noted in section 3 (Study Design); section 6.2.5 Completion/Final Evaluation; 9.1 General Design and 9.5 Additional Exploratory Outcomes and Assessments .

iv) Section 6.1 added collection of Perceived Readiness for Duty questions at baseline for active duty personnel only.

v) Section 6.1 and 6.2.2.2 – added the Pain Body Diagram to the data collection instruments with explanation of the form in section 6.2.2.2.

vi) Section 6.2.2.2 – the wording of the PASS questionnaire was updated for consistency with previously-published studies.

Version 2.4

Version Date: June 17, 2020

Summary of Revisions Made:

i) Study Team Roster and Participating Sites: updated to reflect study personnel changes.

ii) Section 6.1 – added two surveys recommended by the Pain Management Collaboratory for data harmonization. The COVID-19 impact survey was added to the baseline assessment. The Use of nonpharmacological and self-care approaches (NSCAP) was added to the 1-year assessment.

iii) Section 13 – this section was added to document the impacts of COVID-19 on the study. Section 13.1 provides a timeline of COVID-related disruptions. Section 13.2 provides a summary of COVID-related impacts of data management.

Version 2.5

Version Date: December 14, 2020

Summary of Revisions Made:

i) Study Team Roster and Participating Sites: updated to reflect study personnel changes. Tripler Army Medical Center was added as a recruitment site. Fort Hood (Darnall Army Medical Center) was added as an inactive recruitment site.

ii) Section 6.2.2.3 – the description of stratification of randomization by site was updated to reflect the addition of Tripler and inactive status of Darnall Army Medical Center

iii) Section 9.2.2 - the description of stratification of randomization by site was updated to reflect the addition of Tripler and inactive status of Darnall Army Medical Center

Version 3.0

Version Date: June 7, 2023

Summary of Revision Made:

i) Study Team Roster and Participating Sites: updated to reflect study personnel changes

ii) PRECIS, sample size and population section – updated total sample size to 850 from original sample size of 1,200.

iii) Section 1.1,- added clarification for sub-aims 2a and 2b for study Aim 2 with the following statement: "As an exploratory analysis, we will compare the effectiveness of Phase II treatments separately for patients non-responsive to PT and patients non-responsive to M2H"

iv) Section 7.6 – Safety Monitoring, Composition of DSMB section – updated to reflect that the NCCIH appointed the Board members

v) Section 7.6 – Frequency and Character of DSMB Meeting – updated to clarify that the NCCIH biostatistician attends the closed session, consistent with the DSM plan.

vi) Section 9.1 – clarified that the sub-aims for Aim 2 will be considered exploratory analyses

vii) Section 9.2 – updated total sample size to 850 from original sample size of 1,200. Also corrected minimum detectable effects based on revised sample size

viii) Section 9.2 – Power table updated to reflect revised sample size of 850.

ix) Section 9.6 - Data Analyses - clarified that Aim IIa and IIb will be considered exploratory

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PRÉCIS

Study Title: SMART Stepped Care Management for Low Back Pain in Military Health System

Objectives

Our objective is to conduct a SMART trial comparing effectiveness and cost-effectiveness of Phase 1 and 2 treatments in a Stepped Care approach for patients with chronic LBP in the MHS with patient-centered and healthcare cost outcomes. Sub-aims will compare main effects of Phase 1 and 2 treatment options and the sequencing effects of different treatment combinations.

Specific Aims

Our primary Aims are to compare the effectiveness of the Phase I treatments in the full patient population and of the Phase II treatments among non-responders to the Phase I treatments:

I. Compare the effectiveness of Physical Therapy (PT) vs. Move to Health (M2H) as Phase I options for chronic LBP on patient outcomes at 8 weeks.

II. Among patients non-responsive to Phase I treatment with PT or M2H, compare the effectiveness and evaluate cost-effectiveness of treatment with combined M2H+PT vs. Mindfulness as a Phase II interventions on patient outcomes at 26 weeks.

Secondary Aims will compare the effectiveness of the Phase I treatments when followed by Mindfulness or by combined PT+M2H for Phase I non-responders (Aims IIIa and IIIb). We will also compare the four embedded 2-stage treatment strategies (Aim IV). Finally, we will examine the comparisons of Aims I-IV within pre-specified patient sub-groups (Aim V).

III. Compare the effectiveness of the Phase I treatments when followed by Mindfulness or by combined PT+M2H for Phase I non-responders.

IV. Determine which of the four embedded 2-stage treatment strategies provides the optimal average outcomes at weeks 18, 26 and 52 for the patient population with chronic LBP in the MHS. The 2-stage treatment strategies are; a) PT followed by Mindfulness in non-responders, b) PT followed by PT+M2H in non-responders, c) M2H followed by Mindfulness in non-responders, and d) M2H followed by PT+M2H in non-responders)

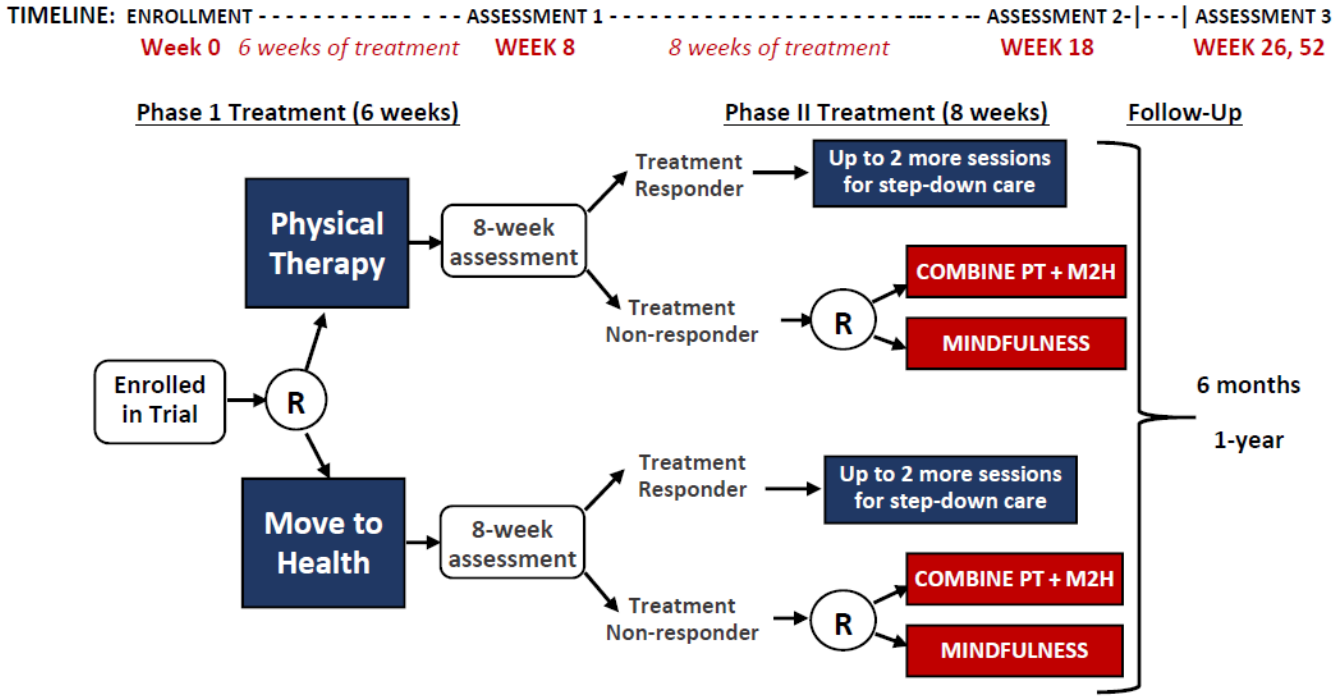
V. Evaluate objectives I-IV within sub-groups of patients defined by key baseline characteristics (sex, age, sleep disturbance, and baseline opioid use).

Design and Outcomes

This study will recruit active duty military members or members of Reserves or National Guard on active duty, family members of active duty personnel, or Tricare beneficiaries receiving care in a participating MHS facility, age 18-65, seeing a primary care provider with chronic LBP based on the NIH Task Force definition.[145] Subjects meeting eligibility criteria and providing informed consent will be enrolled in a Sequential Multiple Randomization Trial (SMART) comparing the effectiveness and cost-effectiveness of Stepped Care pain management options, examining sequencing, and heterogeneity of effects in pre-specified subgroups. All participants will first receive 6 weeks of Phase I care with either physical therapy (PT) or Move to Health (M2H) interventions. Randomization to Phase I treatment will be stratified by site, gender and active duty status. After Phase I we will assess response to initial treatment strategy. Phase I responders will receive up to 2 additional sessions of treatment to facilitate a transition to self-management. Phase I non-responders will be randomly assigned to a more intensive Phase II treatment of either mindfulness or a combined PT+M2H intervention. Phase II randomization will be stratified by site, gender, active duty status and Phase I treatment assignment. Phase II will last for 8 weeks with follow-up assessments at 18 weeks (conclusion of Phase II), 6 months

and 12 months after enrollment. Outcomes include patient-reported measures and health care costs. The overall study design is outlined below.

Interventions and Duration
All participants will receive 6 weeks of Phase I treatment of either M2H or PT based on random allocation. After 6 weeks of treatment participants will be evaluated and determined to be a treatment responder or non-responder based on self-reported change from baseline on the primary outcome



measure. Responders will continue with Phase I treatment receiving up to 2 additional treatment sessions during Phase II. Non-responders will be re-randomized to a more intensive Phase II treatment of either combined PT+M2H or mindfulness. Phase II treatment lasts for 8 weeks. The final follow-up is conducted 12 months after enrollment. Therefore the total time "on study" for a participant is 12 months.

Sample Size and Population
We will recruit a total of 850 participants age 18-65 with non-specific, chronic LBP. Participants will be randomized to a Phase I treatment (PT or M2H). Initial randomization will be stratified by site, gender and active duty status. Individuals determined to be non-responders to Phase I treatment will be re-randomized to a Phase II treatment (PT+M2H or Mindfulness). Re-randomization will be stratified by site. Phase I responders will receive up to 2 additional sessions of the same treatment during phase II.

1. STUDY OBJECTIVES

1.1 Primary Objectives

Our primary study objectives are to compare the effectiveness and cost-effectiveness of Phase I treatments and of Phase II treatments among non-responders. These objectives correspond to specific aims I and II (a and b) respectively:

I. Examine the comparative effectiveness of PT vs. Move to Health as Phase 1 options for chronic LBP after 8 weeks.

II. Among patients non-responsive to Phase I treatment with PT or M2H, compare the effectiveness and evaluate cost-effectiveness of treatment with combined M2H+PT vs. Mindfulness as a Phase II interventions on patient outcomes at 26 weeks.

As an exploratory analysis, we will compare the effectiveness of Phase II treatments separately for patients non-responsive to PT and patients non-responsive to M2H:

IIa. Among patients non-responsive to Phase 1 treatment with PT, examine the comparative effectiveness and cost-effectiveness of treatment with combined M2H+PT vs. Mindfulness as a Phase 2 interventions after 26 weeks.

IIb. Among patients non-responsive to Phase 1 treatment with M2H, examine the comparative effectiveness and cost-effectiveness of treatment with combined M2H+PT vs. Mindfulness as a Phase 2 interventions after 26 weeks.

1.2 Secondary Objectives

Our main secondary objectives are to compare the effectiveness of the Phase I treatments when followed by Mindfulness or by combining PT+M2H (specific aims III a and b). As an exploratory aim we will compare the 4 embedded 2-stage treatment strategies (specific aim IV). Finally, we will examine specific aims I-IV considering pre-specified patient sub-groups (specific aim V).

III. Compare the effectiveness of the Phase I treatments when followed by Mindfulness or by combined PT+M2H for Phase I non-responders.

IIIa. Compare the effectiveness of Phase 1 treatments (PT vs. M2H) with Mindfulness as Phase 2 treatment. (Addresses if the effectiveness of Mindfulness is impacted by Phase 1 treatment).

IIIb. Compare the effectiveness of Phase 1 treatments (PT vs. M2H) with PT+M2H as Phase 2 treatment. (Addresses if the effectiveness of M2H+PT is impacted by Phase I treatment – i.e., evaluates if temporal ordering of PT and M2H impacts effectiveness of combined treatment).

IV. Determine which of the 4 embedded 2-stage treatment strategies provides the optimal average outcomes for the patient population with chronic LBP in the MHS. The 2-stage treatment strategies are; *a*) PT followed by Mindfulness in non-responders, *b*) PT followed by PT+M2H in non-responders, *c*) M2H followed by Mindfulness in non-responders, and *d*) M2H followed by PT+M2H in non-responders)

V. Evaluate specific aims I-IV considering sub-groups of patients defined by key baseline characteristics (sex, age, sleep disturbance, and baseline opioid use).

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Chronic pain is a ubiquitous and growing concern in both civilian and military populations. Incident rates of chronic pain diagnoses for active duty military members have increased over 3-fold, from 30.4 to 107.8 per 10,000 person-years, from 2007 - 2014.[4] More than half of veterans who served in Operation Enduring Freedom, Operation Iraqi Freedom and Operation New Dawn report chronic pain to their primary care provider.[17] One report of active duty members returning from deployment found 40% reported chronic pain lasting at least 3 months and more than half reported experiencing pain almost daily or constantly.[5] Improving pain management is a priority for the VA and DoD as it has for civilian healthcare systems.[6,18,3]

The most common chronic pain condition in the MHS and civilian healthcare is low back pain (LBP).[17,19] About 70% of incident medical encounters for a primary diagnosis of chronic pain in active duty military members have LBP as the secondary diagnosis,[4] highlighting the frequency with which an episode of LBP can transition to chronic pain. LBP is as prevalent among military personnel as with civilian populations.[20] For active duty military, LBP has been the most common reason for a medical encounter every year since 2011, accounting for over 1 million encounters in 2015 involving 223,094 individuals.[10] Spinal pain is the 3rd costliest medical condition in the U.S. overall, behind only diabetes and heart disease, and LBP costs have been increasing at second fastest rate, trailing only diabetes.[8] The

substantial economic burden imposed by LBP is evident in the MHS. Our research team examined direct medical costs for 753,450 episodes of care in the MHS following a new primary care consultation for uncomplicated LBP and found nearly $1 billion in 1-year LBP-related medical costs in these patients.[14] This figure excluded costs for patients with complicated, chronic LBP conditions, which would add considerably to the total medical costs for LBP in the MHS. An additional cost related to LBP for military personnel comes from the adverse impact on readiness. LBP is the leading cause of medical discharge across all military services[9] and is one of the leading causes of seeking healthcare or being evacuated from a combat theater.[10]

The prevalence and burden of chronic pain in the MHS makes the condition a priority for improvement. The 2010 report from the U.S. Army Pain Management Task Force (APMTF) provided 109 recommendations to improve pain management.[6] Based on the APMTF's report, DoD developed a comprehensive pain management policy to address the quality and effectiveness of care within the MHS.[15] The policy recognizes the importance of pain management at both the primary care and specialist levels, supporting implementation of Veterans' Health Administration's Stepped Care Model of Pain Management.[1,18] Stepped care is a strategy to provide a continuum of evidence-based treatment across stages of pain management, emphasizing an individualized, stepwise approach as patients increase in complexity or fail to respond with less intensive interventions.[12]

Stepped care models are attractive because they begin with lower cost, less intensive, more accessible interventions. More costly, intensive treatments are used for those who are not receiving sufficient benefit. This strategy has been beneficial for other conditions such as depression that are highly prevalent and characterized by many patients who are responsive to evidence-based, lower intensity interventions.[34] Providing intensive services to all individuals with a prevalent condition such as LBP overwhelms the delivery system and needlessly escalates costs.

Efforts to improve chronic LBP management align with DoD Pain Management policy recommendations for a Stepped Care approach. The VA//DoD LBP practice guideline also endorses stepped care beginning in primary care and advancing based on patient's responsiveness.[22,35-38] A key challenge in implementing stepped care for LBP comes from the large number of interventions encompassed by each Step and a lack of information on comparative effectiveness, treatment tailoring and sequencing within Steps. Lack of guidance on what treatments to choose for a particular patient is a primary motivation for this project.

2.2 Study Rationale

Improving non-pharmacologic management of chronic pain is a priority for the MHS. Low back pain is the most common diagnosis precipitating a chronic pain condition. Improved LBP management could therefore exert a substantial impact on chronic pain in the MHS. The Army Pain Management Task Force recommends implementation of the VA Stepped Care Model of Pain Management. Stepped Care emphasizes a continuum of evidence-based treatments beginning with less intensive options; proceeding to higher-intensity care for patients who do not respond.[12] Various options exist at each step with little information on tailoring or sequencing treatments to optimize outcomes and manage costs.[13] Step 1 is primary care-based. Physical therapy (PT) is often integrated at this step.[14] Step 1 is also the stage where integration of a holistic approach to health may be beneficial. The Office of the Army Surgeon General has promoted the Move to Health (M2H) program as a strategy to bring a holistic perspective into healthcare to empower and engage patients in self-care with the support of an integrated team. For patients non-responsive to Step 1, Step 2 advocates more intensive or specialized care.[15] Mindfulness-based treatments show promise[13] for patients with chronic LBP requiring specialized care due to post-traumatic stress or post-concussive symptoms; a common post-deployment triad.[16] A combination of PT and M2H may also benefit initially non-responsive individuals.

The MHS has existing resources (e.g., PT) and strategic initiatives (e.g., M2H, integrative care including mindfulness) that can be leveraged to realize the goal of Stepped Care. Key questions exist however

about the relative effectiveness of various strategies at different Steps, how to sequence treatments and individualize care based on specific patient characteristics and the resource implications. These key questions have informed the development of our Project. Addressing these questions can improve chronic LBP management throughout the MHS and provide lessons to inform strategies for other pain conditions.

3. STUDY DESIGN

We will use a sequential multiple randomization (SMART) design (figure 1). We will compare the effectiveness of Phase I treatments for chronic LBP: PT or M2H. Phase I treatment will be 6 weeks in duration with re-evaluation at 8-weeks post-enrollment to allow time to initiate and complete treatment. At the 8-week re-assessment we will examine if the patient has responded to initial treatment using a patient-centered definition of successful response based on change in the primary outcome measure. Patients who are responders to Phase I treatment will receive up to 2 additional sessions of the same treatment to assist transition to self-management. Non-responders will be re-randomized to a second, Phase II strategy of either *combining* the initial treatments (PT+M2H), or mindfulness. The second treatment phase is 8 weeks in duration. Patient-centered outcomes will be collected at re-evaluations occurring 18 weeks (post-Phase II treatment), 6 and 12 months after enrollment using a web-based platform to collect outcome variables. Direct medical costs related to LBP treatments over the 1-year follow-up period will be extracted from the Military Data Repository (MDR) and Military Operational Data Systems (MODS) databases at the conclusion of the participant's time in the study.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Subjects in this study must satisfy all of the following eligibility criteria:

1. Active duty military member (Army, Navy, Air Force, Marines) or member of Reserves or National Guard on active duty, family member of active duty personnel, or Tricare beneficiary receiving care in a participating MHS facility.
2. Age 18 – 65 years at the time of enrollment.
3. Receiving Step 1 chronic LBP care based on VA Stepped Care Pain Management model defined as:
   a. Seen by a health care provider for chief complaint of LBP with or without symptoms into the buttocks or legs within past the 30 days.
      - Chief complaint of LBP which may be self-reported or identified by primary ICD-10 code of LBP (M54.5, M54.9, S33.012), lumbar degenerative change (M51.36, M51.37, M48.06, M47.817), lumbar disc herniation/radiculitis (M54.16, M54.17, M51.26, M51.27, M54.3).
      - Health care provider includes physicians, physician assistant, chiropractor or advanced practice nurse.
   b. May have received interventions for LBP including medication management or primary care-based education/counseling.
4. Meets NIH Task Force[145] definition of chronic LBP based on two questions: 1) *How long has LBP has been an ongoing problem for you*? and 2) *How often has LBP been an ongoing problem for you over the past 6 months*? A response of greater than 3 months to question 1, and "at least half the days in the past 6 months" to question 2 is required to satisfy the NIH definition of chronic LBP.
5. Anticipates ability to attend treatment sessions over a 16 week period following enrollment with no planned absence of 2 weeks or more for training, vacation or any purpose.

4.2 Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be excluded from the study.

1. Signs of serious or systemic pathology as a cause of LBP including spine fracture, neoplasm, inflammatory disease (e.g., ankylosing spondylitis), vertebral osteomyelitis, etc.
2. Knowingly pregnant
3. Has received interventions for LBP that involves providers other than primary care in the past 6 months. This includes physical therapy or behavioral pain management or counseling as well as specialist physician consultations, chiropractic, etc.
4. Has received any interventional pain procedures (e.g., spinal injections), inter-disciplinary pain management, integrated chronic pain and substance use treatment programs, etc. in the past 6 months
5. Has received any spinal surgery in the past year.
6. Pending a medical evaluation board, discharge from the military for medical reasons, or pending or undergoing any litigation for an injury.
7. At elevated acute risk for suicide (i.e., risk is below the level requiring either consultation or urgent action based on VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk for Suicide)[173]

4.3 Study Enrollment Procedures

Participant recruitment will occur using complimentary strategies to ensure participation is offered to a representative cohort. Providers and staff from primary care or other health care provider clinics at participating sites may alert research staff when they see patients with a diagnosis of chronic LBP. The majority of patients schedule an appointment within 72 hours of the appointment time, therefore clinicians and research staff will be able to see a roster of patients with a reason of "back pain" listed before the appointment. The list of scheduled patients appears in AHLTA, the electronic medical record system used by the DoD. A HIPAA waiver allows approved research staff to review the appointment list in AHLTA. Scheduled patients with LBP may be called and notified of the study and their potential eligibility. If interested in further information, the patient is asked to arrive 15 minutes prior to the scheduled provider appointment. Patients interested in more information will be taken to a private room and an approved member of the research team will explain the nature and purpose of the study including: follow-up times, requirements, and the nature and type of data collected. A researcher will meet with patients interested in participation either before or after their provider appointment to continue with the informed consent process and eligibility screening.

Recruitment may also occur via the MOTION platform. As part of standard care, patients attending participating MHS facilities are asked by clinic staff to enter their DoD Identification Number into the tool (on a computer, tablet or phone), which creates a case based on the patient's primary complaint. A clinician is assigned to the case and sent an e-mail link that allows input of evaluation and intervention data related to the case. For patients with a chief complaint of LBP consenting to be part of the outcomes registry at a primary care visit, approved research staff will review and notify individuals of their potential eligibility unless participation was previously offered. Patients interested in more information will meet with a researcher to continue with the informed consent process and eligibility screening.

We will track the status of all individuals with whom participation is discussed in a study screening log. For each individual who discusses participation but does not enroll in the study we will record the reason for ineligibility, or if eligible the reason for declining participation. The screening log will be maintained in RedCap. A separate log will be maintained at each study site. Randomization will occur through the RedCap randomization module. A study statistician will create randomization allocation tables for the initial random assignment to Phase I treatment group and a separate allocation table for re-randomization of non-responders to a Phase II treatment group. Allocation tables are prepared by a study statistician using SAS software and will upload these tables into the RedCap project site. The initial

randomization will occur after completion of all consent and baseline evaluation procedures. After baseline data are input RedCap will display a "Randomize" button in the data entry screen. This button allows the researcher to generate a random intervention group assignment based on the randomization allocation table.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The study interventions are provided across two treatment phases. Phase 1 treatment will begin after enrollment and completion of all baseline assessment procedures. In Phase I participants will be randomly assigned to receive either the Physical Therapy or Move 2 Health intervention. Phase I treatment period will last for 6 weeks. At the 8-week assessment participants will be judged to be treatment responders or non-responders based on responses to patient-reported outcomes. Participants determined to be responders to Phase I treatment will be permitted up to 2 additional sessions of their randomly assigned Phase I treatment during Phase II to facilitate transition to self-management. Participants determined to be non-responders will be re-randomized to a Phase II treatment of either mindfulness or a combined PT+M2H intervention. Phase II treatment will last for 8 weeks.

This study is designed to be a pragmatic clinical trial. Therefore, we are permitting flexibility for providers in determining the precise dosage and administration of all interventions. Parameters are provided within which pragmatic intervention decisions can be made by providers based on individual participant's needs. These parameters are described for each treatment in the following sections. Detailed instructions are provided in the Manual of Operations for each intervention (*see Appendix II*).

5.1.1 Physical Therapy

Participants randomized to receive Physical Therapy (PT) during Phase I will be referred to the physical therapy clinic at the participating MHS facility. Physical therapy interventions will be managed by a licensed physical therapist who may be an active duty or employed civilian physical therapist. The directing physical therapist must have received training in study-related procedures. The initial PT treatment session will occur within 7 days of enrollment in the study. Consistent with a pragmatic study, the precise dosage (i.e, number of PT sessions) will be at the discretion of the physical therapist directing the participant's care, up to a maximum of 2 sessions per week over the 6-week Phase I treatment period. Subsequent care beyond the initial PT treatment may be provided by physical therapy support personnel working at the MHS facility (e.g., physical therapy assistants or aides).

As part of study-related training, managing physical therapists will be trained to guide the dosage and type of activities using an evidence-based risk stratification tool.[133] Evidence-based risk stratification involves identifying physical and psychological factors associated with prolonged disability and tailoring treatments to address the factors present in an individual patient.[134] The 9-item STarT Back screening tool (SBST) is an evidence-based risk stratification tool that categorizes patients into 1 of 3 risk groups for persistent disability (low, medium, high) with treatment and dosage tailored to each category.[136] The low risk category receives care focused on education. Medium risk receives education along with exercise and spinal manipulative therapy to address physical factors. High risk receives education, exercise and spinal manipulative therapy supplemented by principles of cognitive-behavioral therapy to address psychological.[137] The SBST will be administered as part of the baseline assessment by a member of the research staff. The following actions will be taken based on the SBST category for the patient:

- Low Risk: Researcher will provide education and contact patient by phone, text or e-mail after 2 weeks. The need for follow-up PT sessions will be determined at that time.
- Medium Risk: Researcher will schedule patient for follow-up PT with referral noting medium risk status.

- High Risk: Researcher will schedule patient for follow-up PT with referral noting high risk status.

Follow-up PT care will be focused on providing evidence-based physical therapy interventions including patient education and physical treatments.[13] Patient education in a biopsychosocial model of pain is advocated by LBP guidelines and the Stepped Care Model.[22] The DoD/VA LBP guideline[22] identify exercise and spinal manipulative therapy as evidence-based physical treatments provided by physical therapists, with provision and dosage matched to patients' risk for persistent disability.[35,130-132] Consistent with a pragmatic study, the specific activities provided during PT sessions with an individual participant will be at the discretion of the managing physical therapist.

5.1.2 Move to Health (M2H)

Participants randomized to receive Move to Health (M2H) during Phase I will first receive education using video and written materials to introduce the key domains of holistic health in the M2H model and their relationship to chronic LBP. The domains include the following:

- Sleep
- Physical Activity (movement, strength, endurance and agility)
- Nutrition
- Intrinsic Well-Being (Personal Development, Spiritual Well-Being, Emotional Well-Being)
- Extrinsic Well-Being (Family/Social Relationships, Surroundings)

After reviewing education materials guided by a member of the research staff, the participant will complete a Personal Health Inventory. The Inventory will be reviewed by the researcher and patient in order to identify a specific domain of holistic health the patient would like to prioritize and focus on in follow-up treatment. Once the domain is identified, additional domain-specific screening will be completed. Follow-up care will be based on the level of need identified by domain-specific screening, and may range from guided self-management with the researcher to a specialist referral (e.g., sleep specialist, dietician, behavioral health provider, etc.).

Consistent with a pragmatic study, the precise dosage (i.e, number of M2H sessions) will be at the discretion of the clinicians directing the participant's care, up to a maximum of 2 sessions per week over the 6-week Phase I treatment period. Sessions may be delivered in-person or utilize technology including text messaging, telephone, e-mail, skype, app-based self-management etc.

5.1.3 PT+M2H

Participants randomized to receive a combination of PT and M2H as a Phase II intervention will continue their Phase I treatment (either M2H or PT). The participant will begin the treatment component that was not part of their Phase I intervention using the procedures outlined in the Phase I descriptions. The provider of the participant's Phase I intervention will be informed that the other component is being added to treatment.

5.1.4 Mindfulness

Participants randomized to receive mindfulness as a Phase II intervention will discontinue their Phase I treatment. The mindfulness program that will be used in this study is Mindfulness-Oriented Recovery Enhancement (MORE). The MORE treatment was designed specifically to address symptoms and underlying mechanisms of chronic pain in the military context. MORE is designed to be provided in 8 individual sessions with a behavioral health provider trained by the study investigators to provide the MORE treatment. Behavioral health providers may be psychologists, advanced practice nurses, social workers or other licensed providers with behavioral health training. Throughout the 8 MORE intervention sessions, three core areas are emphasized as outlined below. Activities include exercises

and at-home work for participants to reinforce these core areas.

- *Mindfulness*. Participants will be guided in each within-session mindfulness practice to: a) become aware of when their attention is being engaged by pain, uncomfortable physical sensations, and aversive thoughts and feelings; b) acknowledge and accept that this attentional engagement has occurred ("It's okay to have these thoughts and feelings, because I don't have to react to them!"); and c) disengage attention from pain and aversive experience, and then shift and engage attention to neutral or health-promoting stimuli via the practice of mindful breathing.
- *Cognitive reappraisal*. After cognitive restructuring is introduced in Session 3, week, patients will be queried about their use of mindfulness to become aware of and decenter from automatic thoughts, challenge automatic thoughts, and become open to new, more adaptive appraisals.
- *Savoring of positive experiences*. After savoring of pleasant experiences is introduced in Session 4, patients will be queried about their use of mindfulness to become aware of, focus their attention on, and savor day-to-day positive experiences (e.g., the taste of an enjoyable meal, a beautiful sunset, nice weather, etc.).

5.2 Handling of Study Interventions

Consistent with a pragmatic trial, neither participants nor providers will be blinded to the interventions received. We will evaluate the dose of each study intervention as the number of sessions attended during the respective intervention periods. The number of study sessions will be recorded in RedCap based on the fidelity checklist completion as noted below. We will also evaluate provider fidelity to interventions. Direct observation is considered the gold standard of fidelity assessment, but is impractical for a large pragmatic study. Clinician self-reported fidelity can provide an efficient and acceptable alternative, particularly when focused on interventions' core components with checklist formats.[163] We will employ clinician-reported fidelity checklists to identify if core components and essential elements of each study intervention are provided to participants. Fidelity checklists will be completed through RedCap. Detailed instructions on the core components of each intervention and corresponding checklists are provided in the Manual of Operations for each intervention (*see Appendix II*).

5.3 Concomitant Interventions

Consistent with a pragmatic study, we will record all concomitant interventions. We will advise participants on the purpose of the study and the concomitant interventions considered allowed and prohibited based on the study's goals. We will not remove any participant from the study for receiving a prohibited intervention. We will record the occurrence of any prohibited intervention during the study intervention period as a protocol deviation.

5.3.1 Allowed Interventions

Concomitant interventions permitted during the study intervention period include use of medication to control LBP symptoms (NSAIDs, muscle relaxants, opioids, etc.) The use of various medications will be recorded at the baseline examination and through the MDR records across the study period. Visits to health care providers for LBP are allowed during the study period (e.g., physician visits) as long as no interventional procedures (e.g., spinal injections, surgery, etc.) or mind-body interventions inconsistent with the participant's assigned intervention group (e.g., chiropractic, acupuncture, etc.) are received.

5.3.2 Prohibited Interventions

Prohibited concomitant interventions during the study intervention period include any interventional procedures or mind-body interventions not consistent with the participant's assigned intervention group including chiropractic care, massage therapy, acupuncture, spinal injections, surgical procedures, etc. If any prohibited events occur these will be recorded as protocol deviations. Subjects will continue to participate in study-related treatments and assessments unless the off-protocol intervention changes the risk-benefit profile for the participant.

5.4 Adherence Assessment

Treatment adherence will be evaluated based on attendance at scheduled treatment sessions and compliance with core components for each intervention group at attended sessions from provider self-report checklists. AHLTA and checklists will be used to determine the number of intervention sessions attended by each participant. For attended sessions, the provider will complete an intervention core component checklist and provide rationale for non-adherence or off-protocol interventions. All off-protocol events will be recorded, such as use of techniques or procedures not outlined in the protocol.

For purposes of per-protocol analyses we will define adherence as occurring when a participant attends the initial session in their randomly assigned phase I or II intervention group. We will define adherence in the PT group based on attendance at PT sessions consistent with the SBST risk profile for the participant. In the M2H group we will define adherence based on completion of the PHI and attendance at follow-up referral/ session. In the MORE mindfulness group we will define adherence based on attending at least 6 of a possible 8 sessions. Specific definitions of adherence are outlined in the table.

Treatment Group	Definition of "Adherence"
Physical Therapy	Low Risk – attend 1-3 sessions Medium Risk – attend 4-8 sessions High Risk – attend 6-12 sessions
M2H	Attend initial Health Coaching session and complete the Personal Health Inventory. Complete the assigned follow-up session or referral following initial session
MORE Mindfulness	Attend at least 6 of 8 weekly sessions

5.5 Considerations for Future Implementation

The study interventions are designed to be pragmatic and potentially scalable across military treatment facilities depending on the results of this study. The interventions are designed to be scalable by capitalizing on existing resources including services and providers available at most military treatment facilities. We have detailed training manuals (*see Appendix II*) outlining provider training and intervention parameters. We are working with the current directors in primary care at our participating sites. We anticipate turnover in these positions throughout the study period and will continue to engage with incoming directors.

With respect to implementation of study findings at the policy level within DoD, we have engaged key stakeholders both as members of the investigator team and through outreach at the participating sites. Col. Deydre Teyhen, member of the investigator team, leads the stakeholder engagement efforts. Col. Teyhen is currently Commander at the Walter Reed Army Institute of Research. She is also a licensed physical therapist and she has served as the Deputy Chief of Staff for Public Health for the Office of the Surgeon General. In this role she led the development and implementation of the Performance Triad, Move To Health, and other programs to assist Army Medicine in transitioning from a Healthcare System to a "System for Health". LTC Ian Lee, also a member of the investigator team, serves as Allied Health Staff Officer within the Office of the Surgeon General at the Defense Health Agency (DHA). Specifically, LTC Lee works within the Rehabilitation & Reintegration Division at DHA, which provides policy guidance related to rehabilitation, reintegration, psychological resilience and pain. Continued communication with these policy bodies will facilitate dissemination of the study findings and create opportunities for implementation as appropriate based on the results.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

OUTCOME	Screening Assessment	Baseline Assessment (day 0)	8 weeks (post Phase I) (day 50 – 66)	18 weeks (post Phase II) (day 120– 140)	26 weeks (day 180 – 200)	52 weeks (day 360 – 380)
Informed Consent Form	X					
Eligibility Criteria	X					
Demographics	X					
Medical History	X					
COVID-19 impact survey	X					
Randomization		X	X (non-responders)			
Start Back Screening Tool (SBST)		X	X			
Patient Acceptable Symptom State		X	X	X	X	X
PROMIS Pain Interference CAT		X	X	X	X	X
PROMIS Physical Function CAT		X	X	X	X	X
PROMIS Sleep Disturbance CAT		X	X	X	X	X
PROMIS Depression CAT		X	X	X	X	X
PROMIS Anxiety CAT		X	X	X	X	X
PEG-3		X	X	X	X	X
EuroQol-5D		X	X	X	X	X
Perceived Readiness for Duty (active duty only)		X	X	X	X	X
Defense & Veterans Pain Rating Scale		X	X	X	X	X
Pain Body Diagram		X	X	X	X	X
Treatment Side Effects			X	X		
Use of nonpharmacological and self-care approaches (NSCAP)						X
Limited Duty Days (active duty only)						X
Long-Term Opioid Use						X
Direct Medical Expenses						X
	Collected within MOTION or REDCap					
	Collected administratively through MDR or MODS					

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Individuals who meet with a site Research Assistant will be provided information about the study. The Researcher will confirm that the individual meets the eligibility criteria for participation. If the individual meets these eligibility criteria and is interested in participation, he or she will undergo the consenting process outlined below. The individual may begin the consenting process either at that time or within 7 days of eligibility confirmation.

6.2.1.1 Consenting Procedure

Individuals potentially eligible and interested in participation will be provided a written informed consent document using a form approved by the site IRB. The consenting process will be conducted by a Research Assistant who is trained by the Investigators and has completed Biomedical Research Training for Human Subjects research through the Collaborative Institutional Training Institute (CITI) which includes modules on human subjects research ethics and regulations related to informed consent. The Research Assistant will be available throughout the consenting process to explain the study and answer questions. The voluntary nature of the participation will be stressed, and participants will be reminded

that they may elect to withdraw from the study at any time. Participants will be assured that a decision not to participate will have no impact on their military status or ability to access health care.

Individuals will be provided two copies of the informed consent document for signature. One copy of the signed informed consent document will be retained by the researchers and the other will be given to the participant. A single consent form will be used for the project. The Research Assistant consenting the participant will sign an Informed Consent Form checklist which will be retained by the researchers.

6.2.1.2 Screening

Once informed consent is obtained the following screening procedures will be completed within 72 hours to insure eligibility:

- Confirm age on the date of consent is between 18 – 65 years old.
- Confirm participant is not knowingly pregnant.
- Confirm participant is not currently receiving, and has not receive in the prior 6 months, interventions for their LBP other than those provided in primary care.
- Confirm participant has not received any interventional pain procedures, pain management or integrated pain management and substance use treatment programs in prior 6 months.
- Confirm participant has not received any spine surgery procedures in the prior 1 year.
- Confirm participant is experiencing LBP defined as pain between the 12th ribs and buttock with or without symptoms in the buttock(s) or leg(s) without "red flags" suggesting a possible non-musculoskeletal cause (unexplained weight loss, night pain, systemic illness)
- Confirm participant meets NIH definition of chronic LBP based on two questions: 1) *How long has LBP has been an ongoing problem for you*? and 2) *How often has LBP been an ongoing problem for you over the past 6 months*? Responses of "greater than 3 months" and "at least half the days in the past 6 months" to questions 1and 2 respectively are required to meet the definition of chronic LBP.
- Confirm the participant is not at elevated acute risk for suicide based on VA/DoD Clinical Practice Guideline.[173] The Guideline specifies that any individual with recent suicidal ideation or thoughts is at elevated risk. There is no evidence-based screening tool for elevated risk, and ongoing attention to expression of suicidal ideations or thoughts is recommended. We will ask if the participant has had any thoughts about harming him/herself. If the response is yes, or if these thoughts emerge at any point during participation in the study staff personnel will follow standard procedures to address safety issues and obtain appropriate care.

Individuals meeting all eligibility criteria will proceed with study participation. Individuals who are ineligible after all screening procedures will be advised to return to primary care for continued pain management as necessary. Consistent with DoD Guidelines,[175] study personnel will be trained to inform a participant's primary care provider if concerns of an acute stress disorder are detected and access site-specific emergency mental health care. If risk factors for self-harm or danger to others are identified, acute management procedures (direct observation, limit access to lethal means and escort to urgent/emergency care) will be implemented.

6.2.2 Enrollment, Baseline, and/or Randomization

6.2.2.1 Enrollment

This study uses a single informed consent document for both screening and treatment purposes. Thus the enrollment date is the date on which the consent document is signed and eligibility confirmed. We anticipate that screening will be completed on the same day for the majority of participants because of the relatively simple and quick screening procedures required. At the latest screening will be completed within 72 hours of providing informed consent.

6.2.2.2 Baseline Assessments

Assessments involve collection of participant-reported and researcher-reported data. Patient-reported outcome (PRO) measures will be collected using an electronic platform (MOTION or REDCap) based on availability. The Military Orthopaedics Tracking Injuries and Outcomes Network (MOTION), an initiative of the Rehabilitation and Reintegration Division (R2D) of the Army Office of the Surgeon General, is a web-based application for collecting PROs that allows participants to input information from any internet-enabled device. MOTION is programmed to survey enrolled patients on a regular schedule that corresponds to the study Schedule of Evaluations outlined above for assessments through the 6-month assessment. Once enrolled, researchers may "push" a MOTION survey to participants. If surveys are not received the Wounded, Ill and Injured Registry (WIIR) is programmed to send a survey corresponding to the 8- and 18-week assessment time windows.

REDCap (Research Electronic Data Capture) is an NIH-supported, browser-based, software solution that uses secure online forms for data capture, management and analysis. Participants and researchers can input data directly into REDCap and participants can also be sent surveys electronically for completion. We will also create functionality in REDCap to permit all study assessments to be collected through this platform. Research assistants at each site will track participants' data collection completion to avoid duplication of surveys from different platforms. If a participant is unable to directly input data using a computer paper forms will be available with data input into the study database at a later time.

The following assessments are collected at baseline:

- Demographic/Medical History data will include age, gender, physical activity level, race/ethnicity and general medical and LBP history. Current medication use for LBP will be recorded. This information will be used for descriptive purposes and possible covariates in analyses.
- Patient Acceptable Symptom State (PASS): The PASS is a single-item self-assessment of the acceptability of the patient's current symptom status.[146] The PASS question is; "*Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider the current status of your low back satisfactory*?" The PASS permits patients to determine if their symptoms are acceptable in their own assessment.
- PROMIS Pain Interference CAT (PI-CAT): Computer-adapted assessment using a 44-item bank measuring the self-reported consequences of pain on relevant aspects of life including impact on social, emotional, cognitive, physical and recreational activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater pain interference.
- PROMIS Physical Function CAT (PF-CAT): Computer-adapted assessment using a 121-item bank measuring current, self-reported capability related to physical activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater physical function.
- PROMIS Sleep Disturbance CAT: Computer-adapted assessment using a 27-item bank measuring qualitative aspects of sleep and wake function.[65] The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater sleep disturbance.
- PROMIS Depression CAT: Computer-adapted assessment using a 28-item bank measuring affective and cognitive manifestations of depression.[64] The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater levels of depression.
- PROMIS Anxiety CAT: Computer-adapted assessment using a 29-item bank measuring fear (e.g., worry, feeling of panic), anxious misery (e.g., dread), hyperarousal (e.g., tension, nervousness,

restlessness) and somatic symptoms related to arousal (e.g., cardiovascular symptoms, dizziness).[64] The score is reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater levels of anxiety.

- EuroQol (EQ-5D): A generic quality of life instrument covering 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[155] Domain scores are combined to produce a health state ranging from 0 (death) to 1 (perfect health) which is commonly used in economic evaluation of clinical trials.[156]
- Perceived Readiness for Duty: We have used 3 questions in prior studies to assess a service member's self-perceived ability to perform military related tasks (pass a required semi-annual physical fitness test, operate under full combat load, and % mission capability).[98] These questions will be used to assess participants who are active duty military members.
- Defense and Veterans Pain Rating Scale (DVPRS): Pain assessment tool utilizing a numeric pain rating for pain intensity and four supplemental questions reflecting pain interference with sleep, mood, usual activities and stress.[159] The numeric rating scale uses a 0-10 rating scale with o representing "no pain" and 10 representing "pain as bad as it could be, nothing else matters". Interference items are assessed on 0-10 Likert-scale rating anchored by 0 (pain does not interfere with or contribute) to 10 (pain completely interferes or contributes a great deal).[157,158]
- Pain Body Diagram: A pain body diagram is used to quantify the extent and nature of painful symptoms throughout the body. The body diagram uses an outline of the body and permits the participant to indicate the location(s) perceived as painful and the type of symptoms present in each area.[183]
- Pain, Enjoyment, and General Activity Scale (PEG-3): The PEG-3 measure includes 3 items evaluating 1) pain severity, and interference of pain with 2) enjoyment and 3) general activity. Response options for each item range from 0-10 and the PEG-3 score is expressed as the mean of all item scores.[162]

6.2.2.3 Randomization

Following baseline assessment all participants will be randomized to a Phase I treatment group (PT or M2H). A randomization allocation table will be developed prior to enrollment and integrated into REDCap by co-investigator Dr. Greene, Director of the Study Design and Biostatistics Center (SDBC) at the University of Utah. Blocked randomization with block sizes of 4 or 6 will be used. Randomization will be stratified based on site (MAMC, ,TAMC, BAMC, or WHASC), gender and active duty status (yes/no) to balance these variables.

At the 8-week assessment the PI-CAT score will compared with the baseline score to determine if the participant is a "responder" to Phase I treatment or a "non-responder". An improvement from baseline of at least 7 T-score points will be required to be defined as a responder. All other participants will be considered a treatment non-responder. All non-responders will be randomized a second time following completion of all 8-week assessments. Randomization of non-responders to a Phase II treatment will be done through REDCap also based on an allocation table developed prior to enrollment using the same procedures outlined above. Phase II randomization will be stratified by sit, gender, active duty status and Phase I treatment group assignment.

6.2.3 Blinding

As is often the case in pragmatic clinical trials, participants and clinicians cannot be blinded to study treatments. Randomization assignment will not be revealed until baseline examination is complete to reduce potential bias by either the participant or researchers. The use of clinician-compliance audits during the study will allow for assessment of the impact of any differential treatment application.

Study statisticians cannot be blinded to participants' study treatment assignments because they must complete Data Safety Monitoring Reports and analyze the study outcomes by treatment group. An unblinded study statistician will prepare aspects of the Data Safety Monitoring Reports that provide unblinded information for closed session consideration until such time that the study database is closed and locked. The randomization allocation tables will be developed before the study begins by statisticians who are not involved with managing the study databases.

Follow-up assessments will be performed by a research assistant who will be blind to participants' treatment group assignment. Participants will be reminded by the research assistant not to discuss aspects of their treatment during assessments. If a research assistant becomes unblinded during the course of a participant's study participation, he or she will not be allowed to conduct additional follow-up assessments. Instances of unblinding during an assessment will be recorded as an unexpected event.

6.2.4 Follow-up Visits

- Initial Phase 1 Treatment Visit (*completed within the 7 days following day 0)*:
  - Treatment Session Form
- Phase 1 follow-up Treatment Visits (*completed between days 2-49)*:
  - Treatment Session Form
- 8-Week Assessment (*completed from Day 50 – Day 66*):
  - Conducted in-person with an assessor blind to treatment group
  - Participant-reported questionnaires including PI-CAT to determine responder status
  - Participant-reported Treatment Side Effects Questionnaire
- Phase II Treatment Visits - Responders (*completed from Day 50 – Day 135, no more than 2 additional visits of Phase I intervention)*:
  - Treatment Session Form
- Phase II Treatment Visits – Non-Responders (*completed from Day 50 – Day 135)*
  - Treatment Session Form
- 18-Week Assessment (*completed from Day 120 – Day 140*):
  - Conducted in-person with an assessor blind to treatment group
  - Participant-reported questionnaires
  - Participant-Reported Treatment Side Effects Questionnaire
- 26-Week Assessment (*completed from Day 180 – Day 200*):
  - Conducted remotely through RedCap link sent by e-mail or text to participant
  - Participant-reported questionnaires

6.2.5 Completion/Final Evaluation

The final evaluation occurs 52 weeks after Baseline Assessment (*from Day 360 – Day 380*). The following assessments are performed at the final evaluation. If a participant wishes to terminate the study early, this is also the list of assessments we will attempt to complete at termination. Early termination will only be done at a participant's request or if a participant's risk-to-benefit ratio is substantially altered due to a change in status.

- Conducted remotely through RedCap link sent by e-mail or text to participant
- Participant-reported questionnaires

- Collection of Medical Expense and Opioid use from MDR
- Collection of Limited Duty days for active duty participants from the MODS

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Safety parameters intended to reduce risks for adverse events include having licensed clinicians specifically trained in the study procedures carry out all treatments. The potential risk of psychological distress from answering self-report questions about the impact of the individual's chronic LBP on various aspects of his or her life will be minimized by allowing participants to leave some items blank if they are upsetting and conducting assessments in private rooms.

7.2 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

The risk profile of interventions used in this study is minimal. Treatments in the study are standard procedures used in everyday clinical practice and measurement procedures are entirely patient-self reported information.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study follow-up assessments through unsolicited (i.e., without any prompting) means. Each follow-up assessment includes a side effects questionnaire that includes the opportunity for participants to report adverse events in free-text format beyond the expected side effects of treatments provided on the form. Based on the risk status of this project we will not specifically solicit reporting of AEs or SAEs during follow-up sessions.

The occurrence of an AE or SAE may also come to the attention of clinicians providing study treatments to participants through unsolicited means. These individuals will be trained in reporting procedures (outlined below) on reporting these occurrences to the research team in a timely manner. Based on the risk status of this project we will not specifically solicit reporting of AEs or SAEs during study treatment sessions.

7.3 Adverse Events and Serious Adverse Events

Definitions

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

Unanticipated Problems (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Event (SAE)

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

- Results in death
- Is life-threatening (places subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

7.4 Reporting Procedures

The site investigator must immediately report to the University of Utah any serious adverse event, whether or not considered study related, and must include an assessment of whether there is a reasonable possibility that the study caused the event within 72 hours of awareness of the event. Site investigators must also report any unanticipated problems within 7 days. The site PI must also report any other adverse events, protocol deviations or violations within 7 days of PI awareness. Participating sites must submit all reports to their local IRB other entities using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the University of Utah Data Coordinating Center and IRB, local IRBs, DSMB and NCCIH within 5 business days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the University of Utah Data Coordinating Center and IRB, local IRBs, DSMB and NCCIH within 14 days of the investigator becoming aware of the problem.

Should an unanticipated problem need to be reported to the IRB it will be reported to the military IRB and University of Utah. A record of all reportable unanticipated problems will be maintained at the coordinating site and reported during annual DSM reports. In addition, researchers will record at each study visit the occurrence of any other adverse events (e.g., visiting the emergency room or medical provider for pain exacerbation, etc.) A report of all adverse events will be maintained by each site and reported annually on the DSM report.

Characteristics of an Adverse Event

Relationship to Study Intervention

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

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

Expectedness of SAEs

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

Severity of Event

The following scale will be used to grade adverse events:

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

7.5 Follow-up for Adverse Events

All adverse events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

The scope and the purpose of this study qualifies as a Phase III clinical trial, therefore a data and safety monitoring board (DSMB) will be established based on the NIH guidelines and NCCIH input, and commensurate with the level of risk, size, and complexity of this study. At the first DSMB meeting a DSM charter document will be finalized.

Composition of the DSMB: The DSMB will consist of at least 5 members appointed by the NCCIH and will include at least one member with human subject research monitoring expertise, at least one member with relevant disease expertise, at least one member with expertise in the intervention or observation technique under study and a biostatistician. DSMB Members must have no financial, scientific, or other conflict of interest with the study.

Frequency and Character of DSMB Meetings: Because the study involves procedures with minimal risk, we propose to conduct DSMB meetings via conference call on an annual basis. Each DSMB meeting will begin with an open session that will be attended by all trial Investigators, Study Coordinators and representatives from the NCCIH Program Office. Open session will review study procedures, plans for data and safety monitoring, recruitment and retention, gender and minority inclusion, protocol adherence, data management, the occurrence of any adverse events. The open session will be followed by a closed session that will be attended by only the DSMB members and the NCCIH biostatistician as deemed appropriate by the DSMB Chair. The closed session will be used to discuss data to which the other Investigators must remain blinded.

Content of DSMB Meeting Reports: DSMB reports from each meeting will review the topics discussed at the meeting with respect to study procedures, accrual and retention, data management, etc. The DSM report will include a recommendation concerning continuation of the study. Each DSM report will provide a tally of all adverse events in each of the categories listed above in all treatment groups. Blinding of adverse event results will be maintained and will be broken only if the DSMB indicates a need to un-blind groups for serious safety reasons. DSMB reports will be submitted to the Principal Investigator, NCCIH Program Office and University of Utah and Military Institutional Review Boards.

8. INTERVENTION DISCONTINUATION

Investigators will only discontinue a participant's intervention if the risk-benefit ratio for that participant changes substantially such that he or she would no longer meet the project's eligibility criteria. Examples include development of signs of neurologic deficit or presentation of "red flag" symptoms suggestive of a serious underlying condition. These circumstances will be identified by research personnel during study visits for treatment or assessment. If a participant is discontinued we will continue to collect self-report outcomes only.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We will use a SMART study design (fig. 1). The first phase of the design will compare the effectiveness of PT and M2H for treating chronic LBP. Phase I treatment will be 6 weeks in duration with re-

evaluation at 8-weeks post-enrollment to allow time to initiate and complete treatment. At the 8-week assessment we will evaluate if the participant has responded to initial treatment using pragmatic, patient-centered, definition of a treatment responder. Patients who are responders to Phase I treatment will receive up to 2 additional sessions of the same treatment to assist with transition to self-management. Non-responders will be re-randomized to a second, Phase II treatment: Either *combining* the initial treatments (PT+M2H) or switching to Mindfulness. Phase II treatment is 8 weeks in duration. Patient-reported outcomes will be collected again at 18 weeks (post-Phase II treatment), 6 and 12 months after enrollment. Direct medical costs and opioid use for LBP care over the 1-year follow-up period will be extracted from the MDR database and for active duty participants, limited duty days will be extracted from the MODS database at the conclusion of the participant's time in the study.

We have incorporated the feedback provided on the study design and biostatistics from the NCCIH OCRA and the Study Design Work Group of the PMC Collaboratory. A complete listing of these comments and the corresponding responses are provided in *Appendix V*.

Our co-primary aims are to compare the effectiveness and cost-effectiveness of Phase I treatments; and of Phase II treatments in Phase I non-responders. Our main secondary aim will compare the effectiveness of each Phase I treatment when followed by Mindfulness or by combined PT+M2H. Exploratory aims will compare Phase II treatments separately for each Phase I treatment group, as well as seek to identify the 2-stage imbedded treatment regime which provides the optimum average outcome across the four 2-stage treatment strategies and evaluate primary and secondary treatment comparisons in pre-specified sub-groups. Further exploratory analyses will seek to identify the optimum 2-stage treatment strategy after accounting for designated characteristics of each patient.

9.2 Sample Size and Randomization

Power calculations are based on a conservative estimate of 80% project retention, which we have applied across the full follow-up period, and are expressed both as minimum detectable effect sizes for 80% and 90% power and as statistical power to detect minimum clinically important differences (MCIDs) with the planned 850 randomized patients. All power calculations are based on the guidelines for approximating statistical power for SMART trials by Crivello, Levy, and Murphy.[176]

The PROMIS-PI and PROMIS-PF result in T-scores with general population means of 50 and SDs of 10. However, the SDs of the PROMIS-PI and PROMIS-PF have been observed to be somewhat smaller in LBP populations similar to the patient population in this study, and we have assumed SDs of 8 points for both the PROMIS-PI and -PF. The MCID for the PI- and PF-CAT has been estimated between 2.0 - 3.5 T-score points for patients with chronic LBP.[23,24] We assume the response rate to Phase I treatment will fall between 0.30 and 0.45. Also based on data from previous studies, we assume serial correlations of R = 0.40 for PROMIS outcomes. We have also considered intra-class correlations (ICCs) ranging from 0 to 0.05 to account for clustering of each of the outcomes within the therapists who will carry out the mindfulness interventions. We assume the mindfulness intervention will be implemented by 20 therapists distributed across the 4 sites over the study period. Some level of clustering by therapist is also possible for the PT and M2H interventions, but is not incorporated in the power calculations because of the likelihood of patients moving between therapists at different treatments and because the same therapists will often administer both the PT and M2H interventions. We stipulated a 2-sided α of 0.05 for the primary PROMIS-PI outcome.

Under these assumptions the minimum detectable effect sizes with 90% power for Aim I comparison of PT and M2H groups at 8 weeks are 1.83for the PROMIS-PI and -PF. If ICCs for mindfulness providers are assumed to be 0, the minimum detectable effect sizes with 90% power for the Objective II comparisons of PT+M2H vs. Mindfulness range from 2.18to 2.46 for the PROMIS-PI and -PF, if Phase I response rate ranges from 30% to 45%. If ICCs for the mindfulness therapists are assumed to be 0.05, the minimum detectable effect sizes with 90% power for the Objective II comparisons of PT+M2H vs.

Mindfulness range from 2.46-2.71, if Phase I response rate ranges from 30% to 45%. All of these minimum detectable effect sizes are smaller than the minimum clinically important differences, which we have taken to be 2.8 points for the two PROMIS outcomes, which represents 35% of the estimated SD of 8 T-score units in our LBP population, and 28% of the SD for the general population. An effect size of 35% of 1 SD is considered small to moderate,[169] and is highly plausible for the interventions being compared. The rationale for selecting a sample size larger than required to detect the MCIDs for the two primary objectives is to support subgroup analyses and the analyses of the secondary objectives. The supplemental table provides additional power calculations relevant to these secondary analyses.

AIM	DESCRIPTION	Assumed SD and Effect Size					Detectable Effect Size Under Varying Assumptions				Power to detect MCID Effect size	
		Outcome Variable	Alpha	Mindfulness therapist ICC	SD	Outcome MCID and Effect Size	30% Phase I Response Rate		45% Phase I Response Rate			
							80% Power	90% power	80% Power	90% power	With 30% Responder Rate	With 45% Responder Rate
1.	Mean differences in primary outcome between Phase 1 treatments at week 8 (PT vs. M2H) **(Co-Primary)**	PROMIS PI	0.05	-	8 T-score points	2.8	1.58	1.83	1.58	1.83	0.999	0.999
1.i	Mean differences in secondary outcomes between Phase 1 treatments at week 8 (PT vs. M2H)	PROMIS PF	0.025	-	8 T-score points	2.8	1.74	1.98	1.74	1.98	0.997	0.997
		Pain	0.025	-	2.2	2.0	0.51	0.58	0.51	0.58	1	1
2.	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to either PT or M2H **(Co-Primary)**	PROMIS PI	0.05	0	8 T-score points	2.8	1.89	2.18	2.13	2.46	0.986	0.958
2.i	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT or M2H	PROMIS PF	0.025	0	8 T-Score points	2.8	2.08	2.37	2.34	2.68	0.972	0.926
		Pain	0.025	0	2.2	2.0	0.61	0.69	0.68	0.78	1	1
2 and 2.i with varying clinician effect	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to either PT or M2H **(Co-Primary)**	PROMIS PI	0.05	0.025	8 T-score points	2.8	2.01	2.33	2.24	2.59	0.986	0.958
	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT or M2H	PROMIS PF	0.025	0.025	8 T-Score points	2.8	2.21	2.53	2.46	2.81	0.972	0.926
		Pain	0.025	0.025	2.2	2.0	0.65	0.74	0.72	0.82	1	1
	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to either PT or M2H **(Co-Primary)**	PROMIS PI	0.05	0.05	8 T-score points	2.8	2.13	2.46	2.34	2.71	0.958	0.918
	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT or M2H	PROMIS PF	0.025	0.05	8 T-Score points	2.8	2.34	2.68	2.57	2.94	0.926	0.867
		Pain	0.025	0.05	2.2	2.0	0.68	0.78	0.75	0.86	1	1
2.a	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to PT	PROMIS PI	0.025	0	8 T-score points	2.8	2.94	3.36	3.32	3.79	0.756	0.641
2.b	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to M2H	PROMIS PI	0.025	0	8 T-score points	2.8	2.94	3.36	3.32	3.79	0.756	0.641
2.a.i/ 2.b.i	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT (also applies to M2H)	PROMIS PF	0.0125	0	8 T-Score points	2.8	3.19	3.61	3.6	4.07	0.668	0.54
		Pain	0.0125	0	2.2	2.0	0.93	1.05	1.05	1.19	1	1
2a/b and 2.a.i/ 2.b.i with varying clinician effect	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to PT	PROMIS PI	0.025	0.025	8 T-score points	2.8	3.03	3.46	3.39	3.88	0.728	0.619
	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to M2H	PROMIS PI	0.025	0.025	8 T-score points	2.8	3.03	3.46	3.39	3.88	0.728	0.619
	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT (also applies to M2H)	PROMIS PF	0.0125	0.025	8 T-Score points	2.8	3.29	3.72	3.68	4.16	0.636	0.517
		Pain	0.0125	0.025	2.2	2.0	0.96	1.09	1.07	1.22	1	1
	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to PT	PROMIS PI	0.025	0.05	8 T-score points	2.8	3.12	3.56	3.47	3.96	0.701	0.598

AIM	DESCRIPTION	Assumed SD and Effect Size					Detectable Effect Size Under Varying Assumptions				Power to detect MCID Effect size	
		Outcome Variable	Alpha	Mindfulness therapist ICC	SD	Outcome MCID and Effect Size	30% Phase I Response Rate		45% Phase I Response Rate			
							80% Power	90% power	80% Power	90% power	With 30% Responder Rate	With 45% Responder Rate
	Mean difference in primary outcome between Phase II treatments (PT+M2H vs. mindfulness) at 6-mo for non-responders to M2H	PROMIS PI	0.025	0.05	8 T-score points	2.8	3.12	3.56	3.47	3.96	0.701	0.598
	Mean difference in secondary outcomes between Phase II treatments at 6-mo for non-responders to PT (also applies to M2H)	PROMIS PF	0.0125	0.05	8 T-Score points	2.8	3.38	3.82	3.76	4.25	0.606	0.496
		Pain	0.0125	0.05	2.2	2.0	0.99	1.12	1.1	1.24	1	1
3.a	Mean difference in primary outcome at 6-mo between Phase I treatments with Mindfulness in Phase II **(Main Secondary)**	PROMIS PI	0.05	-	8 T-score points	2.8	2.06	2.38	1.96	2.27	0.968	0.979
3.b	Mean difference in primary outcome at 6-mo between Phase I treatments with PT+M2H in Phase II **(Main Secondary)**	PROMIS PI	0.05	-	8 T-score points	2.8	2.06	2.38	1.96	2.27	0.968	0.979
3.a.i/ 3.b.i	Mean difference in secondary outcomes between Phase I treatments at 6-mo with Mindfulness in Phase II (also applies to M2H+PT)	PROMIS PF	0.025	-	8 T-Score points	2.8	2.26	2.59	2.16	2.47	0.942	0.96
		Pain	0.025	-	2.2	2.0	0.66	0.76	0.63	0.72	1	1
V.	Evaluate aims I-IV in sub-groups of patients based on pre-specified baseline characteristics (age, gender, sleep disturbance, opioid use). Aim V is supported by following sub-aims:											
V.1.i	Mean difference in primary outcome between Phase I treatments at week 8 in sub-group with 50% prevalence (AIM 1 subgroup analyses)	PROMIS PI	0.05	-	8 T-score points	2.8	2.23	2.59	2.23	2.59	0.94	0.94
V.1.ii	Mean difference in primary outcome between Phase I treatments at week 8 in sub-group with 33% prevalence (AIM 1 subgroup analyses)	PROMIS PI	0.05	-	8 T-score points	2.8	2.74	3.18	2.74	3.18	0.815	0.815
V.2.i	Mean difference in primary outcome between Phase II treatments at 6-mo for non-responders to PT or M2H in sub-group with 50% prevalence (AIM 2 sub-group analyses)	PROMIS PI	0.05	0.025	8 T-score points	2.8	2.75	3.18	3.08	3.57	0.813	0.721
V.2.ii	Mean difference in primary outcome between Phase I treatments at 6-mo with Mindfulness in phase II (also applies to M2H+PT) in sub-group with 50% prevalence (AIM 2 subgroup analyses)	PROMIS PI	0.05	-	8 T-score points	2.8	2.91	3.37	2.78	3.22	0.768	0.805

Power calculations assume 80% retention for each follow-up assessment (this is conservative for the week 8 assessment). We assume serial correlations of R = 0.40 for the PROMIS outcomes and 0.23 for the PAIN score. *Calculations performed using statistical simulation are conservative, and apply for all possible response rates.

9.2.1 Handling of Missing Data

We will record reasons for missing data and attempt to contact lost-to-follow-up patients to determine reasons. To assess risk of bias from missing data, patterns of missingness across follow-ups will be displayed for all outcomes. We will compare baseline levels of prognostic variables between patients with and without missing data. Our longitudinal analyses will either employ maximum likelihood estimation under mixed effects models or will be performed using generalized estimating equations under generalized linear models, and will be carried out with multiple imputation of missing data.[177] Application of multiple imputation will assure that statistical inference will remain valid in the presence of missing data if missingness follows a missing at random (MAR) mechanism[94,95]. Multiple imputation will be carried out using time-ordered nested conditional imputation models to sequentially impute both missing response after phase 1, subsequent treatment assignment and latter outcome variables.[178] Imputation models will include all variables in the analysis and selected additional variables considered likely to predict outcome and likelihood of missingness.

The sensitivity of the results to a possible missing not at random (MNAR) mechanism will be investigated within the multiple imputation approach by applying an offset term for the mean of the missing outcome variable among those patients for whom this outcome is missing, and evaluating the dependence of the primary outcome results to varying the size of this offset.[181,182]

9.2.2 Treatment Assignment Procedures

Randomization allocation tables will be developed prior to enrollment by the Study Design and Biostatistics Center at the University of Utah. Random permuted block randomization with random block sizes will be used. Randomization to Phase I treatment will be stratified based on site (TAMC, BAMC, MAMC, WHASC), gender and active duty status (yes/no). Randomization to Phase II treatment for non-responders will be based on site, gender, active duty status and Phase I treatment group assignment. Randomization will be done through the project's RedCap site using the Randomization module. Randomization assignments will be programmed in RedCap by study statistician prior to any participant enrollment.

Based on the pragmatic nature of this project, participants cannot be blinded to study treatments and we will not use placebos or attempt to balance clinician time. Randomization assignment will not be revealed until baseline assessment is complete to reduce potential bias by either the participant or researcher. Follow-up assessments will be performed by a Research Assistant who will be blind to participants' treatment assignments. Clinicians providing treatment cannot be blinded. The use of standardized training and guidelines for all treatments and clinician-compliance audits throughout the project will permit the opportunity to assess differential treatment application and explore any influence on outcomes. The PIs of the project will be able to break the blinding if necessary for participant safety considerations.

9.3 Definition of Populations

Intention-to-treat principles will be used to guide the data analyses throughout the project with all participants analyzed in their randomized group regardless of compliance. We will compare compliance between groups and "per-protocol" secondary analyses may be considered if non-compliance is high or disproportionate between groups.

9.4 Interim Analyses and Stopping Rules

Because of the minimal risk of the procedures in this study, the study does not include formal interim analyses for efficacy or futility. The Data Safety and Monitoring Board (DSMB) will monitor the occurrence of adverse events throughout the study. If the number of serious adverse events warrants, the DSMB may recommend suspension of enrollment and a review the safety of the study procedures.

9.5 Outcomes

Outcome measure for the primary and secondary hypotheses of the study are outlined below. These outcomes will not require adjudication.

9.5.1 Primary and Secondary Outcomes

The outcomes used to address the primary and secondary hypotheses of this study are each collected at baseline, and at the 8 week, 18 week, 6- and 12-month assessments. We are using use CAT versions from the Patient-Reported Outcomes Measurement Information System (PROMIS®) as patient-centered assessments of health constructs most relevant to patients with chronic LBP. We are using PROMIS CAT measures because they have been developed and validated with rigorous methods[123] and assess universally-relevant (e.g., physical function, pain interference) instead of disease-specific constructs permitting comparisons with different chronic conditions.[154] The CAT approach uses item response theory to present questions to participants in an adaptive manner based on response to the prior question, limiting the number of questions required to reach a robust measure and reducing burden.[124]

Primary Outcome: PROMIS Pain Interference CAT (PI-CAT): Computer-adapted assessment using a 44-item bank measuring the self-reported consequences of pain on relevant aspects of life including impact on social, emotional, cognitive, physical and recreational activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater pain interference.

Main Secondary Outcome: PROMIS Physical Function CAT (PF-CAT): Computer-adapted assessment using a 121-item bank measuring current, self-reported capability related to physical activities. All PROMIS scores are reported on a T-score metric with a score of 50 points aligning with the general population mean and a standard deviation of 10. Higher scores indicate greater physical function.

Additional Exploratory Outcomes and Assessments

Defense and Veterans Pain Rating Scale (DVPRS): Pain assessment tool utilizing a numeric pain rating for pain intensity and four supplemental questions reflecting pain interference with sleep, mood, usual activities and stress.[159] The numeric rating scale uses a 0-10 rating scale with 0 representing "no pain" and 10 representing "pain as bad as it could be, nothing else matters".

PEG-3: evaluates pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) in the past week. Each item is assessed on a Likert-type scale 0-10, and individual item scores are averaged.[162]

PROMIS Sleep Disturbance CAT: evaluates perceptions of sleep quality, depth and restoration associated with sleep over the prior 7-day period.

PROMIS Depression CAT: evaluates negative mood and perceptions of self (e.g., worthlessness), diminished positive affect or engagement (e.g., loss of interest in activities) over the prior 7-day period.

PROMIS Anxiety CAT: evaluates perceptions of fear, worry, dread, hyperarousal (e.g., feelings of tension or nervousness, somatic symptoms such as dizziness, palpitations) over the prior 7-day period.

EuroQol (EQ-5D):[155] is a generic quality of life instrument covering the domains of covers 5 domains: mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression. Domain scores are combined to produce a health state which is commonly used in economic evaluation of clinical trials.[156]

Perceived Ability to Return to Duty: Readiness represents the service member's ability to accomplish their mission. The inability to deploy for medical reasons is a significant concern for overall readiness. We have used 3 questions in prior studies to assess a service member's self-perceived ability to perform military related tasks (pass a required semi-annual physical fitness test, operate under full combat load, and % mission capability).[98]

Treatment Side Effects: We will collect information about side effects participants may experience with study interventions. We will ask participants about possible physical (e.g., increased pain or stiffness, etc.) and psychological (e.g., increased stress or anxiety, etc.) side effects that they believe resulted from study interventions and extent to which they were impacted by the side effect (ranging from "not at all" to "extremely"). The questionnaire was developed from existing side effect questionnaires used in studies of physical and psychological interventions for individuals with chronic pain.[138,139]

Limited Duty Days: (active duty only): We will extract information about limited duty days for participants on active duty across the entire 1-year surveillance follow-up period. This information is stored in eProfile, a software application within the Medical Operational Data System (MODS) that allows global tracking of type, reason, and length of limited duty days related to medical conditions.

Long-Term Opioid Use: The pharmacy data transaction service (PDTS) file of the MDR captures all medication prescriptions that occur inside the MHS and outside when covered by Tricare. Unique number of prescriptions with therapeutic class codes that represent opioid-based pain medication (280808, 280812) and total days' supply will be calculated for each patient over the course of the 1-year follow-up. We will also calculate daily opioid dose at each follow-up point based on dose of opioids at that time converted to a morphine milligram-equivalent (MME) dosages by multiplying daily dose of a given opioid by published conversion factors.[161] We will define long-term opioid use at each follow-up based on the number of opioid fills recorded, the days' supply for each fill and the morphine milligram equivalents (MME) for each fill. Long-term opioid use will be defined as $\geq$ 90 days of continuous opioid use in the preceding 180-day period. As a sensitivity analysis we will also define long-term opioid use as $\geq$ 120 days or > 90 days with 10 or more fills during the 1-year follow-up period.

Direct Medical Expenses: We will use the MDR to identify total healthcare costs and LBP-related healthcare costs over the 1-year follow-up period. The MDR contains Tricare claims for all inpatient and outpatient medical encounters in any setting (military or civilian network). Each encounter is assigned a cost based on RVUs to represent the cost associated with delivering the care. RVU-based costs allow comparisons on the aggregate level and in specific categories (i.e., medication, inpatient costs, ambulatory care, etc.). We will apply adjustment procedures to account for medical inflation across different years of data collection as needed when evaluating costs and conducting cost-effectiveness analyses. MDR data also contains billing codes which allow for identification of specific utilization outcomes during the follow-up period including lumbar MRI, CT scan, fluoroscopically-guided injections and surgical procedures.

9.6 Data Analyses

Analyses will be carried out by the Study Design and Biostatistics Center, the biostatistics core of the University of Utah CCTS. We will monitor data quality and completeness during the study so discrepancies can be resolved in real time. Intention-to-treat principles will be used to guide the data analyses throughout the project with patients evaluated based on randomized assignment regardless of compliance. Skewed outcomes may be transformed to approximate normality. Analyses for each aim of the project are outlined below.

Aim I: This co-primary aim compares the effectiveness of Phase I treatments (M2H or PT) on the primary outcome (PI-CAT) at 8 weeks follow-up. Because the outcome is evaluated prior to the Phase II treatment, the primary analyses of Aim I conform to a standard 2-group comparison without the complications of a 2-phase design. The primary Aim I analysis will be carried out by fitting a longitudinal linear mixed model for the baseline and 8-week PI-CAT, using an unstructured covariance matrix to account for serial correlation between the two measures, and imposing the constraint that the baseline means for the PI-CAT are equal in the Phase I treatment groups. This model, sometimes referred to as a constrained longitudinal model leads to adjustment for baseline levels as in analysis of covariance (ANCOVA), which has been shown to remove conditional bias in treatment group comparisons due to chance imbalances and improve statistical power over unadjusted comparisons.[179]

By using an unstructured covariance matrix, the model will constitute a special case of a general linear mixed model which avoids imposing specific assumptions concerning distribution of random effects. Restricted maximum likelihood estimation will be used for estimation of the mean adjusted difference in the 8-week PI-CAT between the M2H and PT treatment groups and to provide confidence intervals and hypothesis tests. The same approach will be used to compare the PROMIS-PF between Phase I treatment groups. In this analysis as well in other longitudinal analyses described below, clinical center and the sex and active duty status randomization stratification factors will be included as covariates.

Aim Ii: This sub-aim compares secondary outcomes (pain intensity, sleep, depression, anxiety) between PT and M2H using a similar longitudinal linear model to that described above. We will use generalized estimating equations[86] to relate Phase I treatment to binary indicator variables for long-term opiod use during successive intervals across the 1-year follow-up under a generalized linear model for binary outcomes. GEE analyses will use robust standard errors for statistical inference. Hypothesis tests for the single primary outcome and for secondary outcomes will be performed on a comparison-wise basis without adjustment for multple comparisons.[87]

Aim II: This co-primary aim compares the effectiveness of Phase II treatments (Mindfulness or M2H+PT) in Phase I non-responders, by fitting a longitudinal linear mixed effects model to relate the randomized Phase II treatments to the PI-CAT primary outcome measures at 18 weeks, 6 and 12 months, with the 8-week outcome level included as a covariate to account for the effects of Phase I treatment and serve as the baseline for comparing Phase II treatments. The model will include random effects for the therapists of the mindfulness intervention for those patients who are randomized to the mindfulness intervention. As stated above, clinical site, sex, and active duty status will be included as covariates as will Phase I treatment group. These analyses will be restricted to the subcohort of patients who fail to respond to the Phase I treatment and who remain in follow-up sufficiently long to be randomized to the Phase II treatment. The primary treatment contrast will compare the 12-month PI-CAT between the two Phase II interventions among all Phase I non-responders, while averaging over the Phase I treatments.

Aims IIa and IIb. In exploratory analyses, the longitudinal mixed model of Aim II will be fit separately to nonresponders of the PT intervention and to nonresponders to the M2H intervetention; these analyses will compare the effectiveness of the Phase II treatments separately for non-responders to each of the Phase I treatments. A Bonferroni correction will be applied to these latter analyses to account for separate comparisons in the non-responders to each of the Phase I interventions.

Aim IIIa and IIIb: These aims compare the effectiveness of Phase I treatments contingent on the Phase II treatment. Aim IIIa analyses will be performed in randomized patients who respond to their Phase I treatment or who do not respond and are randomized to Mindfulness in Phase II, and will compare two dynamic treatment regimens imbedded within the SMART design: Treatment with M2H followed by mindfulness in nonresponders to M2H vs. PT followed by mindfulness in nonresponders to PT. The principal analysis for Aim IIIa, which is also designated as the main secondary analysis for the study, will apply weighted estimating equations with robust standard errors designed for analysis of longitudinal outcomes in SMART trials[180] to compare the PI-CAT at weeks 8 and 18 and months 6 and 12 between the patients initially randomized to PT or M2H in Phase I, with covariate adjustment for the baseline level of the outcome. Site, sex, and active duty status will again be included as covariates. The 12-month assessment will again serve as the primary comparison. Inverse probabilty of treatment weighting will account for nonresponders being re-randomized and thus split in two groups and underrepresented relative to responders. We note the Phase I treatment in an optimal 2-stage sequence may differ from the Phase I treatment optimzing outcome at the end of Phase I (Aim 1). For example, M2H may be superior to PT following Phase I, but a sequence of PT followed by Mindfulness may be

the preferred 2-stage sequence. The longitudinal analyses will be adapted analogously to those of Aim 1 to estimate the effects of the Phase I treatments followed by Mindfulness on secondary outcomes.

Analyses for aim IIIb will be performed in randomized patients who respond to their Phase I treatment or who do not respond and are then randomized to PT+M2H in Phase II. Analyses for aim IIIb will be analogous to those of aim IIIa, and will address if the order in which PT and M2H are administered matters when applying these interventions sequentially.

Aim IV: The analyses of Aim IV will compare four embedded 2-stage strategies: *a*) PT followed by M2H+PT in non-responders, *b*) PT followed by Mindfulness in non-responders, *c*) M2H followed by M2H+PT in non-responders, and *d*) M2H followed by Mindfulness in non-responders. The analyses will apply weighted estimating equations with robust standard errors appropriate for analysis of longitudinal outcomes in SMART designs while accounting for clusting by mindfulness therapists to estimate the mean PI-CAT for all four 2-stage strategies at weeks 8 and 18, and months 6 and 12.[180] The dataset will be augmented by including each patient either once or twice depending on whether the patient's treatment is consisent with one or two 2-stage strategies[164,166] (e.g., the treatment sequence of a patient who responds to PT in Phase I is consistent with both regimens *a* and *b* above). As in Aims IIIa and IIIb, we will employ inverse probabilty weighting to account for nonresponders being re-randomized and thus split in two groups and underrepresented relative to responders.

Aim V: The analyses of Aim V will evaluate specific aims I-IV within sub-groups of patients defined by key baseline characteristics (gender, age, sleep disturbance, and baseline opioid use). Specifically, we will examine sub-groups based on gender (male or female), age (using a threshold value of ≥50 years old at baseline), sleep disturbance (using a threshold value of >50 on PROMIS Sleep Disturbance CAT at baseline) and baseline opioid use (using a threshold of regular opioid use for at least 1 month).

For aims I-III, sub-group analyses will be performed by repeating the longitudinal analyses within each pre-specified subgroup, and by extending the statistical models by adding interactions between treatment and the subgroup factors. We will display forest plots of estimated treatment effects within each subgroup with p-values for the treatment by subgroup factor interactions indicated on the plots. Results of subgroup analyses will be assessed primarily based on the treatment by subgroup interactions, using 2-sided $\alpha = 0.05$ for the primary outcome, PI-CAT, without adjustment for multiple sub-groups.

Sub-group analyses for aim IV will use Q-learning methods to investigate the more complex treatment strategies to estimate an optimal intervention in which Phase I and II treatments are tailored to patient sub-group characteristics. We have designated PI-CAT at 1-year as the primary outcome for the Q-learning procedure. We will implement Q-learning[39] by defining subject data as O_1, A_1, O_2, A_2. O_1 designates patient subgroup factors available prior to the Phase I (gender, age and pain-related co-morbidities); A_1 is Phase I treatment (PT, M2H); O_2 is response to Phase I treatment (responder, non-responder); and A_2 is Phase II treatment for non-responders (PT+M2H, mindfulness). Q-learning uses two regression models corresponding to the two treatment Phases to determine the optimal sequence where the selection of Phase I treatment (A_1) takes into account subgroup factors (O_1), and Phase II treatment (A_2) takes into account subgroup factors (O_1), Phase I treatment (A_2) and response to Phase I (O_2). The Phase I regression model incorporates the interaction between O_1 and A_1, and the Phase II model includes interactions of O_1 with A_1, A_1 with A_2, and O_2 with A_2 to account for heterogeneity of Phase I and II treatment effects. The optimized 2-stage sequence depends on the regression coefficients for the models corresponding to the two Phases. Statistical inference will be performed using soft-thresholding[40] or the m-out-of-n bootstrap.[41] The ultimate result of the analysis will be an estimate of the optimal 2-stage treatment sequence for each combination of values for the patient subgroup factors.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Participant-reported measures will be collected via an electronic data capture system; either REDCap or MOTION. REDcap (Research Electronic Data Capture) is an NIH-supported, browser-based platform that allows researchers to create secure online forms for data capture, management and analysis. At each assessment participants can input data directly into REDCap. If a participant is unable to directly input data, paper forms will be available with data uploaded at a later time. MOTION (Military Orthopaedics Tracking Injuries and Outcomes Network) is an initiative of the Rehabilitation and Reintegration Division (R2D) of the Army Office of the Surgeon General. MOTION is a web-based application for collecting patient-reported outcomes that allows patients to input information from any internet-enabled device. MOTION may capture the same study-related measures. To avoid additional participant burden scores from MOTION will be entered into REDCap in these circumstances.

A research assistant blinded to the participant's randomly-assigned treatment group will conduct the assessments to avoid bias. The baseline, 8- and 18-week assessments will be done in-person with a research assistant blinded to the participant's treatment group. The 26- and 52-week follow-ups will be conducted electronically without an in-person meeting with a member of the research team, who will be blinded to the participants' treatment group. These follow-up assessments will collect outcomes data either through MOTION or REDCap, whichever is easier to access for the participant.

Additional participant data will be administratively collected from the Military Health System Data Repository (MDR). The MDR is a comprehensive source of data containing records on every person-level interaction for healthcare where Tricare is the payer regardless of setting, capturing direct care provided in military facilities and purchased care provided in civilian settings.[122] The MDR incorporates historical and demographic beneficiary and coverage data as well as clinical and ancillary care data including pharmacy (prescription, medication type and dosage), radiology, etc. The MDR links claims and demographic data to provide detailed information on co-morbidities, health care utilization and financial data for all service members, retirees and dependents registered in the Defense Enrollment Eligibility Reporting System (DEERS) and eligible for Tricare benefits.

This project will extract data from the MDR for each participant over a 24-month period – 12 months prior to and after enrollment. This will allow us to derive a co-morbidity profile for each participant. The MDR Pharmacy Data Transaction Service file captures all medication prescriptions that occur in either military or civilian settings. The unique number of prescriptions with therapeutic class codes as well as total days supply are available. Of particular interest for this project are opiate-based pain medication (AHSF codes 280808, 280812), which is a study outcome.

Each enrolled subject will receive a site-specific unique Subject Identifier generated prior to enrollment that will be used to de-identify the final study dataset. As a preliminary step required to merge participant-reported and MDR data, an extraction that uses each subject's DoD Identifier is required. This merge will be completed internally on a secured and encrypted government computer. A list containing the DoD Identifier numbers, de-identified Subject Identifier and enrollment date for each subject will be sent to the Program Analysis and Evaluation Division (PA&E) of US Army Medical Command after the Data Sharing Agreement has been approved and signed by the Data Privacy Board of the U.S. Defense Health Agency. The PA&E analyst will extract healthcare utilization for the 12 months prior and 12 months after enrollment utilizing the DoD Identifier number. After data are merged the DoD Identifier number will be removed, leaving only the de-identified unique Subject Identifier on the record. The de-identified dataset will be provided to a member of the DoD research team. At this point, the dataset will be fully de-identified, with all 18 HIPAA identifiers removed.

De-identified datasets will be encrypted and password protected before transfer to the University of Utah SDBC. The preferred method for secure data transfer by the Department of Defense is through the AMRDEC SAFE (SAfe File Exchange) program developed by the U.S. Army Aviation and Missile Research Development and Engineering Center (https://safe.amrdec.army.mil/). Data can be transferred electronically through the use of this encrypted online system, with maximum file sizes of 2GB. Linkages of the Subject Identifier and DoD Identifier will not be transferred to the SDBC but will be maintained by the DoD in an encrypted file, on a password-protected and encrypted military computer. Any participant information collected through REDCap will use the Subject Identifier and linkage with the DoD identifier is not necessary in order to merge these data.

10.2 Data Management

Clinical sites participating in this project will be responsible for collecting electronic data from participants. Any source documents not stored electronically will be maintained in locked cabinets within the personal offices of the PI or study coordinator at each site. Any electronic documents outside of MDR, REDCap or MOTION, as well as any data output from MDR, REDCap or MOTION, will be kept in an encrypted file, on a password-protected and encrypted computers maintained by a member of the research team. Based on responsibility delegation by Military Institutional Review Boards, the local site PI will be responsible for security and confidentiality at each performance site.

The University of Utah SDBC will be responsible for maintaining and analyzing the project database. The database will be kept on a server supplied by University of Utah Health (UUH). The UUH utilizes technology from Hitachi Data Systems called the Universal Storage Platform for providing a virtualized storage area network. This network is maintained on a server by University of Utah Health Information Technology Services. All programming for the analyses are also stored on the same server and coordinated through the University of Utah SDBC.

Transfer of patient-identifiable information for research involving the DHA and University of Utah will be governed by a Data Sharing Agreement (DSA). All data exchanged under the DSA falls under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, implemented at 45 C.F.R., Parts 160 and 164, and the Privacy Act of 1974, as amended, 5 U.S.C. 522a. Data transmission and storage data exchanged between the DHA and the University of Utah will be in compliance with HIPAA security and privacy provisions. All data use will be governed by the DSA and IRB oversight at the University of Utah. All electronic communication between investigators and performance sites that contains data for analysis will be transmitted in compliance with the Office of the Surgeon General/ MEDCOM Memorandum “Security of Electronic Mail (email) Containing Protected Health Information (ePHI).” All datasets will be de-identified with no PHI/PII included.

10.3 Quality Assurance

10.3.1 Training

Project investigators will conduct training sessions for all research assistants and clinicians who will provide study interventions. Investigators from the University of Utah and Department of Defense will train providers at each participating site. Training will consist of in-person, didactic instructions, written instructions for the performance of study-related techniques and hands-on practice as appropriate. Clinicians will receive additional training in all study-related treatment procedures previously described. Training goals will be accomplished by providing theoretical and practical information related to this project and the procedures employed. Management strategies based on group assignment will be highlighted with case examples. All clinicians and research personnel must complete training before participating in any study-related procedures. A training log will record successful completion of training activities. Both Principal Investigators are experienced in training clinicians to successfully perform research-related treatment procedures, and researcher personnel in collection of human subjects

data. All personnel will be trained for their role in the project before enrollment begins. Detailed Study Protocols for each intervention will be compiled under the supervision of the PIs with input from all investigators as described in section 5 of this document. All study personnel will review and familiarize themselves with the Study Protocols in detail prior to participation.

10.3.2 Quality Control Committee

Quality control for study data will be monitored and overseen by the University of Utah SDBC, the Data Coordinating Center for the project. The SDBC is overseen by Dr. Tom Greene with support from Dr. Jincheng Shen and study statistician Molly McFadden. Quality control for data merged into the study database from the MDR is monitored through the Program Analysis and Evaluation Division at the US Army Medical Command overseen by Mr. Richard Thorp.

10.3.3 Metrics

Quality metrics for study-related participant data include counts and percentages of missing or incomplete responses and protocol deviations. These metrics will be reported at least annually on DSMB reports for open and closed sessions. Quality metrics for study-related treatment data will examine the number of intervention sessions completed by randomized group. Goals for compliance include initiating the study intervention and for each intervention session obtaining $\geq$ 90% compliance with receiving the intervention's core components. The SDBC Quality Control Committee will generate monthly reports of recruitment, retention, quality metrics for treatment compliance with core competencies, treatment attendance and protocol deviations across all sites. The format of monthly reports will be similar to open session reports prepared for the DSMB. Monthly reports will be reviewed by the investigator team and research staff at each site.

10.3.4 Protocol Deviations

All protocol deviations and adverse events will be recorded at each study site as outlined in Section 7. Deviations or adverse events will be reported in a timely manner to the site and project PIs and to the IRBs of the participating institutions as required. Annually, a report will be compiled for review by the DSMB and NCCIH representatives. The DSMB may request more frequent reviews if necessary.

10.3.5 Monitoring

Protocol deviations are monitored at each project site and are overseen by the site PI. Protocol deviations will be reported to the University of Utah as the Coordinating Center from each site PI. As specified in Section 7, any protocol deviation that is also an adverse event (e.g., incorrect randomization, failure to obtain informed consent, etc.) will be reported to the site and central IRB as well as the DSMB and NCCIH within 7 days of awareness. Protocol deviation that do not qualify as adverse events (assessments occurring outside the specified time window, participants receiving prohibited interventions, etc.) will be reported to the University of Utah from each site PI in quarterly monitoring reports. A report of all protocol deviations occurring across study sites will be maintained by the University of Utah and reported annually on the DSMB report.

We have developed the study procedures to minimize data quality concerns. Study data is be collected using the REDCap or MOTION platforms. These platforms include functionality that limits data ranges and types, thus reducing the chance for input of out-of-range values or incomplete responses. Restrictions available within REDCap also provide identification verification through login and passwords, required field verification and prevent duplicate records to minimize the chance for data input errors. In addition to passing point-of-entry edits, all study data entered to the central study database will be subjected to extensive monitoring procedures on a routine basis by the SDBC. The SDBC will internally review distributions of baseline and follow-up variables to detect extreme values or inconsistent results and will notify the PI if problematic data are detected.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents from each study site and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., person with power of attorney), this individual must sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's study record.

11.3 Participant Confidentiality

Participant confidentiality will be protected in the data collection process. All personnel involved with the research at both sites responsible for collecting and handling the data will have completed the Collaborative Institutional Training Institute (CITI) modules for Human Subjects Research and Responsible Conduct of Research. Approval will be obtained by the respective Institutional Review Boards. Consent forms that identify the patient by name will be stored in a locked cabinet by the site Investigators. All data are assigned a unique identifier (not containing PHI) to identify each participant in the study database. Participants will be instructed not to identify themselves by name on any instrument. The data file linking names and code numbers will be accessible only to the site PI or Coordinator, and data will be entered into study databases by this unique identifier. If data are used in scholarly presentations or journal articles, the investigators will protect the anonymity of individual participants and will report only aggregate data where appropriate. No audio or video taping will be conducted as part of this study. Information will not be released without written permission of the participant, except as necessary for monitoring by IRBs, NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

This project is guided by a governance plan designed to facilitate decision-making and assist with resolving any disputes that may arise. The governance plan encompasses a committee structure that is designed to align with the NIH-DoD-VA Collaboratory Committee structure. The project has two Principal Investigators; Drs. Fritz and Rhon. Dr. Rhon is the content expert for engagement of military treatment facilities, oversight of DoD regulatory compliance and treatment implementation within military facilities. Dr. Fritz serves as the content expert for data management processes and procedures including data analysis and quality assurance. Drs. Fritz and Rhon talk via phone at least bi-monthly to discuss project management. More frequent meetings occur as circumstances dictate. In addition, the PIs will meet at least quarterly with the investigator team by conference call or in-person. Both PIs are members of the NIH-DoD-VA Collaboratory Steering Committee.

Drs. Fritz and Rhon guide overall execution of the project. They are responsible for assuring regulatory compliance, conducting the project using high ethical standards and completing all close-out and intellectual property requirements. Each PI is responsible for fiscal management of the project within their institution. Resource allocation will be based on the priorities of the project aims. The scientific direction of the proposal will be determined by both PIs in conjunction with the NIH-DoD-VA Pain Management Collaboratory. Members of the investigator team serve on Collaboratory Work Groups as

outlined below. Team members report on decisions from the Collaboratory Work Groups at investigator meeting. If new directions or opportunities present, these are discussed and prioritized by the investigator team. Every attempt to reach consensus among the team will be attempted. If consensus cannot be reached on decisions related to scientific direction and resource allocation, a vote of the investigator team will be taken.

The Project Steering Committee will serve as the operational group responsible for coordination of the activities of the project team centers and interactions with the NIH-DoD-VA Pain Management Collaboratory. The Steering Committee will identify scientific and policy issues that need to be addressed throughout the Project, develop recommendations to the NIH Project Team for addressing such issues, coordinate the primary recommendations for assay distribution within the Network, and coordinate the dissemination of screening data, assay protocols, and other materials with the wider scientific community. The Steering Committee membership will include the two project PIs (Drs. Rhon and Fritz), Dr. Greene, Director of the SDBC, the NIH Scientific Program Manager (Dr. Mudd), Science Officer (Dr. Matocha) and Program Official (Dr. Clark).

Tasks of the Steering Committee Include:

1) Convene at least twice yearly by conference call. The purpose of these meetings will be to assess scientific progress, identify any difficulties or obstacles and discuss strategies.
2) Consider and respond to recommendations and policies from the NIH-DoD-VA Pain Management Collaboratory.
3) Identify additional research opportunities.
4) Evaluate efforts towards dissemination of project findings, research tools and products.

The Responsibilities of the Research Team Members of the Steering Committee include:

- Establish agenda and schedule Steering Committee meetings
- Submit data and progress reports related to recruitment, retention, quality metrics and analysis and interpretation of results
- Present ongoing information on Project progress relative to milestones
- Identify potential challenges or obstacles and work with NIH Project Team Members towards resolution.
- Abide by policies and procedures related to data sharing, publications and presentations in consultation with NIH Project Team Members

The Responsibilities of the NIH Team Members of the Steering Committee include:

- Provide relevant scientific expertise and overall knowledge.
- Assist in the integration of the Project into the broader objectives and goals of the Pain Management Collaboratory
- Participate with the other Steering Committee members in the group process of setting research priorities and the adjustment of research protocols or approaches as warranted.
- Work with the other Steering Committee members to ensure Project objectives and milestones are being met.

13. COVID-19 STUDY IMPACT

13.1 Timeline of COVID-19 Impact and Activities

March 19, 2020: the Regional Health Command - central IRB at Brooke Army Medical Center announced that all research activity with human participants that was non-essential and non-critical were suspended until further notice. All participant screening and enrollment was suspended beginning March 19, 2020 in compliance with this policy.

March 19, 2020: The COVID-19 pandemic and resulting mitigation policies resulted in a partial suspension of the clinical trial. Partial suspension indicates that all new enrollment was suspended across all Military Treatment Facilities participating in the project. Additional details of the partial suspension included:

a) Intervention Delivery: Disruptions in clinical services at participating Military Treatment Facilities disrupted the ability to provide care to individuals who were enrolled in the trial. The study team advised site research personnel to provide services as possible for participants who were randomized into a treatment group at the time of the disruption. No participants are being re-randomized to a Phase II treatment if they were in Phase I at the time of the disruption.

b) Participant Follow-Up/Outcomes Assessment: Follow-up assessments are conducted remotely through Redcap for enrolled participants using the timeframes for assessment specified in our protocol. As noted previously, no participants are being re-randomized into a new Phase II treatment if they are determined to be a non-responder at the first follow-up.

March 30, 2020: The study team had a conference call with the Study Design Working Group of the PMC. There was agreement that providing treatments via telehealth is not the intent of the study. Although the exact procedures that will be used to handle the data from the 32 enrolled participants were not determined at this time; it was decided that the team would not seek protocol or informed consent amendments to permit telehealth to be substituted as an alternative to the in-person protocols in the study. The provision of telehealth to patients in the midst of receiving care at the time of disruption is considered consistent with the commitment to these individuals, and not a study intervention.

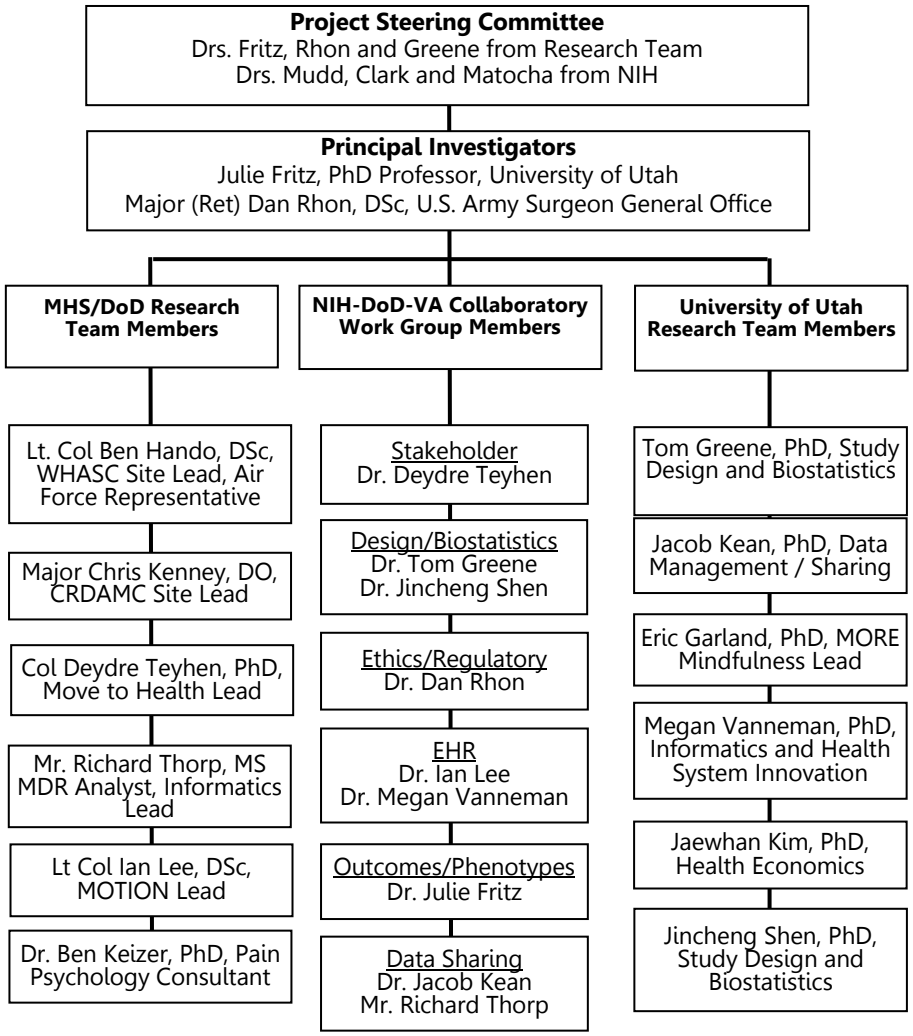
May 11, 2020: The study team met with the Data and Safety Monitoring Board. The report of the DSMB to the study team supported the suspension of enrollment, continued remote follow-up per the current protocol. The DSMB recommended inclusion of COVID-19 survey to collect data on the impact of the pandemic on trial participants.

13.2 Data Management Considerations in Response to COVID-19 Disruptions

The participants who were enrolled in the trial at the time of the partial suspension (March 17, 2020) will continue to receive follow-up assessments using the assessment timeframes identified in the study protocol.

The study team will document the impact of COVID-19 disruptions on these participants including inability to access assigned treatments, completion of treatment visits using remote delivery instead of in-person, inability to transition to Phase II treatment per the study protocol, etc. These disruptions will be recorded as protocol deviations.

Protocol deviations will be provided in subsequent DSMB reports. Prior to finalizing the study database, the study team in consultation with the DSMB and NIH personnel will address any relevant statistical impacts due to protocol deviations and recommend any amendments to the statistical analysis plan.



MHS Study Site Personnel

Wilford Hall Ambulatory Surgery Center

Site PI: MAJ Jeremiah Sampson

Research Coordinator: Tina Greenlee

Director, Primary Care: COL Karen Bowman

Madigan Army Medical Center

Site PI: MAJ Brian Hatler

Research Coordinator: Rachel Mayhew

Director, Department of Family Medicine: COL Robert Oh

Brooke Army Medical Center

Site PI: MAJ Chris Allen

Research Coordinator: Mary Laugesen

Director, Department of Family and Community Medicine: LTC Timothy Switaj

NIH Personnel

Dr. Lanay Mudd, PhD, NCCIH Program Director

Dr. Dave Clark, NCCIH Program Director

Dr. Martha Matocha, PhD, NINR Team Lead, Symptom Science and Genetics

PMC3 Coordination Center

Drs. Robert Kerns, Peter Perduzzi and Cynthia Brandt PIs

Steering Committee (Dr. Kerns Chair)

PMC Operations Core Work Groups

APPENDIX I

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APPENDIX II

Intervention Manual of Operating Procedures

APPENDIX III

Informed Consent Document